endovascular aortic repair

clarifying risk factors, complications and follow-up strategies

Frederico Bastos Gonçalves

ENDOVASCULAR AORTIC REPAIR
CLARIFYING RISK FACTORS, COMPLICATIONS AND FOLLOW-UP STRATEGIES

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Endovascular Aortic Repair: Clarifying risk factors, complications and follow-up strategies
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Verduidelijking van risicofactoren, complicaties en follow-up strategieën

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born in Lisbon, Portugal

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Para a Maria, a Carolina e o Vicente,

"Agir, eis a inteligência verdadeira. Serei o que quiser. Mas tenho que querer o que for. O êxito está em ter êxito, e não em ter condições de êxito. Condições de palácio tem qualquer terra larga, mas onde estará o palácio se o não fizerem ali?" – *Fernando Pessoa, O Livro do Dessassosego*

"To act - that is true wisdom. I can be what I want to be, but I have to want whatever it is. Success consists of being successful, not in having the potential for success. Any wide piece of ground is the potential site of a palace, but there's no palace until it is built." – *Fernando Pessoa, The Book of Disquiet*

CONTENTS

INTRODUCTION

The aorta is the largest artery of the human body. The etymologic origin is Greek and signifies "to lift, heave, raise". Separated from the heart by the aortic valve, it extends upwards, then assumes an arch conformation and follows downwards into the abdominal cavity ending at the iliac bifurcation. Systemic perfusion and vital organ supply of oxygenated blood is provided by the aorta, through its branch arteries. It is a conduction vessel, with unique physical properties that degrade with aging.

Different types of pathological mechanisms may affect the aorta. In the young, traumatic injuries typically located at the isthmus are most prevalent and remain a major cause of death due to injury.[1] This type of lesion is a consequence of extreme tear forces resulting from high-energy impact. Aortic dissections, with a yearly incidence of 3 to 6:100.000, are more frequent in the 6th decade of life.[2] In this disease, the layers of the aortic wall are acutely separated due to severe hypertension and/or intrinsic fragility, potentially leading to rupture or end-organ malperfusion.

More commonly, the aorta is affected by progressive degeneration of the elastin and collagen structure of the *tunica media*, resulting in weakness and gradual dilatation. When the maximum diameter exceeds the expected diameter by more than 50%, an aneurysm is considered present. Due to structural and hemodynamic factors, the infrarenal aorta is most often affected. Aortic aneurysms are common, with prevalence ranging from 1.5% to 4% in elderly men.[3] While typically asymptomatic, they may complicate with rupture, a grave occurrence with exceedingly high mortality. Prophylactic repair is therefore considered when the estimated chance of rupture surpasses the operative risk.

Endovascular aortic repair was introduced over two decades ago,[4,5] and has progressively established itself as a valid alternative to open surgical repair for multiple thoracic and abdominal aortic pathologies. For many, it is the preferred method of treatment for descending thoracic and abdominal aortic aneurysms (AAA), due to the reduced perioperative morbimortality, lower invasiveness and swifter recovery.[6-10] The primary surgical option for dissections and other acute syndromes affecting the descending thoracic aorta has also gradually shifted from open to endovascular repair.[11-14]

Despite the endovascular (r)evolution in the management of aortic disease, this technique is still undefined regarding indications, suitability of patients, selection of devices and procedure-specific complications. The objective of this thesis is to advance our current understanding of different aspects of endovascular aortic repair, thereby promoting an improvement in the treatment of patients.

THESIS OVERVIEW

In *Part I*, controversial issues in thoracic endovascular repair of the aorta are addressed. In **Chapter 1**, the subject of patient and graft selection for endovascular treatment of type-B dissections is reviewed in light of current evidence. **Chapter 2** is a critical analysis of the study design of the recent randomized trial that compares medical therapy endovascular grafting in uncomplicated acute dissection of the descending aorta (ADSORB trial). In **Chapter 3** the authors report on a rare case of paraplegia recovery after endovascular repair of an infected thoracic aneurysm. **Chapter 4** is a commentary regarding the potentially fatal complication of endograft collapse after thoracic endovascular repair, focusing on device selection.

In *Part II*, the authors address the issue of hostile anatomy for AAA repair. Specifically, the proximal fixation zone is scrutinized, attempting to characterize risk factors for early and late adverse outcome. In **Chapter 5**, the authors identify and quantify neck related risk factors using a large multinational registry of patients that have been treated with a late generation endovascular device. In **Chapters 6 and 7**, the early and late outcome of patients with extreme angulation of the proximal neck is presented. In **Chapter 8** the authors assess the influence of significant thrombus at the proximal fixation zone on outcome. **Chapter 9** aims to demonstrate differences in complications for patients with familial or sporadic forms of AAA.

In *Part III*, the authors attempt to demonstrate the applicability and potential benefit of endovascular repair in the setting of AAA rupture. In **Chapter 10**, the authors identify risk factors for early death with endovascular and open repair, and the independent impact of technique on the outcome. **Chapter 11** aims to determine the long-term prognosis of AAA patients, searching for potential differences in outcome for endovascular vs. open repair patients, and for ruptured vs. elective patients. The causes of death are also scrutinized, in order to reveal any potential influence of form of presentation or method of treatment on prognosis.

Part IV is dedicated to determine specific outcomes of endovascular repair when using individual devices. In **Chapter 12**, a review of the specific advantages and pitfalls of current and discontinued models is presented, setting the stage for **Chapters 13 and 14**. The former assesses the long-term outcome (up to 11 years) after implantation of the Gore Excluder, the longest experience published to date. Specificities of this particular device are explored with detailed morphological analysis. In the latter, the authors present a multicentre study on the outcome of patients after implant of the more recent Medtronic Endurant, which also provides the longest available data on this particular device.

In *Part V*, complications of endovascular AAA repair are analysed in detail, to determine their significance, potential influence on the outcome and optimal treatment.

Chapter 15 is dedicated to the poorly understood inflammatory response that occurs shortly after implantation, its significance and associated risk factors. In **Chapter 16**, the authors attempt to determine the outcome of untreated primary type-Ia endoleaks under selected conditions, which challenges current opinion on management of this complication. **Chapter 17** deals with the issue of type-II endoleaks, contextualizing the results of a recent systematic review on the subject. A rare but interesting complication is described in **Chapter 18**, where a type-II endoleak and an aorto-caval fistula coexist. The management and outcome of this case are detailed. **Chapter 19** analyses the long-term outcome of laparoscopic aneurysm sac fenestration to treat aneurysm sac expansion. In **Chapter 20**, the authors describe the poorly understood phenomenon of in-graft mural thrombus deposit. Risk factors for thrombus formation and potential clinical sequelae are presented. **Chapters 21 and 22** are dedicated to the iliac components, analysing specific complications that occur at the distal fixation zone. **Chapter 21** describes the incidence, causes and clinical consequences of endograft limb occlusion using a multicentre cohort. In **Chapter 22**, the authors assess the dynamics of the iliac sealing zone by determining the occurrence of retrograde migration and its relationship with distal sealing zones and iliac dilatation.

Part VI addresses the issue of surveillance after endovascular AAA repair. In **Chapter 23**, the authors attempt to demonstrate that information present in the first postoperative computed tomography angiography can be used to predict the risk of subsequent complications. In **Chapter 24**, early sac dynamics is used as a discriminator for the risk of late complications in a multicentre study. **Chapter 25** provides the rationale and design for a randomized controlled study comparing standard vs. individualized postoperative surveillance strategies.

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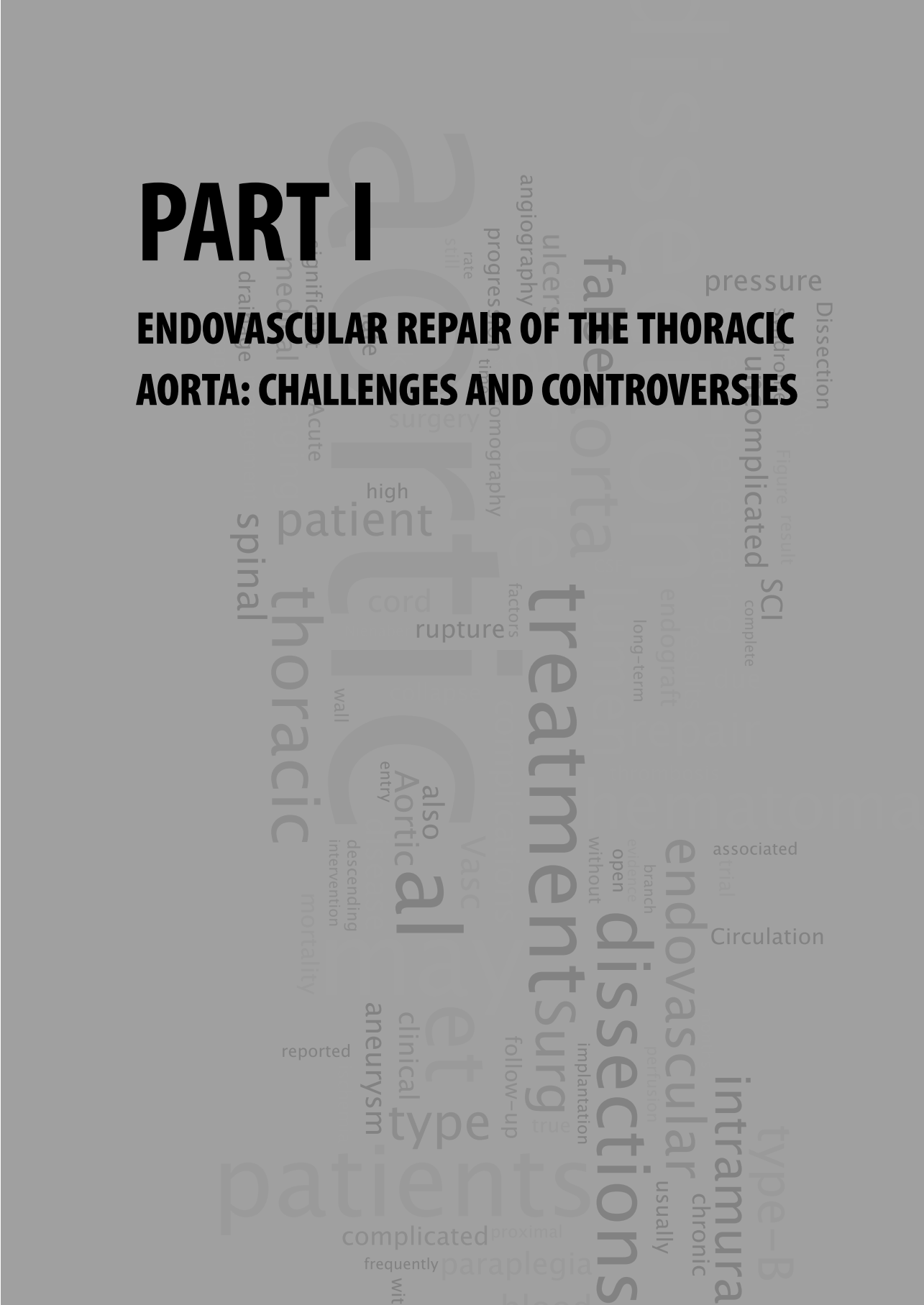
PART I

ENDOVASCULAR REPAIR OF THE THORACIC AORTA: CHALLENGES AND CONTROVERSIES



Chapter 1

Decision-making in Type-B dissection: current evidence and future perspectives

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ABSTRACT

Aortic dissection is a devastating cardiovascular condition with an incidence of 3,5:100 000. It is classified according to anatomic extent, mechanism of lesion, duration from index event and course (uncomplicated vs. complicated). Intramural hematoma and penetrating aortic ulcers share many of the features of classic dissections, but tend to occur in older patients with advanced atherosclerosis.

In uncomplicated type-B dissection, conservative treatment with tight blood pressure and heart rate control is safe and effective. Early stentgraft implantation may, however, result in more favorable aortic remodeling and reduced late complications. For acute complicated cases intervention is usually required. Stentgraft coverage of the entry tear frequently resolves malperfusion, but the role of the false lumen in organ perfusion must be assessed and endovascular revascularization performed if necessary. In chronic type-B dissections, coverage of the entry tear likely results in continued pressurization of the false lumen due to rigidity of the dissecting membrane and distal fenestrations.

Better understanding of the different disease mechanisms involved, imaging advances and introduction of dedicated stentgrafts are expected to further improve patient outcomes in the future. Primary and secondary pharmacological prevention, stricter follow-up protocols and screening of family members may also prove valuable. Better patient selection will allow preventive treatment with low morbidity for those at higher risk of complications.

INTRODUCTION

Aortic dissection is a devastating cardiovascular condition with high morbidity and mortality rates. Its estimated annual incidence is 3.5 per 100.000, with a 5:1 male predominance.[1] Approximately one third of all dissections are classified as Stanford type-B, meaning they affect only the descending thoracic and/or abdominal aorta. Variants of classic dissections – intramural hematoma and penetrating aortic ulcer – are being increasingly recognized due to diagnostic advancements and physician awareness. These are uncommon and affect the descending aorta in a larger percentage of patients.

Classic dissections, intramural hematoma and penetrating aortic ulcers are frequently grouped together as acute aortic syndromes, but mechanisms, evolution and prognosis may differ. Due to their relative rareness and complex nature, these conditions remain difficult to assess and manage for many clinicians. In order to understand what to treat, when to treat and how to treat, one must appreciate exactly "what is going on". Our aim is to provide an updated overview of the evidence for diagnosis and management of these complicated pathologies.

BACKGROUND

The initial event

In classic aortic dissection, disruption of the intima and media layers of the aortic wall is the prime event. In type-B dissection the typical entry tear is transverse, non-circumferential and located just distal to the left subclavian artery, on the posterolateral aspect of the aorta. Flowing blood forces its way in-between the layers of the aortic wall, creating a cleavage plane within the media, which may progress proximally and/or distally. This results in an intimal flap, also called dissecting membrane or *lamella*, dividing the aorta into a true and false lumen. Hemodynamic stress in the aortic wall promotes additional tears in the intimal flap, creating re-entry points or additional points of entry. These generally occur at aortic branch ostia and may create complex communications between the two flow channels.

Any mechanism responsible for weakening the aortic wall may contribute to the initiation of dissection, including longstanding hypertension, connective tissue disorders such as Marfan´s disease or Ehlers-Danlos syndrome type IV, trauma and iatrogenic factors like endovascular intervention or cardiac surgery. Advanced aortic atherosclerosis also plays an important role in the genesis of intramural hematoma and penetrating aortic ulcers.

Excessive chest pain or pain between the shoulder blades are the most common presenting symptoms, commonly in a severely hypertensive patient. Since aortic dis-

section is a dynamic process occurring anywhere in the aorta, the clinical spectrum of presentation is broad.[2] While many cases are straight forward, others may be misleading, resulting in treatment delay. Weakness of one limb or mesenteric ischemia, for example, may be the only presenting signs. A high clinical index of suspicion is thus warranted in order to perform a correct and timely diagnosis.

Classification

Aortic dissections are classified according to location, mechanism, elapsed time from onset and for the presence or absence of complications. The anatomic classification is based on the location of the entry-tear and the extent of the dissection along the aorta (Figure 1). In a Stanford type-A the ascending aorta and/or the aortic arch are involved in the dissection, while in type-B it is limited to the descending aorta. This classification is of great clinical and prognostic value. For example, type-A dissections generally require prompt surgical intervention due to pending cardiac complications. This approach is distinctively different from the initial management of type-B dissection.

More recently, Svensson *et al.* proposed a classification system that accounts for the different mechanisms of lesion, dividing them into 5 classes (Figure 2).[3] This correlates well to different variants of aortic dissection. However, there may be significant overlap between groups and changes over time may result in different classifications for the same patient. For instance, a patient with a small penetrating ulcer (class IV) may develop a large intramural hematoma (class II) or overt double-barrel dissection (class I).

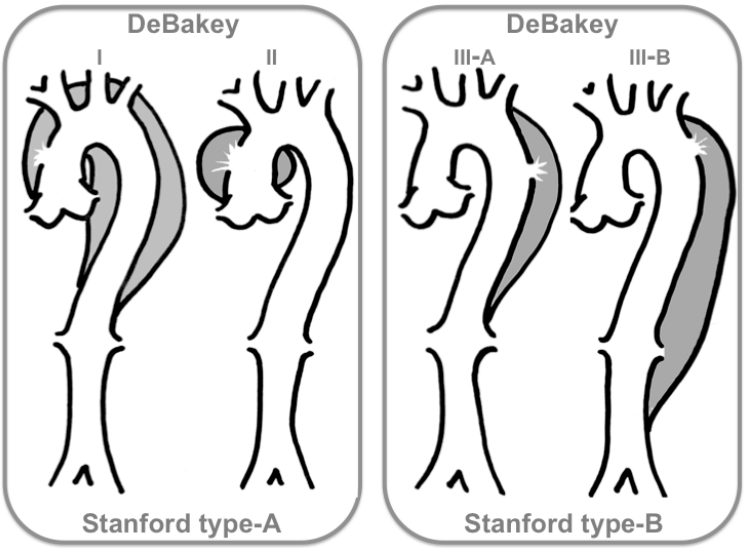

Figure 1. Anatomical classification of aortic dissection according to Stanford and DeBakey. *Left box*: Stanford A / DeBakey I and II. *Right box*: Stanford B / DeBakey IIIa and IIIb.

Dissections should also be classified concerning time from onset of symptoms. When less then 2 weeks, type-B aortic dissections are termed *acute*. By definition, they are named chronic after this period. Although this is arbitrary, complications usually manifest within this time frame, making it practical in determining prognosis[2]. Some authors have suggested a third timeframe – termed sub-acute – that extends from >2 weeks to several months, to accompany the behavior of the dissection flap (from dynamic to rigid).

Weather acute or chronic, it is important to state if the course of the disease is *complicated* or *uncomplicated*: A type-B dissection is considered uncomplicated unless one of the following is present:

1. Impending rupture
2. Malperfusion
3. Uncontrollable pain
4. Uncontrollable hypertension
5. Rapid growth

The concept of change over time (progression) may also be added to the classification. Repeated follow-up may reveal a stable, non-progressing or regressing lesion, or a progressive disease requiring intervention or closer observation.

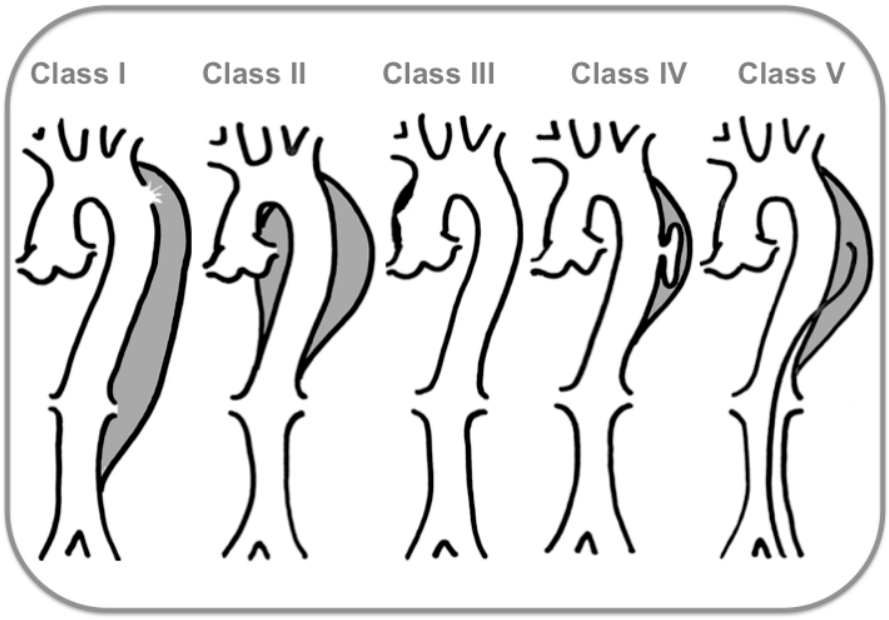

Figure 2. Classification proposed by Svensson *et al.* and later adopted by the European Society of Cardiology. Type I – Classic double-barrel dissection, Type II – Intramural hematoma, without intimal disruption, Type III – Intimal tear, Type IV – Penetrating aortic ulcer, Type V – Iatrogenic injury

Diagnosis

Computer tomography angiography is most commonly used in the diagnosis of aortic dissections (Figure 3) followed by trans-esophageal echocardiography.[4] Although the latter is widely available and accurate in depicting separation of aortic wall layers with or without flowing blood, it is less favorable to document the extent of the dissection in the aortic arch or below the diaphragm.[5] Magnetic resonance angiography provides imaging that compares to computer tomography angiography and may add some hemodynamic information, but availability, time delay, restricted ability to monitor patients and the presence of implants limit its use. In daily clinical routine, the choice of imaging modality may reflect availability rather than preference and more than one technique may be required to confirm or exclude a diagnosis**.**

Natural history

Historically, the mortality for acute type-B dissection was as high as 40% at 3 months, when no treatment was installed. Mortality ranged from 25-50% in early reports on the open surgical treatment for acute type B dissections. Moreover, surgery presented significant technical challenges.[6] More recently, the International Registry of Acute Aortic Dissection (IRAD) reports have shown that in-hospital mortality risk is around 30% when open surgery is required, depending on the exact indication for surgery.[4,6]

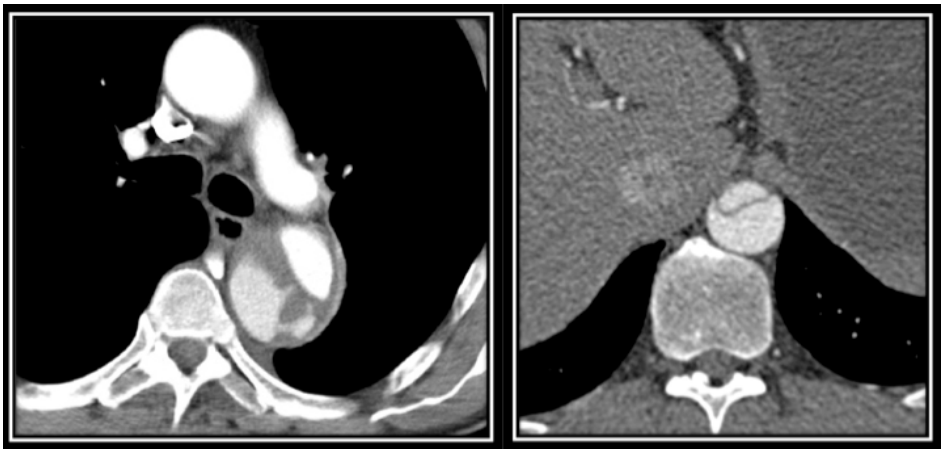

Figure 3. Computer tomography angiography of aortic dissection. On the left is a chronic dissection demonstrating complex false and true lumen communication. On the right is the typical image of an acute dissection (thin "lamella").

WHAT WORKS: CONSERVATIVE TREATMENT FOR UNCOMPLICATED TYPE-B DISSECTION

In uncomplicated type-B dissection medical treatment alone is preferred, with an in-hospital mortality risk of about 10%.[2,4] Medical management should be directed toward immediate lowering of blood pressure, aiming for a maximal systolic pressure of 120 mm Hg, minimizing further cleavage of the aortic wall. Optimal strategy includes admission to a high care unit and intravenous administration of anti-hypertensive medication, using ß-blockers as first-line therapy. These drugs efficiently lower blood pressure and avoid peaks of pressure. Recognition of the importance of blood pressure control was paramount in changing the prognosis of patients with type-B aortic dissections.

Additionally, tight heart rate control has shown to further improve outcome and ß-blocker dosage should be tittered to maintain frequency up to 60 heartbeats per minute[7]. If no clinical deterioration occurs, patients should start long-term oral medication and be enrolled in a close follow-up protocol.[8]

THE CONCEPT AND EVIDENCE FOR STENTGRAFT IMPLANTATION IN ACUTE TYPE-B DISSECTION

One in every five acute type-B dissections presents with complications or evolves from uncomplicated to complicated. This may happen shortly after onset or following an initial uncomplicated period.[9] In the complicated cases there are essentially four possible treatment strategies:

1. Open surgical repair. Operative mortality rate, however, may exceed 50% in the presence of aortic rupture or visceral ischemia.[2]
2. Surgical fenestration. This usually alleviates malperfusion syndromes but still caries a significant mortality risk (approximately 25%) despite a high technical success rate.[10]
3. Stent-graft coverage of the entry tear, followed by selective additional endovascular revascularisation of ischemic organs (Figure 4).
4. Endovascular fenestration and branch vessel stenting.[11]

The basic concept of stentgraft repair of acute type-B dissections is sealing the entry tear. In the ideal situation, redirection of flow is achieved, resulting in depressurization and thrombosis of the false lumen. Limited coverage of the aorta is recommended in an attempt to reduce the risk of paraplegia due to spinal cord ischemia. A covered length of 15cm seems to offer a good tradeoff between sealing the entry tear and the chance of paraplegia.

Correct stent-graft implantation depends upon identification of the entry-tear and the true and false lumina. The proximal part of the endograft should be positioned

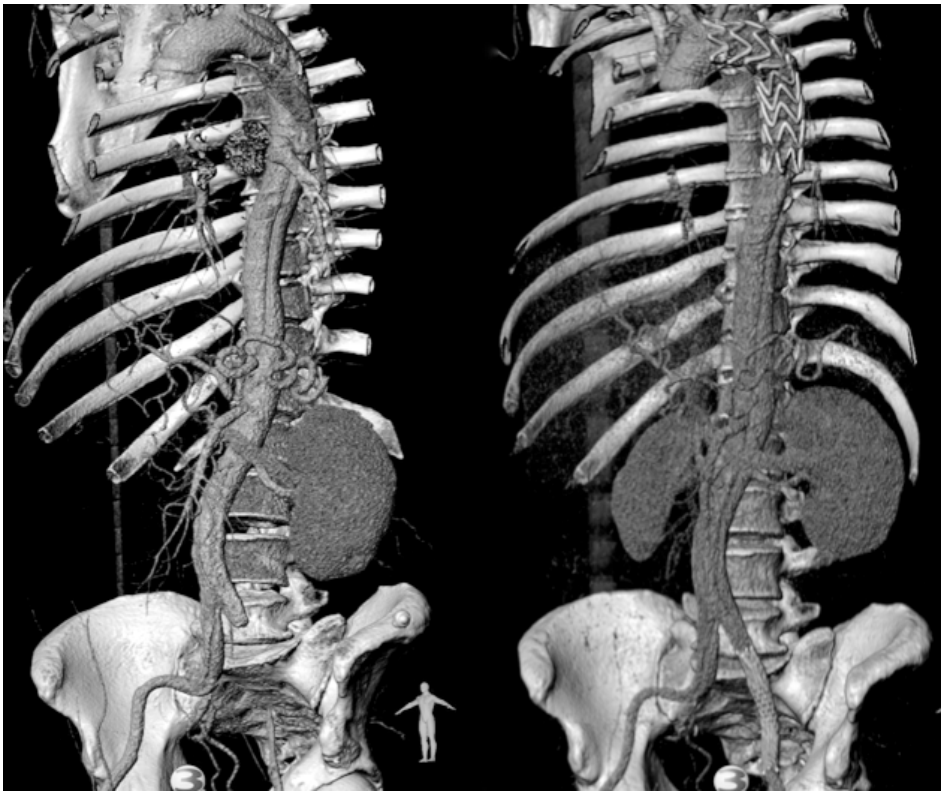

Figure 4. Pre and post-intervention computer tomography angiography post-processing reconstruction of aortic dissection. Notice the re-perfusion of the right kidney after sealing the entry-tear. Iliac patency was achieved by subsequent placement of a covered stent.

in a relatively unaffected part of the aorta, which often requires coverage of the left subclavian artery. Revascularization of this vessel, by means of bypass or transposition surgery, may be performed in order to reduce the risk of spinal chord ischemia, stroke or arm claudication. A selective approach to this seems preferable – indications include patients with long segments of the aorta covered by the endograft, history of prior infrarenal aortic surgery, renal insufficiency and hypoplasic right vertebral artery.[12] A secondary revascularization can still be undertaken safely in most cases, when the initial option was not to revascularize.

One must be aware that the false lumen may play a crucial role in organ perfusion. While usually beneficial, re-expansion of the true lumen may actually worsen organ perfusion. All efforts should be made to characterize branch vessel perfusion (identifying any flow abnormality and differentiating static from dynamic obstruction) and prepare adequately to respond to sudden changes in organ perfusion after stentgraft

implantation. This includes the technical and material capacity to perform emergent endovascular (or surgical) revascularization of visceral vessels.

Results from IRAD on treatment of complicated acute type-B dissections showed a significant decrease in in-hospital mortality (from 33.9% to 10.6%) favoring stentgrafting over open surgery.[7] These and other reports with similar findings have contributed to a drastic change in the management of complicated type-B dissection. However, current evidence showing superiority of endografting over open surgery (or medical treatment) is derived from non-randomized studies and might be subject to referral, selection and publication bias.[9,13]

WHAT MAY WORK: STENTGRAFTING FOR UNCOMPLICATED ACUTE TYPE-B DISSECTION

In spite of the initial benefit favoring medical treatment over open surgery for uncomplicated acute dissections, the life expectancy of the medically treated patients seems to be lower compared to the general population. According to Tsai *et al*., approximately 1 in 4 patients treated by medical therapy alone will die within 3 years from disease onset. Additionally, about 1 in 4 survivors treated medically will encounter late complications, in particular dilatation of the false lumen.[14] Consequently, the optimal management strategy of uncomplicated type-B dissection continues under debate.

Based on the success of stent-grafting in complicated acute type-B dissections, the preferred approach for uncomplicated type B dissections may alter as well. Continued patency of the false lumen in patients receiving medical treatment alone is known to be a risk factor for progression of aortic dissections towards aneurismal dilatation.[15] Early sealing of the entry tear may increase the chance for false lumen obliteration and improve remodeling, resulting in a more "physiological" aortic healing.[16,17] With this, the rate of late complications would theoretically be reduced.

Initial results with early endograft implantation have shown technical success to be high, with 70%-100% of false lumen thrombosis on the short term.[18,19] Long-term results have to be awaited in order to safely generalize this approach, though. The ADSORB trial (Acute uncomplicated aortic Dissections type B: Evaluating Stent-graft placement OR Best medical treatment alone) is initiated to investigate the value of stent-grafting in uncomplicated acute type B dissection, but results will not be available anytime soon. In light of current evidence, prophylactic scaffolding is debatable and best performed in a clinical trial context.

STENTGRAFTS IN CHRONIC TYPE-B DISSECTION: A DIFFERENT CHALLENGE

In the chronic phase of type-B dissection, true lumen/septum malleability diminishes dramatically (due to fibrosis of the dissecting membrane) and so does the ability of the aorta to adequately remodel. Stentgraft repair is therefore more likely to be effective when applied in the acute setting, and it is doubtful that the rationale for stentgrafting in acute dissections applies to chronic cases. While good proximal seal can usually be achieved, retrograde perfusion of the false lumen via one of the many re-entry tears distal to the stent-graft is likely. Although many reports state that stent-grafting for chronic dissections is technically feasible with low morbidity and mortality rates, the pressure within the false lumen may often remain unchanged, making treatment ineffective.

The INSTEAD trial (INvestigation of STEnt-graft in patients with type-B Aortic Dissection) set off to clarify the role of stent-grafting as a preventive treatment in patients surviving acute uncomplicated dissections. Only patients with at least two weeks after index dissection were included (meaning only sub-acute or chronic dissections were evaluated). Two-year results have been recently published and demonstrate no significant differences in mortality between preventive stent-grafting and medical treatment alone. Intervention, however, resulted in a higher adverse event rate.[20] One of the reasons for these results was the unexpectedly favorable outcome of patients treated medically. Moreover, treatment crossover from the medical to the stentgraft group was 16.2%. The authors also recognized favorable aortic remodeling with stentgrafting, with expansion of true lumen, reduction of false lumen and higher tendency for false lumen thrombosis. This did not affect mortality at 2 years, but may do so in latter years.

Endovascular intervention does seem justified for those patients that develop late complications, namely aneurismal dilatation. In most cases, these need to be treated as aneurysms, or continued pressurization of the expanding false lumen will ensue. This comes at the cost of a higher paraplegia risk. Since chronic dissections frequently involve the proximity of aortic branches and true-false lumen communications are multiple, planning and executing these procedures may be difficult. Furthermore, it may be required to revascularize branch vessels in order to achieve adequate sealing zones – the significant morbidity associated with hybrid procedures may offset the benefit of treatment.

THE PARTICULAR CASES OF INTRAMURAL HEMATOMA AND PENETRATING AORTIC ULCER

The term acute aortic syndrome, coined by O´Gara, comprehends a group of diseases that include dissections and also intramural aortic hematoma and penetrating aortic

ulcers.[21] These pathologies share some disease mechanisms and clinical characteristics and there can be significant overlap between them. Aneurysm rupture may also be included in the acute aortic syndrome, since it shares clinical (acute pain) and pathological (disruption of aortic wall integrity) features with the previous group. It is estimated that intramural hematoma and penetrating aortic ulcers account for 5-30% of all acute aortic syndromes. In IRAD, 58/982 patients were classified as intramural hematoma using strict criteria.[22]

Krukenberg, in 1920, was the first to describe intramural hematoma in necropsy subjects, calling it "aneurysma dissecans" or dissecting aneurysm. About a decade later, Shennan reported on ulcerated aortic plaques, recognizing the relationship with dissections in his term "dissecting aneurysm variant". This terminology, inconsistent with current definitions but still used by some, results is added confusion in the characterization of these rare pathologies.

Definition, classification and diagnosis

Intramural hematoma refers to the accumulation of blood within the media layers of the aorta, without disruption of the intima layer, while penetrating ulcers are the result of atherosclerotic ulceration that disrupts the internal elastic lamina. These processes usually present in a similar fashion to classic dissections, with thoracic or abdominal pain in a hypertensive patient, but malperfusion syndromes are rare.

When compared to the typical patient with aortic dissection, these variants tend to occur in older subjects with more advanced atherosclerosis. Evangelista *et al.* found the mean age of patients with classic dissection to be 60, in contrast to 69 for those with intramural hematoma.[22] Previous aortic dilatation and heavy calcification are frequent findings in patients with variant forms (figure 5), but not with double-barrel dissections. These observations suggest that the disease mechanisms are different, regardless of the similarities in presentation and management.[22-24]

In fact, while the initiating mechanism for penetrating aortic ulcers appears straightforward, that is not the case for intramural hematoma. Observation of the intima-media interface integrity has led to the belief that rupture of vasa-vasorum was to blame for the hematoma dissecting the media layer. More recent investigations have challenged this by demonstrating that minor intimal disruption or penetrating ulcers are present in most cases, thus feeding the hematoma. This is consistent with reports in which coverage of a localized intimal defect results in reabsorption of hematoma in the entire aorta.[25-27] It has also been demonstrated by the IRAD investigators that intramural hematoma and penetrating ulcers occur more often in the descending aorta (about 2/3 of cases) as opposed to classic dissections.[22]

Computed tomography is the preferred diagnostic and follow-up imaging technique, in similarity to double-barrel dissections. Also, trans-esophageal echography may

replace or complement observations provided by computed tomography. The role of magnetic resonance in daily practice is still unclear, and currently used primarily for research purposes.

In aortic hematoma (Figure 5), it is frequent to observe some degree of compression of the true lumen, surrounded by a crescent or circular-shaped accumulation of blood within the media. This may be visualized using non-contrast computed tomography, as the wall hematoma appears brighter than the flowing blood in the lumen. Intimal calcifications are usually present and remain concentric to the accumulated blood in the media wall, distinguishing it from old thrombus (frequent finding in aneurysms), which lies within the "calcic lining" of the intima. Associated small ulcers disrupting the intima can frequently be detected in high-resolution imaging studies.

In typical penetrating ulcers, a contained intramural hematoma extending a short distance proximally and distally is associated. It is thought that progression to an intimal flap is prevented by the heavy atherosclerotic burden of the intima.

Natural history and prognostic factors

Intramural hematoma and penetrating ulcer are rare and relatively unstudied diseases of the aorta. From IRAD we know that one in five patients will die during their first admission for intramural hematoma, but involvement of the ascending aorta accounts for most cases.[22,28] In those restricted to the aortic arch or the descending aorta prognosis is much better, with mortality under 10%.

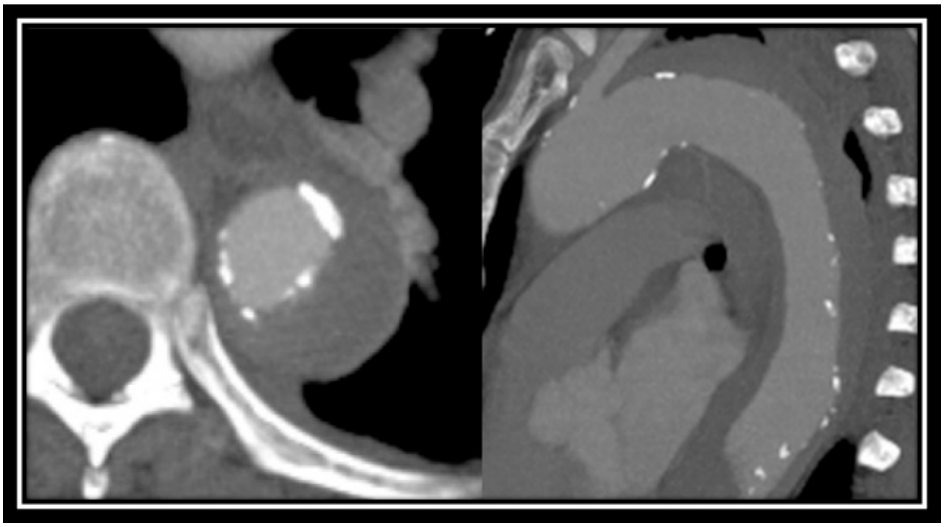

Figure 5. Computed tomography of intramural hematoma of the descending aorta. The hematoma takes a crescent shape surrounding the compressed true lumen with intimal calcification

We also know that over half of patients will show regression of the hematoma on serial imaging after conservative treatment (Figure 6). However, 28-47% of patients will progress to a double-lumen dissection and 20-25% to aortic rupture, again more frequently in those involving the ascending aorta. The risk of progression is about 40% within the first 30 days and 20% after that.[29,22]

Several authors have looked into the prognostic factors for progression.[28,30,31,32] Early progression of intramural hematoma (within 30 days) has been associated with ascending aortic involvement, large aortic diameters (>5,5mm), presence of penetrating ulcers, hematoma thickness greater than 10mm and recurrent/persistent pain. Late progression was correlated only to age and absence of long-term β-blockage.

For penetrating aortic ulcers, association with intramural hematoma is very frequent, but usually localized. Disruption of the aortic layers involving the adventicia results in aortic rupture or pseudoaneurysm formation. Tittle *et al.* found that one in four symptomatic aortic ulcers will progress to pseudoaneurysm and over one third will eventually rupture.[33] Risk factors for progression of these lesions are the presence of symptoms (specially if recurrent or refractory to treatment), old age and advanced atherosclerosis, evidence of high inflammatory plaque content on positron-emission tomography and interval increase in size during image follow-up.[33,25,34]

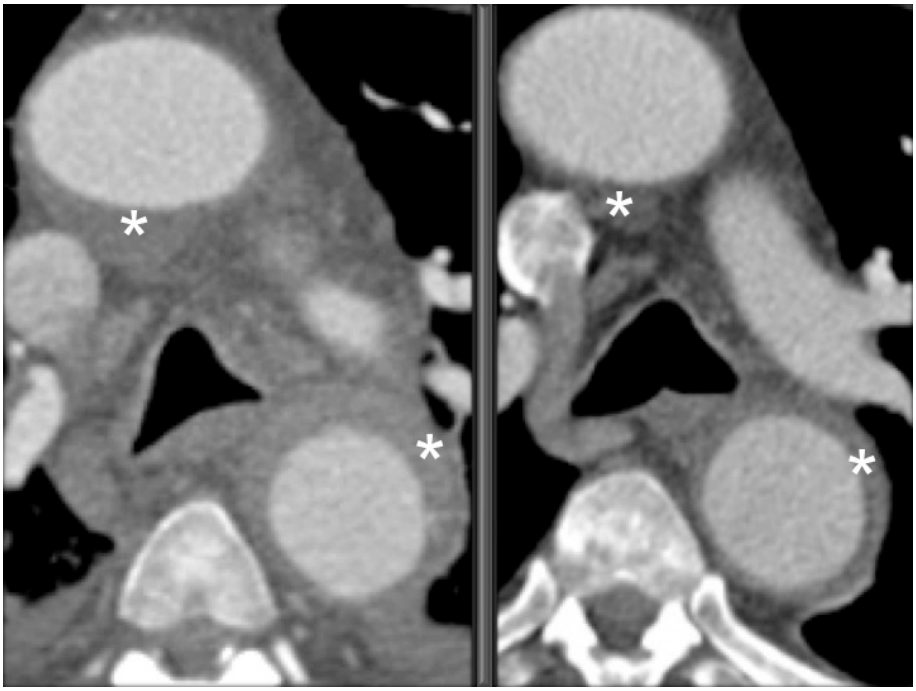

Figure 6. Regression of intramural hematoma (*) documented by computed tomography, 3 weeks after diagnosis (treated conservatively). Notice re-expansion of the true lumen as hematoma regresses.

The role of stentgrafting for type-B intramural hematoma and penetrating aortic ulcers

The mainstay of treatment is blood pressure and heart rate control, like in classic dissection. Similarly, this is best achieved by β-blocker therapy, which should be continued in the long-term, thus reducing the chance of late progression as mentioned. A conservative approach results in regression for the majority of patients and seems indicated for intramural hematoma without evidence of progression and for stable, asymptomatic aortic ulcers. In complicated cases, however, intervention is deemed necessary. Additionally, patients with high-risk of progression may be considered for invasive treatment.

Penetrating ulcers are frequently considered to be easy endovascular "targets", as they are often localized, short lesions. Limited aortic coverage is needed and open repair would be risky due to the highly calcified nature of the aortic wall. Unfortunately, this last characteristic is also the main drawback of endovascular treatment, as catheter manipulation may result in plaque or debris embolization and access-vessel occlusive disease may be significant.

Intramural hematoma may present significant challenges in regard to endograft sizing, branch vessel management and procedure-related complications. Firstly, there may be a large segment of involved aorta that does not need be covered. One must recognize why treatment is being allocated and not attempt to exclude the entire affected area: most agree that coverage of one or more identified ulcers will result in regression. Also, sizing may be difficult due to a miss-match between the luminal diameter (usually compressed by the hematoma) and the outer aortic diameter (usually enlarged). Lastly, catheter and sheath manipulations may result in additional fenestrations due to the frailty of the diseased and compressed intima.

FUTURE PERSPECTIVES ON TYPE-B DISSECTION

ECG-gating and dynamic imaging

In arterial dissections, morphology may change significantly throughout the cardiac cycle. Random "snap-shot" imaging may under or overestimate the gravity of a specific problem, or even miss it completely. Adding time (a fourth dimension) to imaging can further elucidate the true and false lumen interactions and branch vessel compromise. These dynamic imaging studies have provided new insight on physiological aspects of acute and chronic dissections. On dynamic computer tomography angiography it can be beautifully shown that the intimal flap is very mobile in the acute phase of dissection (Figure 7), while thick and rigid in latter stages (Figure 8).

Electrocardiographic-gating also diminishes artifacts significantly in pulsatile structures such as the aorta and the dissection flap, and shows the distensibility of the aorta

enabling more accurate sizing.[35] It also reduces the potential for false positive images that could otherwise result in treatment of non-existing pathology.

Additionally, functional vascular MRI techniques are able to indirectly measure intra-arterial pressure and tissue perfusion. Although the true significance of these findings is yet to be determined, they are expected to shed new light on dissections. Of particular interest may be the indirect measure of aortic stiffness, a predictive factor for dilatation and dissection in patients with Marfan syndrome.[36]

Integrating clinics and imaging – understand what is going on

Imaging for aortic pathology and for dissections in particular is of paramount importance. Current good practice demands that every patient with an acute aortic dissection undergoes either computer tomography angiography or magnetic resonance angiography with high-resolution imaging on admission. In fact, some institutions have adopted

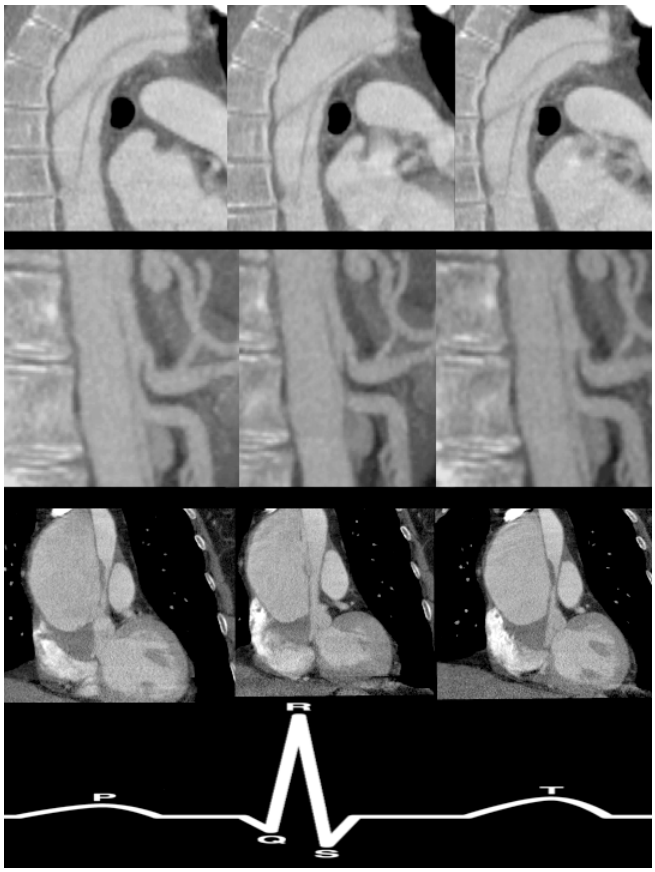

Figure 7. Dynamic electrocardiography-gated computer tomography angiography of acute aortic dissection showing the mobility of the intimal flap.

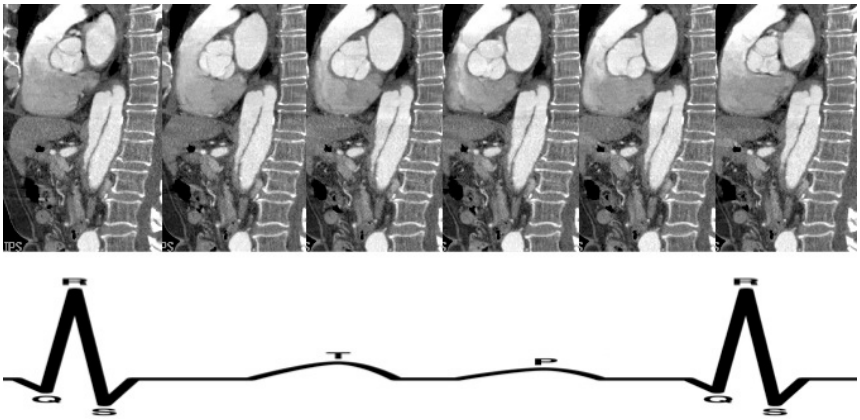

Figure 8. Dynamic electrocardiography-gated computer tomography angiography of chronic aortic dissection showing no mobility of the intimal flap.

the "triple rule out" computer tomography strategy for patients with acute chest pain, offering quick differential diagnosis for acute coronary syndrome, aortic dissection and pulmonary thromboembolism.

The use of a workstation with analysis and volume-rendering reconstruction software provides clinicians with valuable additional information on the pathology. Moreover, it enables accurate sizing and planning, particularly important in aortic endovascular procedures. Its applicability and utility can be extrapolated from the extensive experience in aneurismal disease.

Dedicated stentgrafts

Endovascular treatment of aortic dissections is currently performed with devices designed for treating aneurysms. The particular anatomical (such as juxta-subclavian entry tear), structural (thin and fragile walls) and physiological (such as dynamic branch vessel mechanisms) characteristics of type-B dissections warrant dedicated grafts. The ideal stentgraft for acute type-B dissections should be very flexible and conformable, with no hooks or barbs and avoid infolding while adapting to positional changes in the aortic axis. It should allow proximal "steering" in order to achieve optimal and precise fixation. The concept of distal open stents (PETTICOAT concept) to permit spinal and side branch perfusion while promoting apposition of the dissection flap as far down as needed during treatment of acute type B dissection is appealing and already being applied in a phase-I trial.[37]

Using bio-absorbable materials has potential benefits in acute dissections as well. After successful aortic healing and remodelling, normal aortic physiology and the absence of late device-related complications are obviously desirable. Bio-absorbable

stents have been tried in humans with success, but the applicability of this technology in the thoracic aorta is unknown.

Patient Selection

Proper patient selection is likely to result in improved early and late outcomes in type B-dissections. Predictors of aortic enlargement after conservative treatment are a large aortic diameter, large false lumen diameter, patent entry site, presence of blood flow in the false lumen, Marfan syndrome, chronic obstructive pulmonary disease, age > 60 and female gender. Similarly, predictors of aortic rupture after conservative treatment are old age, chronic obstructive pulmonary disease, hypertension, patent false lumen (especially partial thrombosis) and aortic diameter over 55 mm.[14,35,38,39] Patients with uncomplicated type B dissection but with large initial aortic diameters, patent false lumen or persisting hypertension will likely benefit most from early endovascular treatment.

The same concept could be applied to intramural hematoma and penetrating aortic ulcer patients. Patients at high-risk for progression (especially those with localized lesions and adequate sealing zones) may be subject to stentgraft implantation, in order to prevent future complications. This may be done with exceptionally low morbidity and high success rates.

Aggressive medical therapy, primary and secondary prevention

It is well established that all patients with acute dissections should be promptly admitted to medical treatment. The effect of medical therapy on early and late outcome has been well demonstrated in reports from IRAD.[14,40] In fact, patients who maintain adequate blood pressure and heart rate control over time have been shown to have a better late prognosis, despite previous surgical or conservative treatment and regardless of the exact type of aortic lesion. Treatment with ß-blockers is an essential part of long-term therapy in type-B aortic dissections.[8]

Recently, the importance of angiotensin II blocking agents has been investigated. Their effect may be two-fold: reduce central arterial pressure and conduit arterial stiffness and modulation of the transforming growth factor-β. Patients with Marfan syndrome manifest TGF-β abnormalities[41,42] responsible for many of the phenotypic characteristics of the disease and there is growing evidence that interference in this pathway improves prognosis. A randomized trial is currently underway to further investigate this issue.[43] The benefits of angiotensin-converting enzyme inhibitor drugs on the secondary prevention of patients with aortic dissections has also been suggested, and may significantly reduce the rate of late events.[42]

Family members of patients with aortic dissection may benefit from screening for genetic abnormalities, particularly connective tissue disorders that may predispose them to dissection, aortic dilatation or sudden death. Doing this may offer a window

of opportunity for primary prevention of asymptomatic patients at risk. In patients with Marfan syndrome many phenotypic characteristics may pass unnoticed due to the extensive clinical variability associated with different fibrillin-1 gene mutations. Dissection patients with Marfan-like syndromes, such as those with bicuspid aortic valve, familial thoracic aortic aneurysm or Loeys-Dietz syndrome, are also increasingly being recognized.

A detailed clinical evaluation of patients and family members, complemented with echocardiography for detection of valve abnormalities and aortic root dilatation (and perhaps MRI for high-suspicion cases) is recommended. Genetic testing is feasible for confirmation and research purposes, but still limited by a high variability of mutations, especially in less clear-cut cases. As more culprit mutations are recognized, easier diagnosis and family screening will be possible.

Follow-up

Serial imaging is the cornerstone of long-term follow-up and should include the entire aorta. Magnetic resonance has been proposed as first-line imaging for follow-up mainly because of radiation exposure concerns, but computed tomography is usually more easily available. At the author's institution, follow-up is performed after approximately 10 days, three months, one year and yearly thereafter. More frequent imaging may be necessary, depending on findings.

CONCLUSION

Diagnosis and treatment of aortic dissection and its variants – intramural hematoma and penetrating aortic ulcer – has progressed significantly in recent years. Nevertheless, no other aortic disease remains so difficult to manage. This is especially true in complicated cases, which present as rupture or malperfusion. As medical treatment becomes more efficient and endovascular procedures are better understood, appointing the correct treatment to the right patient is still not evident, and there is a certain degree of unpredictability associated with every treatment option.

On basis of current knowledge, all patients need immediate and continued medical therapy that includes ß-blockers and intervention should be reserved to those with a complicated course and perhaps those considered at high risk for complications. When feasible, endograft implantation offers better overall results than open surgery or endovascular fenestration and promotes favorable aortic remodeling. Close and life-long follow-up is mandatory for all patients with dissections, as early and late progression is frequent and may require treatment.

Better understanding of the different disease mechanisms involved, alongside with imaging and endograft improvements are expected to further improve patient outcomes in the future. For the time being, the need for evidence in type-B dissection requires an effort from physicians to document cases, provide follow-up and participate in trials.

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Chapter 2

Commentary on "ADSORB: A Study on the Efficacy of Endovascular Grafting in Uncomplicated Acute Dissection of the Descending Aorta"

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Hence J. M. Verhagen

European Journal of Vascular and Endovascular Surgery 2012;44:37

To the Editor, Jean-Baptiste Ricco:

We would like to congratulate the ADSORB trialists with the initiative of the much awaited trial on management of acute type B aortic dissections. Many of us in the vascular community are looking forward to hearing the answers ADSORB set out to provide. The trial design printed in this Journal is well written, but it does raise a few methodological questions.

Firstly, the primary endpoint of this study comprises a composite of aortic rupture, aortic dilatation and/or observation of blood flow in the false lumen. However, aortic dilatation and complete false lumen thrombosis (surrogates of aortic remodelling) correspond to outcomes on imaging studies, but their true clinical significance is not completely understood.[1,2] Consequently, this study may fail to answer the question of added clinical benefit from stent grafting acute uncomplicated dissections.

Also, bias may be introduced by the endpoint definitions. For instance, complete false lumen thrombosis, is defined as total thrombosis of the descending thoracic false lumen for the medical therapy arm. In the stent group, however, complete thrombosis is defined as thrombosis of only the segment parallel to the stent graft, excluding the last 2 cm, meaning the remainder of the false lumen may be patent. Since the lamella is slim and mobile in the (sub)acute stages, implantation of a correctly sized endograft would expectantly compress the majority of the false lumen, as confirmed by INSTEAD.[3] It is doubtful that medical therapy alone will result in false lumen collapse. Since this is the "driving force" behind the primary endpoint, it may seem that the trial is designed to favour stengrafting.

Finally, a reflection is required regarding the dramatic change in sample size, based on data from false lumen thrombosis (which was published long after the initial ADSORB-trial design). Is a trial still required to show such a large difference in the rates of false lumen thrombosis in medical vs. stent graft groups (target effect size = 0.58)? In other words, is there still equipoise to justify a randomized trial? Naturally, if more "conventional" endpoints had been chosen (such as long-term freedom from rupture, dissection-related complications, re-intervention or death) much larger numbers would be required, but more definitive and clinically relevant data would be obtained.

The vascular community is eagerly looking for final answers on how to manage uncomplicated type B dissections, but it is still unclear if ADSORB will deliver these.

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Chapter 3

Late neurological recovery of paraplegia after endovascular repair of an infected thoracic aortic aneurysm

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Frederico Bastos Gonçalves
Peter J. Koudstaal
Hence J. M. Verhagen

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ABSTRACT

Spinal cord ischemia is a potentially devastating complication after thoracic endovascular aorta repair (TEVAR). Patients with spinal cord ischemia after TEVAR often develop paraplegia, which is considered irreversible, and have significant increased postoperative morbidity and mortality. We report the case of a patient with unusual late complete neurologic recovery of acute-onset paraplegia after TEVAR for an infected thoracic aortic aneurysm.

INTRODUCTION

Spinal cord ischemia (SCI) is a widely feared complication after thoracic and thoracoabdominal aneurysm repair. Due to advances in operative technique and the application of various neuroprotective adjuncts, the average incidence of SCI has declined from 16% down to 5% to 10% for open surgical repair[1,2,3] and to 3.9% for thoracic endovascular aorta repair (TEVAR).[4] However, patients with SCI show considerable mortality and morbidity and a significant decrease in quality of life. We report the case of a patient who underwent urgent TEVAR complicated by complete paraplegia due to SCI but who made a remarkable, nearly complete recovery between 1 and 12 months after the event. To the best of our knowledge, recovery from SCI after such a long interval has never been reported.

CASE REPORT

A 67-year-old man with a history of osteoarthritis was admitted to a rural hospital with persistent abdominal pain, weight loss, and constipation. The patient subsequently developed back pain, fever, and hypertension. Blood cultures grew Streptococcus pneumonia. Antibiotics and antihypertensive drugs were administered. Computed tomographic (CT) angiography performed 3 days after admission showed a 6.5-cm aneurysm of the mid-descending thoracic aorta with a sickle-shaped bulge containing rupture and periaortic fat infiltration and a 4.5-cm aneurysm of the abdominal aorta without signs of rupture (Figure 1). The patient was immediately transferred to our unit while he remained hemodynamically stable.

Urgent TEVAR was performed with the patient under general anesthesia. Two Valiant stents (Medtronic, Minneapolis, Minn) were deployed just proximal to the celiac trunk, covering 19 cm of the thoracic aorta, including two large intercostal arteries at the T11-T12 level (Figure 2) and guaranteeing proximal and distal sealing in relatively healthy aorta. Completion angiogram showed successful exclusion of the rupture. In the perioperative period, blood pressure remained between 150 and 90 mm Hg. The procedure was uneventful. The patient was extubated immediately after the procedure but woke up paraplegic. Prompt formal neurologic examination by two independent and experienced neurologists found complete paralysis of the legs, total loss of pinprick and vibratory sensation caudal from the T9 level, and laxity of the anal sphincter. A clinical diagnosis of SCI was made, and a spinal catheter for cerebrospinal fluid (CSF) drainage was immediately inserted, maintaining a pressure <10 cm H2O with no restriction on CSF volume drained. Mean blood pressure was continuously maintained above 95 mm Hg. These efforts did not result in improvement of neurologic function, and the CSF

catheter was removed 4 days postoperatively. The patient was discharged for rehabilitation 3 weeks after TEVAR with unchanged total paraplegia and sensory loss due to spinal ischemia at the T8-T10 level. Chronic antibiotic therapy included rifampicin for 6 weeks and lifelong levofloxacin.

Surprisingly, the patient's neurologic condition suddenly improved 1 month after TEVAR and continued to improve despite magnetic resonance imaging clearly showing atrophy of the spinal cord at the T6-T9 level (Figure 3). Function recovered with proximal muscle strength and simultaneous sensory improvement first, followed by distal improvement. At 5 months, he was able to stand and walk under guidance. CT angiography after 6 months revealed a completely vanished aneurysm sac without signs of infection, correct position of the stents, and stable abdominal aneurysm. The patient was discharged home 9 months after TEVAR. One year after treatment, neurologic investigations demonstrated almost complete recovery of motor and sensory function of the lower extremities. The patient was able to walk several blocks with the use of a walking frame. At follow-up 36 months after TEVAR, the patient was fine without signs of recurrent aortic infection. No change in spinal cord collateralization was perceivable in late-phase CT angiography compared with the first postoperative examination.

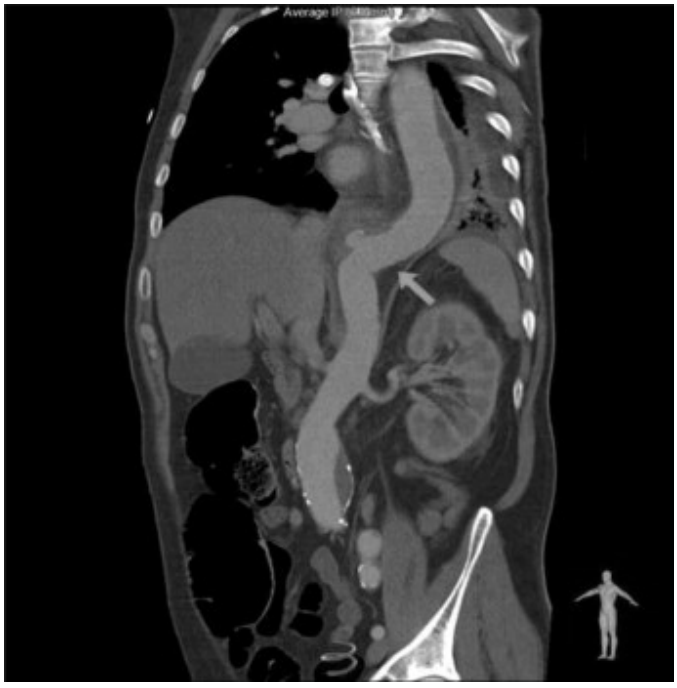

Figure 1. Preoperative computed tomographic (CT) angiogram showing a 6.5-cm aneurysm of the descending thoracic aorta with a sickle-shaped bulge containing rupture (arrow) and a 4.5-cm abdominal aortic aneurysm.

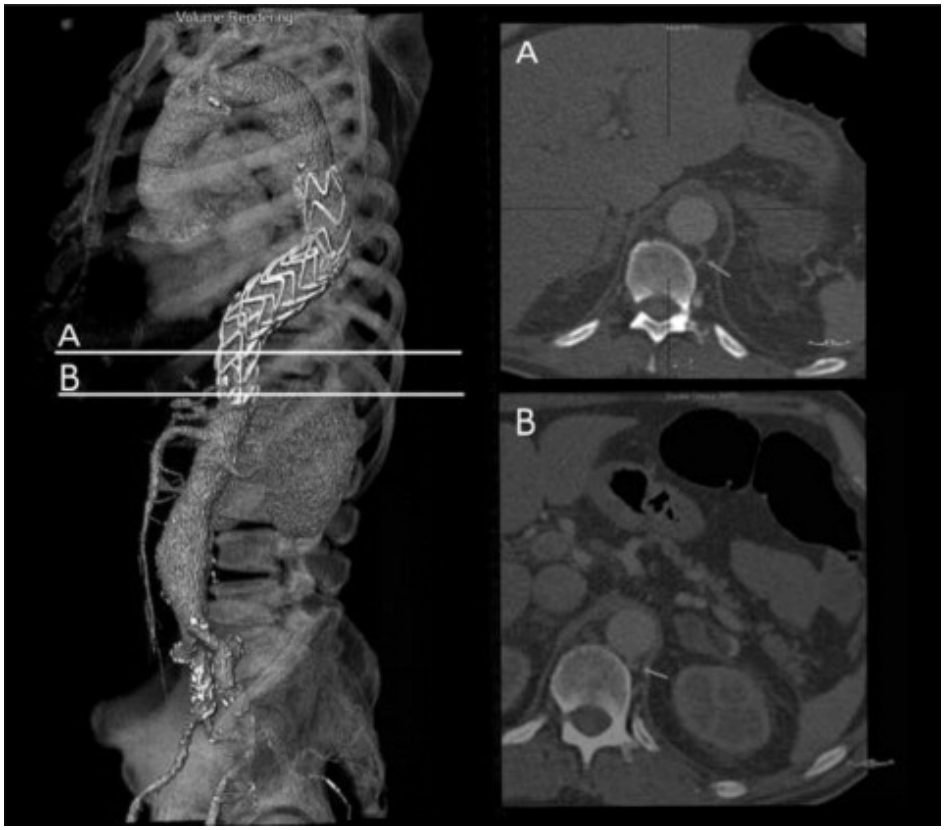

Figure 2. Preoperative and postoperative computed tomographic (CT) angiograms showing the position of significant intercostal arteries at the T11-T12 level (arrows) covered by the stent graft. Five of seven pairs (on preoperative CT angiography) of intercostal arteries in the descending aorta were covered, including the large pair shown, which is the largest and located in the classic position of the artery of Adamkiewicz. One pair of lumbar arteries at the visceral aortic segment and four pairs at the infrarenal aorta were not covered and remained patent. The left subclavian and vertebral artery, the inferior mesenteric artery, and both hypogastric arteries with numerous collaterals all were patent.

DISCUSSION

Crawford has classified the severity of SCI deficit (SCID) as paraplegia (patient has minimal function) or paraparesis (patient has motion against resistance or gravity across all joints).[1,3] Recently, another SCID score was developed based on the American Spinal Injury Association (ASIA) impairment classification. SCID I category represents flaccid paralysis (ASIA A), SCID II <50% muscle function (ASIA B and C), and SCID III >50% function. Although patients in categories SCID II and III had the same survival as patients without SCI, patients in category SCID I had perioperative mortality of 46% and 5-year survival of 0%.[5]

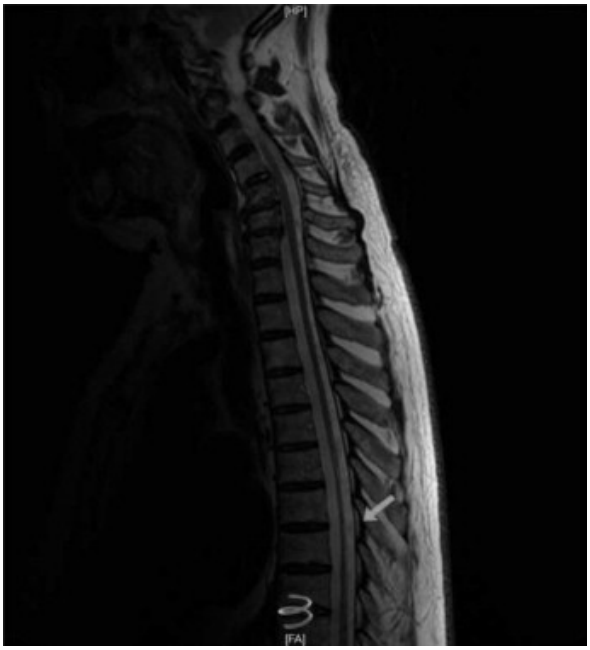

Figure 3. Magnetic resonance imaging of the spinal cord showing spinal cord atrophy with significant narrowing at the T9 level (arrow).

Risk factors for development of SCI after TEVAR include coverage of the left subclavian or hypogastric artery, embolization during intervention, renal failure, perioperative hypotension, prior abdominal aortic aneurysm repair, and greater proportion of aorta coverage (>20 cm).[6,7] In case of development of paraplegia (SCID I), several of these risk factors most likely simultaneously play a role.

Spinal cord injury can be categorized as acute (immediate or upon wakening) or delayed (occurring after a period of normal neurologic function). The etiology of acute-onset SCI probably is hypoxic injury after hypoperfusion of the spinal cord, whereas delayed-onset SCI is thought to be mainly due to either reperfusion injury after hypoperfusion of the spinal cord or edema formation.[8] In our patient, a combination of hypoxic injury due to coverage of important intercostal arteries and possibly an exaggerated inflammatory insult primed by a pre-existing septic condition is the most likely explanation for the acute SCI.

Several approaches to reducing the incidence of SCI after TEVAR, such as prophylactic lumbar CSF drainage, augmentation of blood pressure, and somatosensory-evoked potential monitoring, have demonstrated reduction in development of SCI.[9,10,11,12] Certain clinical situations may prevent placement of a prophylactic spinal drain, as in patients with symptomatic or ruptured thoracic aortic pathology or with prior lumbar spine surgery. The safety and feasibility of a selective postoperative CSF drainage protocol

have been described.[13] Future approaches to minimizing SCI after TEVAR may include the design of a novel stent graft with fenestration for one or more intercostal arteries.[14] Previous studies have reported reversal of paraplegia after a wide variety of interventions, such as prompt CSF drainage, blood pressure augmentation, or urgent surgical revascularization.[15,16,17] Recently, a case of total reversal of acute-onset paraplegia occurring after open thoracic aorta surgery and apparently failed CSF drainage was reported.[18] However, in that case, neurologic symptoms were ameliorated after several attempts to drain CSF and lasted only a couple of hours.

In our patient, the emergent nature of the intervention, the relatively small covered portion of the aorta, the patency of the subclavian and hypogastric arteries and of several lumbar artery pairs, and the positive blood cultures led us to consider spinal drainage only if and when SCI symptoms were observed. Therefore, the patient was promptly treated with CSF drainage and blood pressure increase immediately after SCI became evident. However, despite this treatment, no improvement was noted, and the patient was discharged 3 weeks postoperatively with a spinal ischemia deficit of category SCID I. An explanation for the patient's unusual late recovery could be improvement in spinal perfusion by the development or recruitment of collateral arteries from intercostal, lumbar, or hypogastric branches, but this was not demonstrated by consecutive CT angiography. Possible neurologic explanations include brain reorganization, such as increased activation in secondary motor brain areas and spatial shift in activation, neural plasticity, or progenitor cell-induced spinal cord regeneration, all possibly stimulated by intense rehabilitation protocols.[19,20] Future neuroimaging studies might be able to provide more insight into possible reorganization of brain networks and spinal cord regeneration.

This case illustrates that even after unsuccessful (CSF drainage) treatment of SCI following TEVAR, late recovery of paraplegia seems to be possible by intense rehabilitation.

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Chapter 4

Commentary on "Insights on the prevention of endograft collapse after thoracic endovascular aortic repair"

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Collapse of thoracic endoprosthesis is a devastating, yet rare complication of thoracic endovascular aortic repair. With growing experience and longer follow-up, the risk factors, preventive measures, and treatment of collapse are becoming clearer. In this issue of JEVT, Jonker et al.[1] provide an elegant review of all reported cases of thoracic stent-graft collapse, their suspected causes, and outcomes. In short, their messages are:

- Collapse is most frequent in blunt aortic injuries and dissections (i.e., outside the instructions for use of most devices), where endografts must follow the curvature of the aortic arch in order to achieve proximal seal. These are typically patients with small aortic diameters, very pulsatile aortas, steep aortic arches, high displacement forces as a result of high peak systolic velocities, and proximal/distal diameter mismatch.
- Collapse occurs most frequently within the first month, so close observation is mandatory. More than half the patients are asymptomatic at diagnosis, providing a window of opportunity for successful treatment if adequately identified.

Two important limitations must, however, be considered. Firstly, the rarity of this complication is clear from the small number of reported cases, yet underreporting is likely, and no real conclusions can be drawn regarding its true incidence. The definition of collapse itself is not uniform, and not all authors state theirs, adding to the confusion in data. Also, oversizing was considered the most important overall cause of collapse; however, this is difficult to confirm.

Secondly, distensibility of the thoracic aorta (particularly in young, healthy patients) may vary considerably during the cardiac cycle,[2,3] and measurement methods were uneven and usually not performed using appropriate three-dimensional reconstruction techniques. Furthermore, as many patients suffered from acute pathology, the true diameter of the thoracic aorta may have been unknown at the moment of implantation due to hypovolemic (shock) contraction of the aorta at the time of computed tomography (CT).[4] We feel that when precise electrocardiographically-gated measurements are unavailable, intraoperative confirmation of the aortic diameter should be performed using calibrated catheters, as adequate sizing is of utmost importance.

The identification a bird-beak configuration on the final angiogram is a known warning sign of potential trouble.[5] This may be corrected with balloon modeling (preferably using a nonocclusive balloon, e.g., trilobar, to avoid inadvertent displacement of the graft). While a bird-beak configuration is present in nearly all grafts that collapse, it is frequently a benign finding, so further prophylactic treatment is probably not advised in most cases. Close observation is prudent, however.

As reported in other articles,[6,7] the Gore TAG endoprosthesis has been associated with collapse. The manufacturer has acknowledged this sequela and recently reported 135 cases of device compression (out of ~20,000 treated patients worldwide); most have been resolved successfully with secondary interventions. In their own registry, Gore

reported 10 fatalities due to endograft collapse.[8] Market shares are uncertain, but it is fair to say that the Gore TAG endoprosthesis has been used more frequently than other models (especially in the US), so it is therefore logical that complications with this device are reported more often. For that reason, we cannot conclude that the TAG is more likely to collapse than its competitors. Collapse of the Zenith TX2 has also been reported, while the Medtronic Valiant and Bolton Relay (which generally have been used less often for non-aneurysmal disease) have rarely been associated with this complication.

The industry has already recognized the need for technological improvements specifically directed at non-aneurysmal disease if endovascular treatment is to be extended to these pathologies. All manufacturers have progressed toward devices that are more resistant to infolding and collapse and demonstrate greater arch conformability and more accurate deployment systems. The new conformable TAG (C-TAG) is especially designed to adapt to curvatures without tension, avoiding the use of bare stents or active fixation. The Valiant Captivia uses a tip-capture system of the bare stents for very accurate proximal placement, preventing the migration associated with the windsock effect during deployment. Similarly, the Zenith TX2 Pro-Form and the Bolton Relay NBS also have new delivery systems in which the proximal end is the last to be deployed, using effective and precise tip-capture mechanisms without proximal bare stents. Moreover, most grafts are now offering shorter devices, smaller diameters, and tapered designs to better adapt to the needs of traumatic injuries and dissections. These adaptations represent a significant step forward in the short term, but they still need to prove their longevity.

Close follow-up of patients at higher risk of collapse is mandatory. Our protocol for traumatic aortic injuries includes a CT angiogram (CTA) within the first 4 weeks after treatment and quadriplanar thoracic radiography every 3 months to confirm device expansion and integrity. When all is well, the CTA is repeated at 1 year and at 5-year intervals thereafter; radiography is done every 12 months. In young patients, magnetic resonance angiography can be used as an alternative, but image quality is usually poor due to the significant artefacts caused by the stent material.

When reintervention is being considered, sufficient evidence supports the perception that balloon dilation alone is insufficient and leads to potentially fatal recurrence. A second endograft or open repair are generally the best options and should not be delayed, as consequences may be dramatic.

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PART II

CLARIFYING RISK FACTORS FOR EVAR

Chapter 5

Risk factors for proximal neck complications after endovascular aneurysm repair using the Endurant Stentgraft

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ABSTRACT

Objective

To assess the incidence and risk factors for proximal aneurysm neck related complications with a late generation device for endovascular abdominal aneurysm repair (EVAR).

Methods

Data were retrieved from a prospective registry (Endurant Stent Graft Natural Selection Global Postmarket Registry) involving 79 institutions worldwide. The risk factors tested were age, gender, surgical risk profile, proximal neck length (<10 mm), diameter (>30 mm), supra- and infrarenal angulation (>60° and 75°), mural thrombus/calcification (>50%) and taper (>10%), and AAA diameter (>65 mm). Two neck related composite endpoints were used, for intra-operative (type-1a endoleak, conversion, deployment/retrieval complication or unintentional renal coverage) and post-operative (type-1a endoleak or migration) adverse events. Independent risk factors were identified using multivariable backwards modeling.

Results

The study included 1263 patients (mean age 73, 10.3% female) from March 2009 to May 2011. Twenty-three (1.8%) intra-operative adverse events occurred. Neck length <10 mm (OR 4.9, 95% CI 1.1–22.6) and neck thrombus/calcification >50% (OR 4.8, 95% CI 1.7–13.5) were risk factors for intra-operative events. The planned 1 year follow up visit was reached for the entire cohort, and the 2 year visit for 431 patients. During this time, 99 (7.8%) events occurred. Female gender (HR 1.9, 95% CI 1.1–3.2), aneurysm diameter >65 mm (HR 2.8, 95% CI 1.9–4.2), and neck length <10 mm (HR 2.8, 95% CI 1.1–6.9) were significant post-operative risk factors. Neck angulation, neck taper, large diameter neck, and presence of thrombus/calcification were not predictors of adverse outcome in this study.

Conclusion

These results support the adequacy of this device in the face of adverse neck anatomy, and confirm neck length as the most relevant anatomical limitation for EVAR. Additionally, the study confirms the decline in early to mid-term intervention rates with a newer generation device in a large patient sample. Lastly, it suggests that neck related risk factors affect outcome and impact on prognosis in varying degrees.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is an accepted treatment modality for infrarenal abdominal aortic aneurysms (AAA). Technical and technological innovations have been progressively introduced over the last two decades, generally leading to improved early and late outcomes. Careful evaluation of newly introduced devices for EVAR is essential to guarantee patient safety and provide evidence for the gradually expanding indications.

The most limiting factor for EVAR is adverse proximal neck anatomy.[1] Extensive research has shown that characteristics of the proximal neck, such as length, diameter, angulation, taper, and irregularity affect outcome significantly.[1,2,3,4,5,6] Manufacturers have focused much attention on proximal neck limitations in their Instructions For Use (IFU), which are the most common reason for ruling out EVAR.

The Endurant Stent Graft System (Medtronic, Santa Rosa, CA, USA) has been specifically designed to cope with unfavorable anatomic characteristics, therefore potentially expanding the treatment range for EVAR. Specifically, the proximal geometry of the main body stents allow for extra flexibility and conformability, while maintaining adequate radial force. Also, the suprarenal active fixation and precise tip capture deployment mechanism are designed for more precise and controlled deployment and durable fixation. The manufacturers' expectations on the performance of this device are reflected in the IFU, which are among the most liberal. Even so, physicians often exceed these recommendations, with the expectation of reduced complications during follow up.

Very favorable outcomes have been reported in small series of patients with adverse neck features. However, these studies are generally retrospective and based on single institution experiences, and therefore subject to publication bias. The objective of this study is to assess the importance of different adverse anatomical characteristics of the proximal attachment site when using a late generation device. To do so, a large prospective, multicenter cohort of patients from the Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) was studied.

METHODS

Eligibility

Patients with AAAs considered suitable for elective endovascular repair were eligible for inclusion in this registry. Although adherence to IFU was advised, enrollment of patients outside IFU was permitted. Enrolment was conducted on an intention to treat basis, and a minimum of five consecutive patients per center was advised. Unfortunately, no information is available on the number of patients offered EVAR with other devices,

open repair, or no treatment for each participating center, and therefore the extent of selection bias is impossible to determine. However, all patients included in the registry were also included in this study. All patients were asked for signed informed consent. The study was conducted according to the Helsinki declaration on research ethics and registered under the ClinicalTrials.gov Identifier> NCT00890051.

Data collection and definitions

Individual patient data were entered prospectively by participating hospitals and stored electronically locally. The pre-operative data collected included demographics, medical comorbidities (smoking, hypertension, hyperlipidemia, diabetes, cardiac disease, pulmonary disease, renal insufficiency, cerebrovascular disease, and peripheral arterial disease), and anatomical characteristics (proximal neck diameter, length, angle, presence of mural neck thrombus/calcification, neck taper, and AAA maximum diameter). Intra-operative details included technical success, presence of type Ia or undetermined endoleak, additional devices used, and procedures performed during the implant procedure. Follow up visits were scheduled at 30 days, 1, and 2 years, with mandatory imaging studies. At follow up visits, any protocol defined adverse event was registered and imaging studies were assessed for the presence of complications and AAA maximum diameter changes. Any secondary procedures were also registered. External auditors closely monitored all clinical data in this registry.

For this study, candidate adverse neck characteristics were selected on the basis of previous literature and accounting for the recommended anatomical limits for this particular device. Specifically, the chosen cutoffs for adverse neck were length <10 mm, presence of thrombus/calcification >50%, and neck angulation greater than 60° (suprarenal) or 75° (infra-renal). In addition, the presence of neck taper >15% and large diameter aortic necks (requiring 32 or 36 mm proximal diameter stentgrafts) were considered as potential risk candidates based on previous literature. Surgical risk was calculated according to the modified Lee score and ASA classification. Migration was defined as downward displacement of the endograft by at least 10mm. Sac growth was defined as an increase in maximum aneurysm diameter of at least 5 mm, as recommended in the SVS reporting standards.[7]

Study endpoints

For this study, two composite endpoints were chosen: for intra-operative neck related adverse events, the endpoint was composed of intra-operative (or undetermined) type Ia endoleak, unintentional renal artery coverage, presence of deployment or retrieval complication or need for conversion to open repair. For post-operative neck related adverse events, the endpoint was composed of any postoperative type Ia (or undetermined) endoleak, proximal device migration, need for proximal neck secondary intervention

or post-implantation rupture. The individual components of each endpoint were also studied to assess their specific contribution to the endpoint.

Statistical methods

Categorical variables were presented as count and percentage and compared with Pearson's chi-square tests. Continuous variables were presented as mean and standard deviation (SD) and compared using Student *t* tests if normally distributed, or presented as median and interquartile range (IQR) and compared with Mann–Whitney U tests if the distribution was skewed. Each variable of interest (age, gender, baseline AAA diameter, ASA classification, proximal neck diameter, proximal neck length, proximal neck thrombus or calcification, proximal neck taper, supra- and infra-renal angle) was tested separately as a risk factor for intra-operative and post-operative neck related adverse events, and independent significance was tested for variables with $p < .1$ using multivariate logistic regression and proportional hazard regression, respectively. Based on the hazard ratios obtained for significant risk factors for post-operative neck related adverse events, a risk model was generated and tested using the area under the curve of the resulting receiver operating characteristic curve (ROC). A cut-off was determined based on the optimal sensitivity and specificity of the test (maximum sum value method), and patients scoring greater than the cut-off were considered high risk. Kaplan–Meier survival estimates were calculated for freedom from neck related adverse events and compared using the Log Rank (Mantel-Cox) test of equality. Differences were considered significant if $p < .05$. Statistical analysis was performed by an independent statistical office (Secic Statistical Consulting, Inc), using IBM SPSS Statistics 20 (IBM Inc., Chicago, IL, USA).

Table 1. Baseline characteristics.

	N = 1263
Variable	*N* (%)
Age ≥80	290 (23.0)
Female gender	133 (10.5)
ASA III/IV	658 (52.1)[a]
Proximal graft diameter 32 or 36	398 (31.5)
Neck length <10 mm	27 (2.2)[a]
Neck thrombus/calcification (>50%)	74 (6.0)[b]
Neck taper ≥15%	218 (17.5)[b]
Maximum AAA diameter ≥65	317 (25.4)[b]
Suprarenal angle >60°	44 (3.6)[b]
Infrarenal angle >75°	62 (5.1)[b]

Legend: a) Missing values ≤1%. b) Missing values >1% and ≤3%.

RESULTS

From March 2009 to May 2011, 1263 patients were included in the ENGAGE registry and were included in the present study. All patients had an expected minimum follow up of 1 year and a maximum of 3 years. At the time of this study, all surviving patients had reached the 1 year mark and 431 (38%) had reached the 2 year mark. Baseline characteristics are detailed in Table 1.

Intra-operative neck related adverse events

Twenty three patients (1.9%) suffered from intra-operative neck related adverse events. The majority were type Ia endoleaks (*N* = 12, 1.0%), of which seven were corrected intra-operatively. For the remaining five patients, three resolved spontaneously at the 1 month CTA, and no further adverse events were reported through 24 months. One patient was treated successfully with a proximal extension after 5 days and died after 1.5 years because of lung cancer. The last patient died 5 days after the procedure because of bowel ischemia and myocardial infarction. None of the intra-operative conversions were caused by type Ia endoleaks. Of the five renal coverage cases, one was subjected to hepato-renal bypass and died after 22 days because of multiorgan failure, one was successfully converted to open repair, one was treated with renal artery stenting, and the remaining two were treated conservatively without significant worsening of renal function. Only one of the delivery/retrieval complications was possibly caused by complex proximal anatomy. In this case, inability to withdraw the delivery system was reported and the patient underwent successful open conversion. The contribution of individual adverse events to the composite endpoint is described in Table 2.

Only neck length <10 mm (OR 4.9, 95% CI 1.1–22.6) and presence of neck thrombus/calcification (OR 4.8, 95% CI 1.7–3.5) were independent risk factors for intra-operative neck related adverse events (Table 3).

Table 2. Intra-operative neck related adverse events.

	N = 1263
Intra-operative neck related adverse events	*N* (%)
Endoleak type 1a	12 (1.0)
Corrected by remodeling the stent graft	3/12 (25)
Corrected with extension cuffs (prox or dist)	3/12 (25)
Corrected (others)	1/12 (8)
Conversion to open repair	4 (0.3)
Unintentional renal artery coverage (partial/total)	5 (0.4)
Deployment/retrieval complication	7 (0.6)
Total (patients)	23 (1.8)

Table 3. Uni- and multivariate model for intra-operative adverse events.

Characteristic	Event total = 23 N (%)	Univariate *p* value	Multivariate OR (95% CI)
Age ≥80	7/290 (2.4)	0.39	–
Female gender	4/133 (3.0)	0.29	–
ASA III/IV	14/658 (2.1)	0.40	–
Proximal graft diameter 32 or 36	8/398 (2.0)	0.73	–
Neck length <10 mm	2/27 (7.4)	0.047	4.9 (1.1–22.6)
Neck thrombus/calcification (>50%)	5/74 (6.8)	0.003	4.8 (1.7–13.5)
Neck taper ≥15%	2/218 (0.9)	0.28	–
Maximum AAA diameter ≥65	9/317 (2.8)	0.13	–
Suprarenal angle >60°	2/44 (4.5)	0.18	–
Infrarenal angle >75°	2/62 (3.2)	0.39	–

Intra-operative neck related adverse events occurred in two (7.4%) patients with neck length <10 mm, and in five (6.8%) patients with neck thrombus or calcification in >50% of the neck circumference.

Post-operative neck related adverse events

After the index operation, 18 patients suffered neck related adverse events. Of these, one was also included in the intra-operative adverse events and the remaining 17 were additional events. There were no endograft migrations, and all events corresponded to type Ia endoleaks. All these endoleaks were imaging findings resulting from post-operative surveillance, with no associated symptoms (Table 4). Treatment was not offered to six patients for the following reasons: metastatic cancer with very short life expectancy ($N = 2$), decision for surveillance with spontaneous resolution without intervention ($N = 2$), one because of decision of the patient, and another because of a decision of the physician (unfit for open conversion and no endovascular solution available).

Table 4. Post-operative neck related adverse events.

	N = 1263
Post-operative neck related adverse events	*N* (%)
Endoleak type 1a	18 (1.4)
Corrected by remodeling the stent graft	2/18 (11)
Corrected with extension cuffs (prox or dist)	6/18 (33)
Corrected (others)	4/18 (22)
Proximal device migration (>10 mm)	0 (0)
Total (patients)	18 (1.4)

Table 5. – Risk factors for post-operative neck related adverse events.

	Event total = 18		
Characteristic	*N* (%)	Univariate *p* value	Multivariate HR (95% CI)
Age ≥80	6/290 (2.1)	0.26	–
Female gender	6/133 (4.5)	0.003	5.6 (2.0–15.3)
ASA III/IV	12/658 (1.8)	0.20	–
Proximal graft diameter 32 or 36	4/398 (1.0)	0.40	–
Neck length <10 mm	3/27 (11.1)	0.040	8.9 (2.5–31.2)
Neck thrombus/calcification >50%	0/74 (0)	–	
Neck Taper ≥15%	4/218 (1.8)	0.99	–
Maximum AAA diameter ≥65	11/317 (3.5)	0.61	6.4 (2.3–17.7)
Suprarenal angle >60°	3/44 (6.8)	0.003	–
Infrarenal angle >75°	3/62 (4.8)	0.010	–

Female gender (HR 5.6, 95% CI 2.0–15.3), neck length <10 mm (HR 8.9, 2.5–31.2), and AAA maximum diameter ≥65 mm (HR 6.4, 95% CI 2.3–17.7) were identified as independent risk factors for post-operative neck related adverse events (Table 5). For patients with <10 mm proximal neck, the crude complication rate was 11.1% (3/27 patients). For patients with large AAAs it was 3.5% (11/317), and for female patients it was 4.5% (6/133).

A risk model was created, based on the proportional HR obtained from the multivariate analysis. This model was highly predictive of post-operative neck related adverse events, with an AUC of 0.80 (Figure 1), and a cutoff point of 6 was obtained. Based on this, patients were categorized into high or low risk groups for post-operative adverse neck events. This resulted in 335 patients, having a neck length <10 mm or AAA maximum diameter >65 mm. Nine patients (2.7%) had both AAA diameter >65 mm and neck length

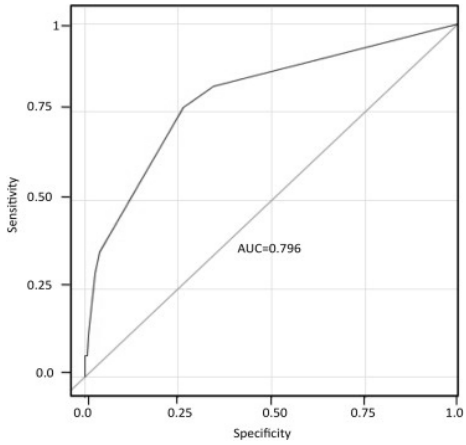
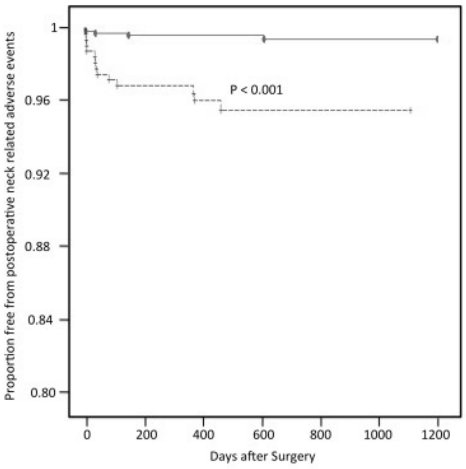


Figure 1. Receiver operating characteristic curve for the post-operative risk model.



Final Risk	Days after EVAR	KM Event Free (%)	Standard Error	N
Low	0	100	0	908
Low	2	100	0,0011	907
Low	35	100	0,00157	894
Low	148	100	0,00194	867
Low	608	99	0,00285	476
Low	1199	99	-	0
High	0	100	0	335
High	2	100	0,00299	333
High	4	99	0,00423	331
High	5	99	0,00518	329
High	6	99	0,00597	328
High	32	98	0,0067	321
High	34	98	0,00735	320
High	38	98	0,00795	317
High	42	98	0,0085	315
High	80	97	0,00904	309
High	110	97	0,00956	303
High	369	97	0,0103	252
High	373	96	0,011	243
High	461	96	0,0121	183
High	1106	96	-	0

Figure 2. Estimated event free survival for patients at low and high risk for post-operative neck related complications.

<10 mm. At 2 years, the event free survival expectancy was 99% for low risk patients and 96% for high-risk patients ($p < .001$, Figure 2).

DISCUSSION

The proximal attachment site is a major contributor for adverse outcome after EVAR, and is generally considered the primary reason for EVAR turndown.[8] The main finding of this study is that risk factors for intra- and post-operative neck related complications differ in type and relative importance. Neck length was the most relevant predictor, increasing the risk of intra-operative complications fivefold and the risk of mid-term complications nine-fold, and angulation, neck taper or diameter and presence of significant thrombus/

calcification had no important contribution for neck related adverse events at mid-term. Additionally, this study suggests that the overall risk of neck related complications is reduced compared with historical series, implying an improvement in safety and efficacy for EVAR.

The association between anatomical characteristics and increase in risk has been well characterized in several retrospective studies and registries and recently compiled into two systematic reviews.[9,10] In the meta-analysis by Antoniou et al,[9] patients treated outside neck IFU were compared with those treated according to different manufacturer's recommendations. These authors found that hostile neck patients had a threefold increase in the need for intra-operative adjuncts to achieve proximal seal and a fourfold increase in the risk of developing type I endoleaks within the first year. Stather et al.[10] used different classification criteria, defining hostile neck anatomy as any of the following: neck length <15 mm, neck diameter >28 mm, and angulation >60°. They found a near twofold increase in both the risk of intra-operative complications and of type I endoleaks over time. Although these studies did not attempt to evaluate the independent contribution of each adverse neck characteristic, the proportional risk increase for patients with adverse necks was comparable with this study.

The determinant difference is, however, in the total number of complications. Although both meta-analyses identified the need for intra-operative adjunctive neck procedures in 3% to 5%, only 1.8% of 1263 patients included on an intention to treat basis in this registry suffered intra-operative neck related complications, and of these only 12 (0.9%) were type Ia endoleaks. More importantly, only 1.5% of patients suffered from subsequent neck related complications, whereas meta-data revealed a much higher proportion, ranging from 5% to 11%, in an equivalent time interval. In Engage patients, freedom from neck related adverse events at 2 years was 96% for patients at high risk for complications, and 99% for patients at low risk. Because of the prospective and multicentre nature of this registry, the chance of publication bias is smaller than in single centre observational studies, suggesting the reduction in incidence may be even greater. The results of this study corroborate that specific characteristics of this device make it a good choice for treatment of less favourable neck anatomy. It also confirms the results of smaller, single centre retrospective studies that could be the reflection of bias and/or irreproducible experience of centres of excellence.[11,12,13,14,15]

The independent contribution of each patient characteristic for neck related complications is a relevant finding. Although the ENGAGE protocol recommended against inclusion of patients treated outside IFU, these were allowed in the logic of consecutive enrolment. A total of 226 patients (18%) included were outside IFU, of which 112 (9%) were caused by adverse proximal neck anatomy. These inclusions made it possible to test the influence of each individual neck related risk factor in a multivariate model,

allowing grading of individual risk with a high degree of certainty, as reflected by the AUC of 0.8.

For intra-operative neck related adverse events, only neck thrombus/calcification >50% and neck length <10 mm were independent risk factors. These both increased risk approximately fivefold. The present findings are compatible with previous literature on risk factors for intra-operative complications, although thrombus could not be differentiated from calcification. Interestingly, angulation outside the IFU (supra-renal >60° and/or infra-renal >75°) was not a risk factor for intra-operative complications, which confirms a previous observation on the early results of this endograft in patients with extreme angulation of the proximal neck.[16]

At mid-term, the most important predictor for adverse outcome was neck length, with <10 mm necks having a nine-fold risk increase. It is important to note that 3/27 patients (11.1%) of patients with neck length <10 mm were identified as having a type Ia endoleak during follow up. As no migrations were observed, it can be concluded that neck length does not increase mid-term risk of migration with this device, but does increase the risk of developing type Ia endoleaks. This was expected, and parallels previous large studies on the adverse influence of neck length.[9] Given the cost and treatment delay involved, fenestrated or branched alternatives for patients with neck length <10 mm should outweigh the risk involved in treatment of these adverse neck patients with standard off the shelf infrarenal devices.[17,18,19] Also, fenestrated and branched technology cannot be universally applied, because of anatomical constraints. The chimney techniques for endovascular repair of short necks should be reserved, in the authors' view, for urgent or bailout cases, as the results are largely unknown. It is not the intention of this study to defend standard EVAR for patients with short proximal neck, but to present data on the expected outcome if this solution is considered the most adequate for an individual patient. Open surgical repair may still be the preferred strategy for low risk patients with adverse proximal anatomy.

Aside from neck length, also female gender and maximum AAA diameter were found to be risk factors at mid-term, increasing risk 5.6 and 6.4-fold, respectively. These differences cannot be explained by difficulties during implantation, as these risk factors are not predictors of technical failure. Aneurysm diameter is a well characterized risk factor,[20,21] probably because of the risk of graft displacement in the aneurysm sac over time. Information of the luminal volume (rather than diameter) or on endograft displacement over time in patients at risk could help clarify this issue. The gender effect is enigmatic, but may reflect a higher anatomical complexity, not identified by the variables used for this study. This is a topic requiring further clarification.

As a prospective registry, ENGAGE is limited by the voluntary nature of inclusion. Also, it is a single graft study and the results may not be applicable to other late generation devices. Despite these limitations, the ENGAGE registry provides multicentre, worldwide

data on a large sample of patients reducing greatly the risk of selection bias and type II statistical errors. Another relevant shortcoming is the relatively low number of patients with neck length <10 mm, which restricts the analysis for this most interesting subgroup. Although this risk factor emerged in multivariate models as highly predictive for both intra- and post-operative complications, the conclusions must be interpreted with care because of the overall low number of events. Another important limitation is that the cut-off for migration in the Registry was 10 mm as recommended in the Reporting Standards,[7] which may be excessive especially when considering patients with complex anatomy. For illustration purposes, patients were artificially divided into low and high risk for post-operative adverse events using a cut-off. However, it is not suggested that this classification should be used in clinical practice, instead the hazard ratio for each predictor is recommended as a more reliable method of estimating risk. Finally, it is acknowledged that individual features may have specific interactions that increase risk exponentially (such as short + angulated proximal anatomy), and this is not fully expressed in this or other publications regarding adverse proximal anatomy. Expert opinion for case selection is still a valuable asset for risk estimation in cases where multiple adverse features co-exist.

In conclusion, the results of this study support the adequacy of this device in the face of adverse neck anatomy, and confirm neck length as the most relevant anatomical limitation for EVAR. Additionally, it confirms the decline in early to mid-term intervention rates with a newer generation device in a large patient sample. Lastly, it suggests that neck related risk factors affect outcome and impact on prognosis with varying degrees.

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Chapter 6

Severe proximal aneurysm neck angulation: early results using the Endurant stentgraft system

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ABSTRACT

Objective

Angulation of the proximal aneurysm neck has been associated with adverse outcome after EVAR. We aim to investigate the influence of angulation on early results when using the Endurant Stentgraft System.

Methods

A retrospective analysis of a prospective multicentre database identified 45 elective patients treated with the Endurant stentgraft with severe angulation of the proximal neck, which were compared to a control group without significant angulation. Endpoints were early technical and clinical success, deployment accuracy and differences in operative details.

Results

Mean age was 74 with 86.4% males. Mean infrarenal angle (β) was 80.8°±16 and mean suprarenal angle (α) was 51.4°±21. Patients in the angulated group had larger aneurysms (mean 309 cc vs. 187 cc), shorter necks (mean 27 mm ± 14 vs. 32.6 mm ± 13) and 74% (vs. 56%) were ASA III/IV. Technical success was 100%, with one patient requiring an unplanned proximal extension. No differences were found regarding early type-I endoleaks (0% vs. 0%), major postoperative complications (6.7% vs. 6.2%; $p = 0.77$) or early survival (97.8% vs. 96.9%, $p = 0.79$). Distance from lowest renal artery to prosthesis was 2.4 mm ± 2.7 vs. 2.3 mm ± 4.8, $p = 0.9$. Operative details were equivalent for both groups.

Conclusions

Treatment with the Endurant stentgraft is technically feasible and safe, with satisfactory results in angulated and non-angulated anatomies alike. No sealing length was lost in extremely angulated cases, confirming the device's high conformability. Mid- and long-term data are awaited to verify durability, but early results are promising and challenge current opinion concerning neck angulation.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has become commonplace for abdominal aortic aneurysm (AAA) treatment across the world. Originally reported in 1991,[1,2] for long it was only considered a safe alternative to open repair in face of favourable anatomy. Over the years, many technical and technological advances have been introduced, with progressive improvement of results. Consequently, EVAR has emerged as an alternative to open surgery for anatomically less suitable patients.

Proximal neck anatomy is considered a major limiting factor when determining suitability for EVAR. In particular, implantation of endografts in patients with very angulated proximal neck anatomy resulted in considerable technical problems during the procedures and adverse short-term clinical outcomes.[5,6,7,8] The Endurant endograft (Medtronic AVE, Santa Rosa, CA, USA) is a late-generation device for AAA repair that has been specifically designed to conform to more challenging anatomy. Together with its easy-to-handle and precise delivery and deployment system, it may indeed be better suitable to treat high-risk AAA patients with challenging anatomy.

We hypothesise that severe proximal neck angulation has no influence on early post-EVAR results when using the Endurant Stentgraft System.

MATERIAL AND METHODS

We designed a case-control study to demonstrate the early efficacy and safety of EVAR in severely angulated proximal aneurysm necks, using the Endurant Stentgraft System. This was based on the review and analysis of a prospective database from three high-volume centres in the Netherlands (AZ-Nieuwegein, UMC-Utrecht and EMC-Rotterdam).

Patient selection

From May 2008 to December 2009, 418 AAA patients were treated in the three centres, of which 271 patients were elective implantations with the Endurant Stentgraft System. Selection of patients for endovascular repair, open repair or no treatment was individualised, taking into consideration anatomical features, health status, history of previous abdominal surgery (hostile abdomen) and patient preference (informed consent). In general, patients with severe angulation (>90°) and short (<10 mm) or wide (>32 mm) proximal necks were considered unsuitable for endovascular repair and offered either open repair or observation. However, in our experience, short proximal necks are rarely seen together with severe angulation. All subjects with angulated proximal anatomy selected for endovascular treatment were implanted consecutively with the same device.

Patients with infrarenal angle (β) > 75° and/or suprarenal angle (α) > 60° combined with neck length of ≥15 mm, or β > 60° and/or α > 45°, if neck length > 10 mm, were included. Based on these criteria, we treated 45 patients (16.5% of all elective operations using the Endurant device). These cut-offs correspond to the limits of proximal neck angulation allowed by the Instructions for Use (IFU) for this endograft. Twenty-three patients (51.1% of the angulated group) were included only due to β angulation, 14 (31.1%) were included due to both α and β angulation and 8 (17.8%) due to α angulation.

The control group was selected from the sample of elective infrarenal EVARs using the same device during the same time period. For homogeneity, patients with neck length <10 mm or neck width >32 mm were excluded. We also excluded patients with previous aortic surgery. This population was than matched for baseline characteristics, resulting in a non-angulated matched control group of 65 patients. Anatomic characteristics were not corrected for, to reveal possible differences between groups.

Image analysis and angulation measurements

All measurements (diameter, length and volume) were performed using a workstation with dedicated reconstruction software and centre lumen line (CLL) reconstruction (3Mensio Medical Imaging B.V., Bilthoven, the Netherlands). Measurements and data entry were performed at the time of surgery for every patient. Three trained physicians (AD, JK and FG), one from each centre, performed all the measurements using a standardised method that has been previously described and validated.[3] Briefly, analysis of the tridimensional image of the aorta is turned 360° in a perpendicular fashion to the middle of the CCL flexure (Figure 1). The sharpest angle is considered the true angle of the aortic axis. The angles between the suprarenal aorta and the aneurysm neck (α) and between the aneurysm neck and sac (β) were measured.

After CLL reconstruction, subsequent measurements were performed. The length of the proximal neck was defined as the distance between the origin of the lowermost renal artery and the start of the aneurysm. Volumes were acquired for both neck (first 10 mm) and total aneurysm (up to bifurcation). All patients performed a postoperative computed tomography angiography (CTA) within 30 days from the date of surgery, and measurements were again performed after CCL reconstruction.

Endpoints

The primary endpoint is combined early technical and clinical success. Technical success was defined as the ability to adequately deploy the endograft in the intended position and complete the endovascular procedure without complications. Clinical success was defined as the absence of any significant intra-operative, 30-day or in-hospital morbidity.

Secondary endpoints were the distance from the lowest renal artery to the first graft-covered segment of the stentgrafts (measured by CLL reconstruction images from

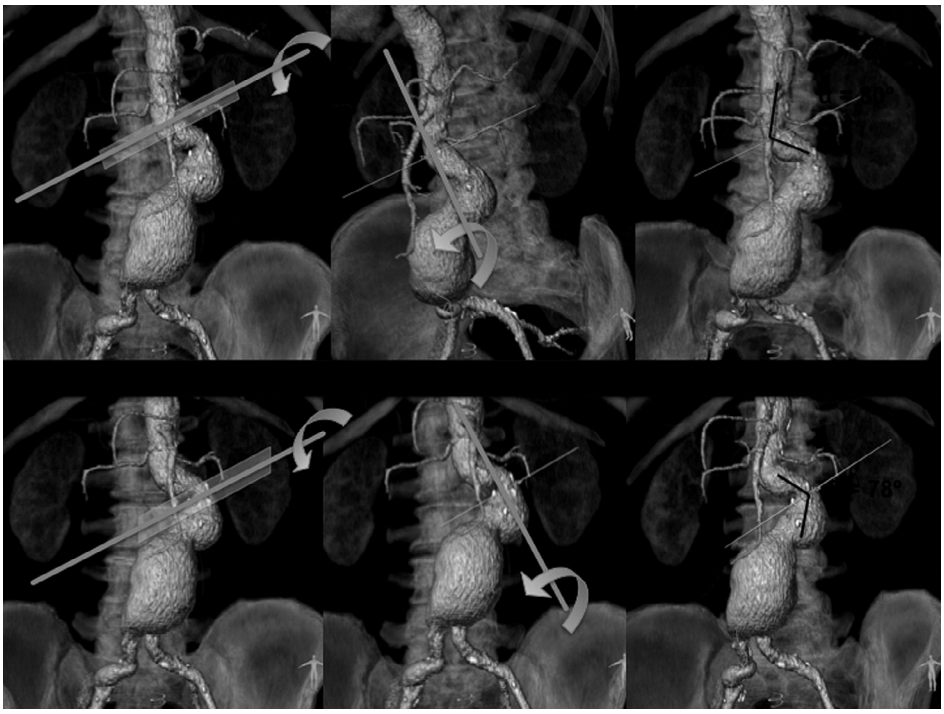

Figure 1. Measuring α (top) and β (bottom) angles using a centre lumen line.
Legend: First find the perpendicular plane to the corner of the angle. Than rotate 360° on the axis of the perpendicular plane and select the greater angle formed by the axial lines above and below the selected plane.

the first postoperative CTA) and operative details, namely duration of the procedure, contrast use and radiation exposure. Analysis of planning details, particularly the degree of oversizing, was undertaken to detect differences in planning between groups.

Statistical analysis and reporting standards

Means (± standard deviation, SD) were used to describe continuous variables. Absolute numbers and percentages were used for categorical factors. For continuous variables, differences between groups were analysed using Student's t-test and significance with the independent samples test. Categorical variables were compared using Pearson's chi-square test. The 95% confidence intervals were used and statistical significance considered if $p < 0.05$. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 17.0 (IBM, Chicago, IL, USA). Reporting was done according to the guidelines from the Society for Vascular Surgery/American Association for Vascular Surgery (SVS/AAVS) ad hoc Committee for Standardized Reporting Practices in Vascular Surgery.[4]

RESULTS

Clinical baseline characteristics are presented in Table 1. Mean age was 73.9 (SD:7.9) with 86.4% male predominance. Individually, there were no significant differences in co-morbidities between both population groups. However, patients within the angulated group were more often classified as American Society of Anaesthesiology (ASA) class III and IV when compared with controls. Applying the Glasgow aneurysm score, 67% of patients in the angulated group were considered high-risk for open repair (79 points or more).

Anatomical characteristics and distribution of angles are presented in Table 2 and Figure 2. In all patients with significant α and β angulation, the α deflection was opposite the β deflection, resulting in an 'S'- or 'Z'-shaped neck. Two patients had an additional infrarenal 'C' shape. In these two cases, only the most proximal infrarenal angle was considered and assumed as the β angle. The configuration of the infrarenal neck differed significantly between the angulated and non-angulated groups, as demonstrated in Figure 3. The first group had a more diverse sample of neck configurations, and was more likely to have a non-cylindrical (hence, less favourable) configuration (relative risk (RR): 1.77 95% confidence interval (CI) 1.01–3.09; P value = 0.031).

Both AAA volume and diameter were larger in the angulated group. In the angulated group, mean β angle was 80.8° (range 52–125, SD: 15.6) and mean α angle was 51.4° (range 8–98, SD: 21.1). This was significantly different from the non-angulated group, in which mean α angle was 35.4° and mean β angle was 17.9° ($p < 0.001$).

Table 1. Baseline characteristics.

Baseline characteristics	Angulated (*N* = 45)	Non-angulated (*N* = 65)	*P* value
Age, mean (SD) years	75.6 (6.5)	72.7 (8.5)	0.49
Male gender, no. (%)	36 (80.0)	59 (90.8)	0.11
Smoking, no. (%)	32 (71.1)	51 (78.5)	0.38
Hypertension, no. (%)	25 (55.6)	35 (53.8)	0.70
Cardiac disease, no. (%)	22 (48.9)	27 (41.5)	0.45
COPD, no. (%)	14 (31.1)	13 (20.0)	0.18
Diabetes, no. (%)	6 (13.3)	15 (23.1)	0.20
Renal disease, no. (%)	16 (35.6)	20 (30.8)	0.60
Cerebrovascular disease, no. (%)	4 (8.9)	12 (18.5)	0.16
PAOD, no.(%)	11 (24.4)	15 (23.1)	0.87
ASA class III/IV, no. (%)	33 (73.3)	43 (66.2)	–

Legend: SD – Standard Deviation; COPD – Chronic Obstructive Pulmonary Disease; PAOD – Peripheral Artery Obstructive Disease; ASA (American Society of Anaesthesiology).

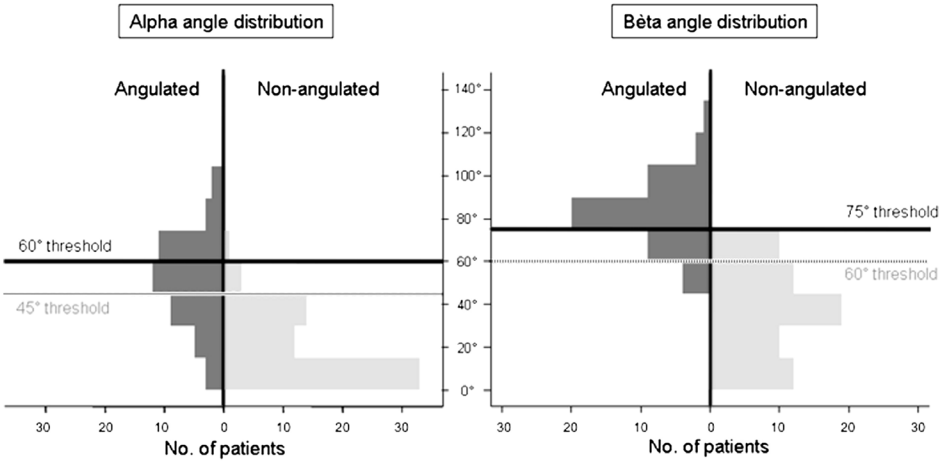

Figure 2. Neck angle distribution.
Legend: The threshold lines represent the inclusion criteria for the study – for the suprarenal (α) angle a 60° threshold was chosen (45° if neck length was 10–14 mm) and for the infrarenal (β) angle a 70° threshold (60° if neck length 10–14 mm). These thresholds correspond to the IFU for the Endurant device.

Technical outcomes and operative findings (Table 3)

The endovascular procedure was successfully completed in all patients. Planned intra-operative adjunctive procedures were performed in seven patients of the angulated group and eight patients of the non-angulated group. One patient in the angulated group required an unplanned intra-operative adjunctive procedure (see below). Further, one patient from the non-angulated group needed an unplanned postoperative adjunctive procedure – renal stent placement – due to partial coverage of a renal ostium. This was undetected intra-operatively but diagnosed within 24h due to *de novo* renal impairment and hypertension. The treatment was successful and resulted in complete recovery of renal function. All adjunctive procedures are reported in Table 3.

Table 2. Anatomic characteristics.

Anatomic characteristics	Angulated (*N* = 45)	Non-angulated (*N* = 65)	*P* value
AAA Ø, mean (SD) mm	68.6 (14.2)	58.8 (7.6)	<0.001
AAA volume, mean (SD) cc	309.5 (30.1)	187.4 (8.2)	<0.001
Proximal neck Ø, mean (SD) mm	25.2 (4.2)	25.5 (4.5)	0.71
Proximal neck length, mean (SD) mm	27.2 (14.8)	32.6 (13.1)	0.05
Neck thrombus >25% of circumference, no. (%)	8 (17.8)	10 (15.4)	–
Neck calcification >25% of circumference, no. (%)	3 (6.7)	1 (1.5)	–
α Angle, mean (SD) degrees	51.4 (21.1)	17.9 (17.0)	<0.001
β Angle, mean (SD) degrees	80.8 (15.6)	35.4 (20.0)	<0.001

Legend: Ø – diameter; α – suprarenal; β – infrarenal.

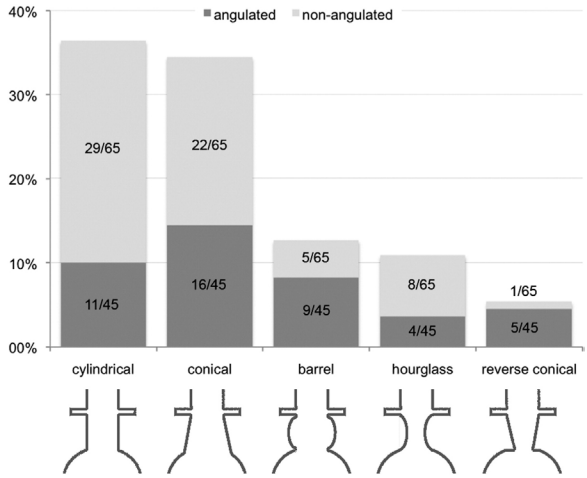

Figure 3. Neck shape distribution.
Legend: The likelihood of a non-cylindrical shape is greater on the angulated group (RR: 1.77 95%CI 1.01–3.09) P value = 0.031.

Endoleaks were detected intra-operatively in 22.2% and 24.6% of angulated and non-angulated groups, respectively (Table 3). In one case, it corresponded to a type-I proximal endoleak that was resolved with implantation of a proximal extension. This patient is included in the angulated group and corresponds to the only primary technical failure of this series. All of the remaining endoleaks were type-II, and no further action was attempted intra-operatively. No differences were found regarding duration of the procedure, radiation exposure and contrast use.

In the first postoperative CTA, a similar number of type-II endoleaks were detected. Notably, no type-I endoleaks were detected at 30 days in either group. The mean distance from the lowest renal artery and the start of the covered stent was 2.4 mm in the angulated group and 2.3 mm in the non-angulated group.

Clinical outcomes (Table 4)

Combined in-hospital/30-day mortality was 2.2% in the angulated group and 3.1% in the non-angulated group, corresponding to one and two patients, respectively (p = 0.77). The mortality case in the angulated group corresponded to a patient with previous kidney dysfunction that aggravated after treatment. He was transferred to another institution on the 10th postoperative day and died on the 45th postoperative day due to renal complications. In the non-angulated group, there were two deaths. These corresponded to a patient with cardiac insufficiency and known valvular disease, who required urgent cardiac surgery and died in the postoperative period, and a patient with previous renal and respiratory disease, who developed severe renal insufficiency and respiratory distress postoperatively and died on the 13th postoperative day.

Table 3. Technical outcome within 30 days and operative findings.

Outcome measure	Angulated (*N* = 45)	Non-angulated (*N* = 65)	*P* value
Primary technical success, no. (%)	44 (97.8)	65 (100)	0.28
Primary assisted technical success, no. (%)	45 (100)	65 (100)	–
Necessary adjunctive procedures, no. (%)	8 (17.8)	8 (12.3)	0.49
Planned, no. (%)	7 (15.5)[a]	7 (10.8)[b]	
Unplanned, no. (%)	1 (2.2)[c]	1 (1.5)[d]	
Intra-operative EL, no. (%)	10 (22.2)	16 (24.6)	0.77
30-day EL, no. (%)	11 (23.3)	12 (18.5)	0.54
30-day type-I EL, no. (%)	0	0	–
30-day endograft migration, no. (%)	0	0	–
Procedure duration, mean (SD) min	105.8 (25.8)	104.4 (36.5)	0.83
Radiation exposure, mean (SD) min	12.3 (2.3)	13.6 (2.1)	0.69
Contrast use, mean (SD) mL	87.6 (28.6)	88.4 (17.3)	0.89
Distance renal to graft, mean (SD) mm[e]	2.4 (2.7)	2.3 (4.8)	0.90
Oversizing, mean % (SD)	21.4 (10.2)	16.1 (9.4)	0.01

Legend: EL – Endoleak; SD – Standard Deviation. a) Femoro-femoral crossover (3), iliac balloon angioplasty (2), femoral endarterctomy (2). b) Femoro-femoral crossover (3), iliac balloon angioplasty (3), femoral endarterctomy (1). c) Proximal extension cuff. d) Renal angioplasty. e) Measured as the distance between the distal end of the lowermost renal artery and the first covered stent of the endograft.

Table 4. Clinical outcome within 30 days or during hospitalization.

Outcome measure	Angulated (*N* = 45)	Non-angulated (*N* = 65)	*P* value
Major post-op complications, no. (%)	3 (6.7)	4 (6.2)	0.77
Minor post-op complications, no. (%)	2 (4.4)	4 (6.2)	0.68
Re-intervention, no. (%)	0	0	–
Aneurysm rupture, no. (%)	0	0	–
AAA related mortality, no. (%)	0	0	–
All-cause mortality, no. (%)	2.2% (1)	3.1% (2)	0.79
Hospital stay, mean (SD), days	6.8 (11.7)	4.2 (5.7)	0.19

Legend: EL – Endoleak; SD – Standard Deviation.

The combined in-hospital/30-day morbidity was 6.7% for the angulated group and 6.2% for the non-angulated group. In the angulated group, this corresponded to three patients with the following complications: one myocardial infarction, one respiratory failure requiring ventilatory support and two severe renal insufficiency, one needing temporary dialysis and one deep vein thrombosis with a sub-clinical pulmonary embolism. The latter group included four patients with the following diagnosis: one myocardial infarction, two respiratory failures requiring ventilatory support and two renal failures requiring temporary dialysis (one patient had two major complications registered). Minor complications were present in 4.4% and 6.3% of patients, respectively,

and corresponded to surgical wound haematoma (two), surgical wound infection (one), transient amnesia (one) and unexplained transient fever (one). There were no aneurysm-related deaths, aneurysm ruptures or need for re-intervention in either group.

DISCUSSION

Proximal neck anatomy – and angulation in particular – has been associated with significant technical difficulties and adverse short-term outcomes.[5,6,7,8] We believe that two factors are mainly responsible for this: inadequacy of the implantation material to allow for easy access, accurate deployment and proper fixation; and excessive mechanic and haemodynamic stress resulting from altered blood flux patterns induced by angulation, resulting in a greater likelihood of endograft migration.[9] The introduction of newer devices specifically designed to treat more challenging anatomies is expected to improve results in severely angulated anatomy, safely expanding the spectrum of patients amenable for this technique. The findings of the present study confirm this hypothesis by demonstrating a striking similarity with respect to operative details (an indirect measure of the technical difficulty of the procedure) and a similar early clinical outcome between angulated and non-angulated groups.

Dillavou et al. reported their results on patients with hostile necks, treated with the EVT/Ancure endograft system.[7] They found that the concept of active fixation and unsupported (therefore flexible) mainbody provided good early results. The idea is to provide adequate fixation and minimal rigidity or columnar strength (i.e., high conformability). The Endurant Stentgraft System was introduced in 2008 in the European market, featuring specific characteristics that make it appealing for challenging anatomies. These include a flexible small-diameter delivery system that allows for easy access, a highly conformable yet kink-resistant mainbody, suprarenal active fixation and a tip-capture delivery system. This last attribute greatly increases control over the deployment, which results in enhanced proximal positioning. We confirmed this by measuring the average distance from the lowest renal artery to the covered part of the stent graft (reflecting the correct proximal positioning of the device) on the first postoperative CTA: distances were 2.3 mm in non-angulated cases and 2.4 mm in angulated ones, with little variability.

We included patients with extremely angulated proximal necks, both in suprarenal and infrarenal locations, measured using a previously validated, precise method. Most patients in the angulated group were ASA III or IV and had a Glasgow aneurysm score higher than 79, reflecting a higher risk for open surgery. Our sample confirms previous observations that patients with angulated proximal necks tend to have larger aneurysms and a poorer health status.[8 and 10] We have also found that there is a greater variability of the neck shape in patients with angulated necks, meaning these are less often cylindri-

cal. This may explain the difference in the mean percentage of oversizing between non-angulated and angulated patients (16.1% vs. 21.4%, respectively). In fact, correcting for neck shape resulted in no difference between groups. Importantly, these observations of neck shape and endograft sizing had no influence on our early results.

Unplanned procedures were needed for two patients, one from each group and both relating to the proximal neck. A type-I endoleak was found intra-operatively in the patient from the angulated group, and corrected by successful implantation of a proximal extension. This may have occurred due to increased difficulty in achieving an adequate deployment position, as this patient had significant α and β angulation (64° and 78°, respectively) and also a short aneurysm neck (11 mm). Moreover, oversizing was only 12%, which may have contributed to the primary failure. Although the problem was repaired without further early complications, it suggests that compound anatomical adversities exponentially increase the risk of complications and offset the treatment benefit, as previously demonstrated.[11] Curiously, the other unplanned procedure, on a non-angulated patient, was also deployment related, due to unintentional partial coverage of a renal artery.

A EUROSTAR report has been published regarding the influence of proximal neck angulation on early complications.[8] The authors found that, in the short-term (previous to discharge), there was a significantly higher risk of proximal type-I endoleak (odds ratio (OR) 2.32, 95% CI: 1.60–3.37, p = 0.0001) and stentgraft migration (OR 2.17, 95% CI

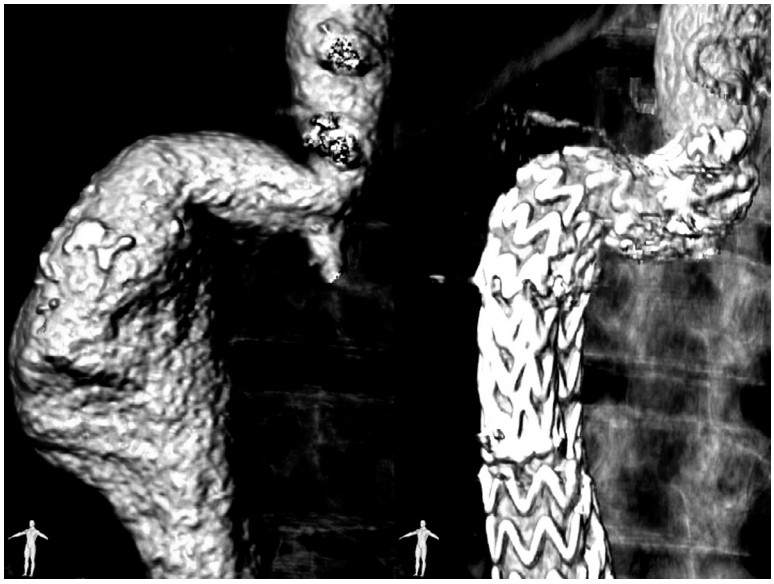

Figure 4. CTA 3-dimensional reconstruction of the abdominal aorta, pre- and post-implantation.
Legend: Notice the adaptation of the endograft to the underlying anatomy without significant change in the shape of the vessel. The first covered stent lies parallel to the axis of the vessel.

1.20–3.91, p = 0.0105). They also showed that patients treated with the Excluder (W. L. Gore & Associates, Inc, Sunnyvale, CA, USA) device presented a significantly higher risk of post completion proximal type-I endoleak (OR 4.49, 95% CI 1.31–15.32, p = 0.0166). The greater incidence of type-I endoleak may result from the inability to position the graft perpendicular to the axis of the aorta, resulting in asymmetrical deployment. Adequate seal in not achieved and lateral displacement forces push the device out of the intended position.[12] Highly conformable devices (such as the Endurant) adapt to the underlying anatomy and therefore follow the original axis of the artery more closely. We believe this to reduce the displacement forces on the graft and avoid the gaps that originate type-I endoleaks (Figure 4).

Other authors have specifically looked into the effect of angulation on early outcome. Sternbergh et al. have found proximal neck angulation >40° to result in a greater likelihood of early adverse events, including early death (20% vs. 0%, p = 0.0007) and need for acute open conversion (20% vs. 0%, p = 0.0007).[5] Their analysis only included patients treated with the Talent endograft, and only 21 patients were included in the angulated groups, limiting the results. Albertini et al. found a strong correlation between angulation and early type-I endoleak and graft migration when analysing risk factors for 184 patients treated with a home-made endovascular device.[13] Two studies found no differences in the primary technical success and early clinical outcome among patients with or without adverse proximal necks, although angulation was not specifically considered. Inclusion criteria for these studies included neck calcification, thrombus and neck length, meaning the actual number of patients included due to angulation was very small, again limiting the conclusions.[11,14]

Other devices have also been evaluated in the treatment of angulated anatomies. The Aorfix (Lombard Medical Technologies, Didcot, UK) was shown to provide acceptable results on 20 patients with adverse anatomy, with one technical failure and one misplacement with renal artery coverage, both attributable to angulation.[15] No early type-I endoleaks or migration was reported. Results on 37 patients with >60° angulation using the Powerlink (Endologix Inc, Irvine, CA, USA) device also provided good results, with selective addition of a giant Palmaz stent for enhanced fixation.[16] They encountered one technical failure due to vessel rupture, two (5.6%) intra-operative type-I endoleaks and the need for two or more proximal cuffs in seven (19.4%) patients. No migration occurred. Robbins et al. studied the influence of suprarenal fixation on very angulated aortic necks.[10] In their study with 1-year follow-up, angulation was not associated with adverse outcome. They did notice, however, that device kinking was more frequent in angulated cases, as a result of the stiffer body of the endograft used (Talent, Medtronic AVE, Santa Rosa, CA, USA). As drag forces are higher in angulated necks,[9] relying solely on radial force for fixation seems undesirable. Our results suggest that suprarenal fixa-

tion (and especially active fixation) is an important aspect for the prevention of early migration and consequent primary type-Ia endoleaks.

There are some limitations to this study, the most important being the reduced time of follow-up, which confines the conclusions to technical aspects and combined in-hospital/30-day success. However, in the particular case of proximal neck angulation, this is also the timeframe for most complications to arise. It thus remains important to demonstrate that there is no negative influence of angulation on early outcome of EVAR or on the difficulty of the procedure, as revealed by these homogeneous results from three independent centres. Longer follow-up will allow for comparison regarding late complications, in particular, migration or secondary endoleaks, which have previously been shown to also occur more often in angulated cases.[5,6,8,13]

The non-consecutive, retrospective nature of the study may result in significant bias. However, all patients selected for EVAR were treated in a consecutive fashion with the same endograft. Patients within the angulated group were individually appointed either to open, endovascular or no treatment according primarily to their co-morbidities, skewing this group towards a generally lower health status. This did not result in any difference in the short-term, but may do so in the future. The large EVAR practice of the participating centres must also be accounted for, as these results may not be reproducible in less-experienced departments. Lastly, the relatively small numbers presented may be insufficient to reveal differences between groups. Nonetheless, with the exception of the study derived from the EUROSTAR registry, this study represents the largest published series looking specifically at outcomes of patients with severe proximal neck angulation.

CONCLUSION

In our high-volume centres with over 13 years of experience with EVAR, treatment with the Endurant Stentgraft System is technically feasible, safe and results in successful early aneurysm exclusion regardless of the severity of proximal neck angulation. No loss of sealing length was found in extremely angulated anatomy, confirming the high conformability of this device and efficacy of the deployment system. Duration of procedures, intra-operative contrast use and radiation exposure time were similar in both the angulated and the control groups, indirectly demonstrating an absence of additional intra-operative difficulties.

The particular characteristics of this device seem to make it appropriate for treatment of highly angulated necks, especially in patients of high surgical risk. Mid- and long-term data are awaited to verify the durability of the procedure, but early results are promising and challenge current opinion concerning the negative influence of neck angulation on EVAR.

CONFLICT OF INTEREST

Prof. F. Moll, Prof H. Verhagen, Dr. J.P. de Vries and Dr J. van Herwaarden are consultants for Medtronic AVE.

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Chapter 7

Mid-term results of EVAR in severe proximal aneurysm neck angulation

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ABSTRACT

Objective

To determine if mid-term outcome following endovascular aneurysm repair (EVAR) with the Endurant Stent Graft (Medtronic, Santa Rosa, CA, USA) is influenced by severe proximal neck angulation.

Methods

A retrospective case–control study was performed using data from a prospective multicenter database. All measurements were obtained using dedicated reconstruction software and center-lumen line reconstruction. Patients with neck length >15 mm, infrarenal angle (β) >75°, and/or suprarenal angle (α) >60°, or neck length >10 mm with β >60°, and/or α >45° were compared with a matched control group. Primary endpoint was primary clinical success. Secondary endpoints were freedom from rupture, type 1a endoleak, stent fractures, freedom from neck-related secondary interventions, and aneurysm-related adverse events. Morphological neck variation over time was also assessed.

Results

Forty-five patients were included in the study group and were compared with a matched control group with 65 patients. Median follow-up time was 49.5 months (range 30.5–58.4). The 4-year primary clinical success estimates were 83% and 80% for the angulated and nonangulated groups ($p = .42$). Proximal neck angulation did not affect primary clinical success in a multivariate model (hazard ratio 1.56, 95% confidence interval 0.55–4.41). Groups did not differ significantly in regard to freedom from rupture ($p = .79$), freedom from type 1a endoleak ($p = .79$), freedom from neck-related adverse events ($p = .68$), and neck-related secondary interventions ($p = .68$). Neck angle reduction was more pronounced in patients with severe proximal neck angulation (mean Δα −15.6°, mean Δβ −30.6°) than in the control group (mean Δα −0.39°, mean Δβ −5.9°) ($p < .001$).

Conclusion

Mid-term outcomes following EVAR with the Endurant Stent Graft were not influenced by severe proximal neck angulation in our population. Despite the conformability of the device, moderate aortic neck remodeling was identified in the group of patients with angulated neck anatomy on the first computed tomography scan after implantation with no important further remodeling afterwards. No device integrity failures were encountered.

INTRODUCTION

Proximal neck anatomical features, such as angulation, have been associated with increased risks of aneurysm-related complications and have restricted suitability for endovascular aneurysm repair (EVAR).[1] Owing to an expected increase of risk following EVAR in the presence of very angulated necks, different thresholds of proximal neck angulation have been set by each manufacturer's instructions for use (IFUs), reflecting the different extent to which each endograft is expected to perform in these challenging anatomies.

The Endurant Stent Graft (Medtronic, Santa Rosa, CA, USA) is a late-generation endograft that has been specifically designed to treat more challenging anatomy by increasing conformability, proximal seal, and fixation, allowing the treatment of a broadened group of patients.[2] Some data suggest that these features are well suited for the treatment of severely angulated proximal anatomy,[3] but long-term data are lacking.

The hypothesis of this study is that severe proximal neck angulation has no influence on mid-term outcome after EVAR with the use of the Endurant Stent Graft System.

METHODS

One hundred and ten patients who were included in a previously published case–control study that reported on 30-day outcomes after EVAR with the Endurant Stent Graft in severely angulated proximal aneurysm necks were reviewed.[4] This study was based on a prospectively maintained database from three high-volume centers in the Netherlands (St. Antonius Hospital, Nieuwegein, University Medical Center, and Utrecht and Erasmus University Medical Center). This study complied with the principles of the Declaration of Helsinki. Informed consent was not required according to institutional policy on retrospective research.

Patient population

Study design and patient selection have been reported previously, in detail.[4] In summary, in the period 2008–09, 418 patients with abdominal aortic aneurysms (AAAs) were treated in the three centers. Of these, 271 patients electively received an Endurant Stent Graft for a degenerative AAA. Patients with mycotic aneurysms or prior aortic reconstructive surgery were excluded. The treatment decision and type of repair offered were individualized according to anatomical determinants, health status, and history of previous abdominal surgery (hostile abdomen). Patient preference was also taken into account before obtaining informed consent. All patients with severely angulated

proximal anatomy selected for endovascular repair were treated consecutively solely with an endurant bifurcated endograft.

Angulation measurement has been reported previously.[4] Briefly, following three-dimensional image reconstruction, the aorta is turned 360° perpendicularly to the center lumen line (CLL) flexure, and then rotated along its longitudinal axis until the sharpest angle is found. The alpha angle is formed between the suprarenal aorta and the aneurysm neck, and the beta angle between the aneurysm neck and sac. Angulation inclusion criteria were defined according to the maximum proximal neck angulation described in Medtronics' IFUs for the Endurant Stent Graft.[5] Accordingly, patients were included in the angulated group if one of the following two combinations occurred: a neck length >15 mm with an infrarenal angle (β) >75°, and/or suprarenal angle (α) >60°, or neck length >10 mm with β >60° and/or α >45°. Forty-five (16.5%) of the patients electively receiving an Endurant Stent Graft were included in the angulated group and thus treated outside the device's IFUs. Twenty-three (51.1% of the angulated group) patients were included owing to β angulation, 14 (31.1%) owing to both α and β angulation, and eight (17.8%) owing solely to α angulation. A control group matched for baseline clinical characteristics of 65 patients was selected from the remaining elective infrarenal EVAR patients from the same hospitals in the same time period using the same Endurant endograft.[4]

Postoperative surveillance

Follow-up protocols consisted of a contrast-enhanced computerized tomography angiography (CTA) at 1 and 12 months, and annually thereafter. According to the treating physician's expectation, in selected patients with expected lower risk of complications or renal function impairment, CTA was replaced by colored-duplex ultrasound or by noncontrasted CT.

Data management

Baseline clinical, anatomic, and intraoperative data were acquired at the time of surgery. All subsequent long-term follow-up data were prospectively obtained upon outpatient clinical visits.

Image analysis and measurements

All measurements (diameters, length, and volume) were performed using semiautomatically generated CLL reconstruction on a workstation with dedicated reconstruction software (3Mensio Vascular 4.2; Medical Imaging B.V., Bilthoven, the Netherlands). All long-term imaging data were obtained by a single observer with experience in image analysis (N.F.G.O.). In previous reports, our group demonstrated high rates of interobserver agreement in respect to aneurysm diameter, neck diameter, neck length, and

proximal seal length measurements,[6,7,8] obtained according to this methodology. Aneurysm volume was measured according to previously validated methodology.[7] Angulation measurements were executed in a standardized and previously validated method.[9]

Definitions

Reporting was performed according to the guidelines from the Society for Vascular Surgery/American Association of Vascular Surgery ad hoc Committee for Standardized Reporting Practices in Vascular Surgery.[10] Clinical success, primary clinical success, primary assisted clinical success, and secondary clinical success were defined accordingly.[10] Oversizing was determined by dividing the difference between the implanted main body diameter and the reference neck diameter in the first 15 mm of the infrarenal neck by the latter. Proximal seal length was defined as the extension of complete circumferential apposition between the endograft and the aortic wall, and was determined according to a previously published method.[8] The length of the neck was defined as the distance between the most distal point of the origin of the lowermost renal artery and the beginning of the aneurysm. For proximal seal determination and barb detachment, center lumen markers were placed from the origin of superior mesenteric artery and at every 2 mm, and progressed caudally until reaching the flow divider. Distance from the lowermost renal artery to the endograft was measured on CLL reconstruction as the distance between a tangent horizontal plan passing through the most distal point of the circumference of the lowermost renal artery ostium and the first covered stent of the endograft on last imaging available. Migration was defined by subtracting the distance from the lowermost renal artery to endograft measured on first postoperative imaging from last available imaging exam.

Sac growth was defined as a >5% increase in aneurysm sac volume or as a >5 mm increase in sac diameter.[10] Long-term sac dynamics were defined as the difference in maximum diameter between the first (within 30 days) and the last postoperative imaging examinations. Barb detachment was defined on CLL reconstruction as nonapposition of a proximal uncovered stent barb to the aortic wall and distance of detachment was measured between the outer surface of the barb and the inner limit of the aortic wall. Posterior neck bulging was defined by the increase of neck diameter in quadrant defined by the convexity of the suprarenal angle, despite maintenance of adequate endograft apposition to the aortic wall in the remaining quadrants on surveillance imaging.

AAA-related adverse events were defined as a composite of the following: direct (type 1 or 3) or undetermined type endoleaks, aneurysm sac growth, migration >10 mm, device integrity failure, AAA-related death, late postimplantation AAA rupture, or any AAA-related secondary intervention. Undetermined endoleak was considered if contrast was identified within the aneurysm sac but outside the endograft and if its origin could not be imputed to failure of proximal or distal seal or patent aortic branch vessels.

Secondary interventions were considered if performed to resolve or prevent a possible complication, and included endovascular procedures (proximal cuff and stent implant, distal extension implant, catheter-based thrombolysis, iliac angioplasty, coil or glue embolization of aortic branch vessels), as well as surgical procedures (balloon thrombectomy, femoro-femoral crossover, conversion to open repair, open or laparoscopic ligation of collaterals).

Endpoints

The primary study endpoint was primary clinical success. Secondary endpoints were freedom from rupture, freedom from type 1a endoleak, freedom from neck-related secondary interventions and aneurysm-related adverse events. Additional individual elements of the latter composite endpoint—aneurysm expansion (diameter ≥5 mm, volume ≥5%), type 1b and type 3 endoleaks, graft or limb thrombosis, graft infection, conversion to open repair or death as a result of aneurysm-rupture or aneurysm-related treatment—were also explored separately. Variation of neck-related morphological features and device-related outcomes in the proximal neck were also assessed.

Statistical analysis

Categorical variables are presented as count and percentage, and were compared using the Pearson's chi-square test. Continuous variables are presented as mean, SD, median, interquartile range (IQR), and range. Differences between groups were analyzed using the Mann–Whitney *U* test for independent samples with non-normal distributions, with the Student *t* test and significance with the independent samples test for nonrelated variables with normal distributions, and the paired Student *t* test for paired variables. Survival curves for primary clinical success and freedom from neck-related secondary interventions were estimated by Kaplan–Meier methods, and equality was evaluated with the Mantel–Cox log-rank test. Long-term outcome variables were assessed by Cox hazards regression models. Multivariate regression was performed to include the most significant morphologic features determined by previous univariate analysis (neck diameter and neck length). Confidence intervals (CIs) of 95% were used and statistical significance was considered if $p < .05$. All statistical analysis was performed using SPSS 21.0 (IBM, Armonk, NY, USA).

RESULTS

Clinical and anatomical baseline characteristics are presented in Table 1. At the time of surgery, the mean age of the patients was 73.9 ± 7.9 years, and 86.4% were men. Both groups were not significantly different regarding comorbidities. Anatomic characteriza-

tion has been exhaustively described elsewhere.[4] Mean α angles were 51.4 ± 21.1 and 17.9 ± 17.0, and mean β angles were 80.8 ± 15.6 and 35.4 ± 20.0 for the angulated and control groups, respectively. Intraobserver variability for neck angulation measurements was tested for a sample of 44 patients, with very good agreement (Pearson's correlation coefficient, α angle −0.965, $p < .01$; β angle −0.932, $p < .01$), and Bland–Altman plots were created (Figure 1).

Patients in the angulated group presented significantly larger aneurysms, with a mean aneurysm volume of 309.5 ± 30.1 cc ($p < .001$) and shorter proximal neck lengths (mean 27.2 mm ± 14.8; $p < .01$). Procedural-related and early outcomes have been previously reported. [4]

Median follow-up time was 49.5 months (IQR 30.5–58.4; range 0.43–67.1 months). Follow-up time differed between groups, with median of 45.3 months (range 1.5–61.6 months) for the angulated group and a median of 52.1 months (range 0.4–67.1 months) for the nonangulated group ($p = .03$).

Early postoperative mortality occurred in one patient in the study group and two patients in the control group as previously reported.[4] Of the remaining 107 patients,

Table 1. Baseline clinical and anatomic characteristics.

Characteristic	Angulated ($n = 45$)	Nonangulated ($n = 65$)	p
Age (y), mean (SD)	75.6 (6.5)	72.7 (8.5)	.49
Male	36 (80.0)	59 (90.8)	.11
Smoking	32 (71.1)	51 (78.5)	.38
Hypertension	25 (55.6)	35 (53.8)	.70
Cardiac disease	22 (48.9)	27 (41.5)	.45
Diabetes	6 (13.3)	15 (23.1)	.20
COPD	14 (31.1)	13 (20.0)	.18
Creatinine clearance <60 mL/min/1.73 m^2	16 (35.6)	20 (30.8)	.60
Cerebrovascular disease	4 (8.9)	12 (18.5)	.16
Peripheral arterial disease	11 (24.4)	15 (23.1)	.87
ASA class III/IV	33 (73.3)	43 (66.2)	.42
AAA Ø (mm), mean (SD)	68.6 (14.2)	58.8 (7.6)	<.01
AAA volume (cc), mean (SD)	309.5 (30.1)	187.4 (8.2)	<.01
Proximal neck Ø (mm), mean (SD)	25.2 (4.2)	25.5 (4.5)	.71
Proximal neck length (mm), mean (SD)	27.2 (14.8)	32.6 (13.1)	.05
Neck thrombus >25% of circumference	8 (17.8)	10 (15.4)	.74
Neck calcification >25% of circumference	3 (6.7)	1 (1.5)	.16
α Angle (degrees), mean (SD)	51.4 (21.1)	17.9 (17.0)	<.01
β Angle (degrees), mean (SD)	80.8 (15.6)	35.4 (20.0)	<.01

Legend: Values given as *n* (%) unless otherwise indicated. COPD = chronic obstructive pulmonary disease; ASA = American Society of Anesthesiologists; AAA = abdominal aortic aneurysm.

postoperative CTAs were available for 44 (98.0%) patients of the angulated group and 62 (95.0%) patients in the control group. Only one patient did not undergo postoperative CTA owing to impaired renal function and an uneventful follow-up. A 1-year CTA was obtained for 91, a 2-year CTA for 77, a 3-year CTA for 52, and a 4-year CTA for 36 patients.

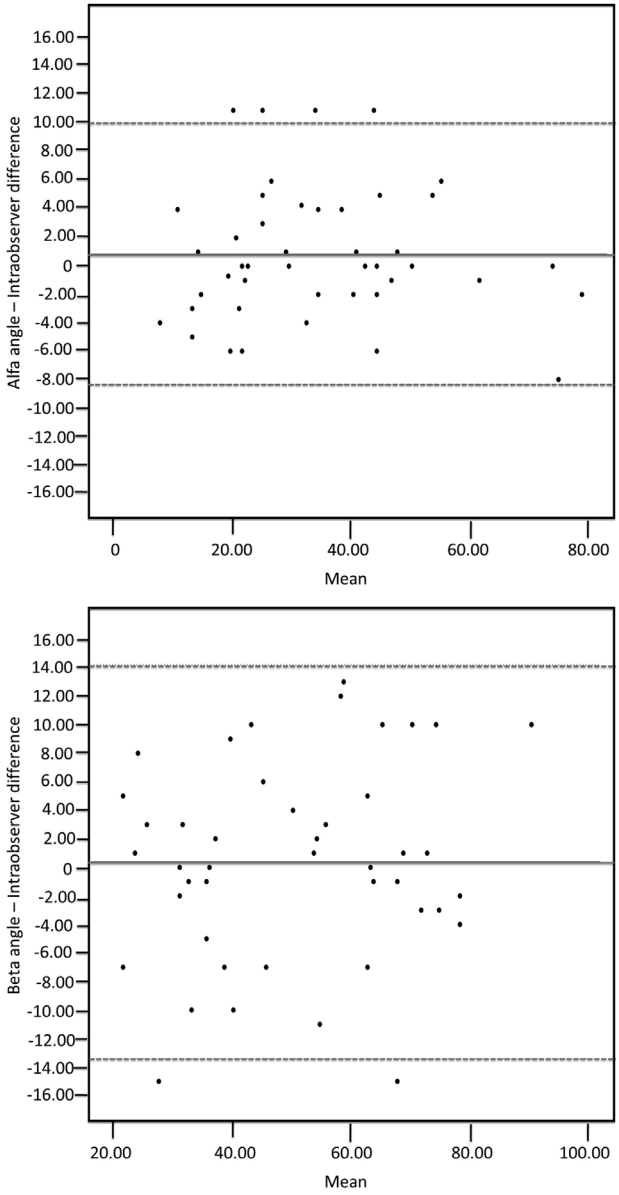
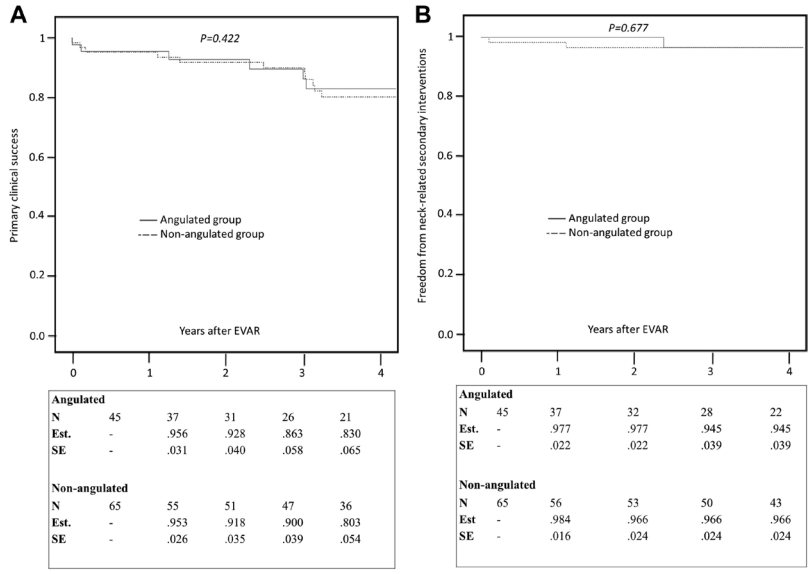


Figure 1. Bland–Altman plots showing intraobserver variability for suprarenal (top) and infrarenal (bottom) neck angulation on last imaging available in a group of 44 patients.

Clinical success

Primary clinical success was obtained in 86 (78.2%) patients. Forty of these patients had angulated proximal anatomy (88.9%) and 46 had less challenging necks (70.8%) (p = .02). Kaplan–Meier survival estimates for primary clinical success were not different for patients with or without proximal angulated anatomy (p = .42; Figure 2A). The 2- and 4-year estimates for primary success rates were 93% and 83% for the angulated group, 92% and 80% for the control group. On multivariate regression analysis, patients with severe proximal neck angulation were not at increased risk of presenting worse primary clinical success compared with the control group (Hazard ratio [HR] 1.56, 95% CI 0.55–4.41; p = .40). Overall primary-assisted and secondary clinical success were not different among both groups (Table 2).

Freedom from late aneurysm rupture: Late aneurysm rupture occurred in three (2.7%) patients, one in the angulated group (2.2%) and two in the nonangulated group (3.1%) (p = .79) and resulted in the death of one patient in each group (1.8%) (p = .79; Table 3). In the nonangulated group, one patient developed an infection of the endograft with subsequent type 1a endoleak and aneurysm rupture. Despite undergoing a proximal cuff insertion, this patient died 26 days after secondary intervention. The other patient from the nonangulated group presented a type 1b endoleak with rupture, which was successfully treated with a limb extension. In the angulated group, one patient presented with aneurysm rupture due to a type 1b endoleak.



Angulated					
N	45	37	31	26	21
Est.	-	.956	.928	.863	.830
SE	-	.031	.040	.058	.065
Non-angulated					
N	65	55	51	47	36
Est.	-	.953	.918	.900	.803
SE	-	.026	.035	.039	.054

Angulated					
N	45	37	32	28	22
Est.	-	.977	.977	.945	.945
SE	-	.022	.022	.039	.039
Non-angulated					
N	65	56	53	50	43
Est	-	.984	.966	.966	.966
SE	-	.016	.024	.024	.024

Figure 2. (A) Kaplan–Meier analysis of long-term primary clinical success. (B) Kaplan–Meier analysis of freedom from neck-related reinterventions.
Legend: EVAR = endovascular aneurysm repair.

Table 2. Long-term clinical outcomes.

	Angulated (n = 45)	Nonangulated (n = 65)	p
Primary clinical success	40 (88.9)	46 (70.8)	.02
Assisted primary clinical success	42 (93.3)	60 (92.3)	.84
Secondary clinical success	43 (95.6)	63 (96.9)	.71
Late aneurysm-related mortality	1 (2.2)	1 (1.5)	.79
All-cause mortality	11 (24.4)	11 (16.9)	.33

Legend: Values given as n (%).

Freedom from proximal type 1 endoleaks and neck-related reinterventions

Secondary interventions due to neck-related adverse events occurred in three patients. In the angulated group, one patient who had received a limb relining owing to a type 3 endoleak became symptomatic 5 months later, without rupture, and was converted to open repair. Intraoperatively a position-dependent type 1a endoleak reported. In the nonangulated group, two patients required proximal cuffs: one patient who developed an endograft infection and consequent proximal type 1 endoleak, as reported above; the other patient was treated for a secondary type 1a endoleak with a proximal cuff but required also a proximal Palmaz stent 1 year later owing to progressive neck dilatation and endoleak relapse. No differences between Kaplan–Meier survival curves were demonstrated for proximal neck-related secondary intervention (p = .68) (Figure 2B). The 2- and 4-year estimates for freedom from neck-related secondary interventions were 98% and 95% in the angulated group, while in the control group they were both 97%. In addition to these three patients listed, one further patient with severe proximal neck angulation developed a proximal type 1 endoleak but died before receiving treatment for the endoleak owing to unrelated medical complications following refractory lower intestinal bleeding. Patients in the angulated group did not present more proximal type 1 endoleaks when compared with the control group (p = .79).

AAA-related adverse events

During the follow-up period, aneurysm-related adverse events were registered in 23 (20.9%) patients, six (13.3%) of whom had severely angulated necks; the remaining 17 did not (26.2% of the control group) (p = .10; Table 3). Patients with severe proximal angulation were not at increased risk for adverse events (HR = 1.65, 95% CI 0.57–4.75; p = .35).

Patients in the angulated group underwent less secondary interventions than in the control group (p = .04). On multivariate analysis, an increased risk of having a secondary intervention could not be identified among the study group (HR = 1.19, 95% CI 0.35–4.02; p = .78).

Sac growth >5 mm did not occur in the angulated group but was identified in six (9.7%) patients in the nonangulated group (p = .03). Type 2 endoleak was considered the cause of sac growth in three patients; two of these patients underwent glue/coil embolization, which did not prevent progressive sac growth. The remaining cases of sac growth occurred in the presence of direct endoleaks.

Table 3. Abdominal aortic aneurysm (AAA)-related events.

	Angulated (n = 45)	Nonangulated (n = 65)	p
AAA-related adverse events, patients	6 (13.3)	17 (26.2)	.10
Aneurysm rupture	1 (2.2)	2 (3.1)	.79
Late aneurysm-related mortality	1 (2.2)	1 (1.5)	.79
Secondary endoleaks			
Type 1a—patients	2 (4.4)	2 (3.1)	0.79
Type 1a—events	2	3	
Type 1b	2	8	
Type 2	3	7	
Type 3	1	0	
Sac growth	0 (0)	6 (9.7)	.03
Sac shrinkage ≥10 mm	17 (38.6)	22 (35.5)	.74
Graft infection	0	1	
Limb thrombosis, events	1	7	
Endograft occlusion	1	0	
Buttocks claudication	0	1[a]	
Access artery thrombosis	1[a]	0	
Migration	0	0	
Device failure	0	0	
Secondary interventions—patients	4 (8.9)	16 (24.6)	.04
Secondary interventions—events	5	22	
Proximal stent/cuff	0	3	
Limb extension	2	9	
Coil/glue embolization	0	4	
Relining	0	0	
Conversion to open repair	1	0	
Conversion to aortouniiliac	0	0	
Open/laparoscopic fenestration	0	0	
Thrombolysis and iliac PTA	2	4	
Isolated iliac PTA	0	2	

Legend: Values given as n (%). PTA = percutaneous transluminal angioplasty. a) No intervention took place in these patients.

Device-related outcomes in the proximal neck

Postoperative CTAs were available for 44 (98.0%) patients in the angulated group and 62 (95.0%) patients in the control group.

Mean distance from the lowermost renal artery was not significantly increased in patients with angulated anatomy (4.9 ± 3.9 mm) when compared with the patients without severe proximal angulation (3.9 ± 3.5 mm) ($p = .15$) on last CTA. Mean endograft migration distance measured between the first and the last postoperative imaging available did not differ significantly among groups (Table 4).

Mean proximal seal length was significantly shorter for the angulated group (16.7 mm) in comparison with the nonangulated patients (23.7 mm) ($p < .01$) on last imaging available. Moreover, patients with severe proximal neck angulation were at higher risk of presenting short (<10 mm) proximal seal lengths (HR 4.91, 95% CI 1.58–15.31; $p < .01$). However, significant differences were already present on the first postoperative CT, where mean proximal seal length was 16.8 ± 8.5 mm in the angulated group and 22.1 ± 8.8 mm in patients without proximal neck angulation ($p = .01$) and were not dissimilar from the proximal seal lengths measured on the last imaging for both angulated ($p = .18$) of nonangulated ($p = .36$) groups.

Stent fracture was not identified among any of the groups. Barb detachment was encountered in 13 (11.8%) patients: eight (17.8%) in the study group and five (7.8%) in the control group, which was not significantly different ($p = .12$). Mean distance from wall to barb was also not significantly different among groups (angulated patients: 3.6 ± 2.2 mm; controls 2.2 ± 0.65 mm [$p = .13$]). On multivariate regression, patients with very angulated proximal neck anatomy were found to be at a higher risk of presenting barb detachment (HR 3.59, 95% CI 1.14–11.33; $p = .03$). Multiple barb detachment was not identified in our population.

Table 4. Long-term morphologic and device-related outcomes in the proximal neck.

	Angulated	Nonangulated	
	($n = 44$)	($n = 62$)	p
Migration distance (mm), mean (SD)	1.9 (2.6)	1.1 (1.6)	.22
Proximal seal length on last imaging (mm), mean (SD)	16.7 (9.3)	23.7 (10.9)	<.01
α Angle on last imaging (degrees), mean (SD)	35.5 (17.6)	16.7 (12.1)	<.01
β Angle on last imaging (degrees), mean (SD)	50.4 (19.4)	29.8 (16.7)	<.01
Δα Angle compared with 30-d CTA (degrees), mean (SD)	−1.1 (11.9)	−1.6 (10.8)	.81
Δβ angle compared with 30-d CTA (degrees), mean (SD)	−1.0 (21.0)	4.3 (15.9)	.14
Neck dilatation compared with baseline (mm), mean (SD)	3.0 (2.0–5.0)	4.0 (1.0–5.3)	.55

Legend: CTA = computerized tomographic angiography.

Proximal neck morphological outcomes

Suprarenal and infrarenal angles remained significantly different between the two groups ($p < .01$) after EVAR. Angle reduction was significantly more pronounced in patients with severe proximal neck angulation when compared with the control group (Table 4). However, when comparing the last available CTA with the first postoperative one, the suprarenal and infrarenal angles did not change significantly in either angulated or nonangulated neck patients (Figure 3).

Mean baseline neck diameter was 25.2 ± 4.2 mm in the severe neck angulation group and 25.5 ± 4.5 mm in the control group. Patients with angulated proximal necks had shorter neck lengths (27.2 ± 14.8 mm) when compared with the control group (32.6 ± 13.1 mm) ($p = .05$). Mean neck dilatation was 12.6 ± 12.5% and 13.8 ± 10.7% when compared with baseline diameters among patients with and without severe proximal neck angulation, respectively, and did not differ significantly ($p = .59$). Mean device oversizing was 21.4 ± 10.2% in the angulated group and 16.1 ± 9.4% in the control group ($p = .01$). Posterior bulging occurred in three patients (6.8%) in the angulated group and in one patient (2.2%) without angulated anatomy, which was not significantly different between both groups ($p = .17$). However, in one of the patients in the angulated group it was associated with a proximal type 1 endoleak but no intervention took place as this patient died in the sequence of lower intestinal bleeding, as reported above.

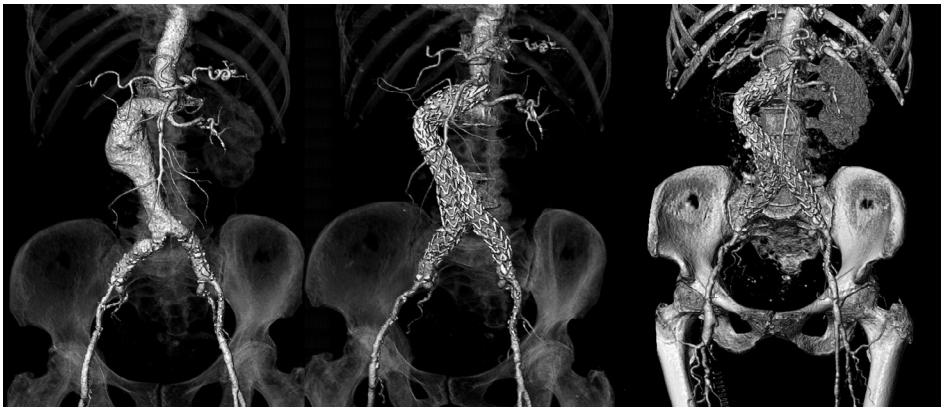


Figure 3. Evolution of proximal aneurysm neck angulation following endovascular aneurysm repair with the Endurant Stent Graft
Legend: left, baseline, middle 30-d imaging; right, 4-year follow-up.

DISCUSSION

The present study is the first to evaluate mid-term outcome and morphology changes of patients with severely angulated proximal neck treated with a late-generation

endograft. Despite concerns over implantation accuracy and durability after EVAR in angulated proximal aneurysm necks, our results suggest that EVAR with the Endurant Stent Graft in adequately selected patients with severe proximal neck angulation results in acceptable mid-term outcomes. In our study, secondary interventions were unexpectedly more frequent in the control group and were mostly performed owing to complications unrelated to the proximal neck (distal type 1 endoleaks, type 2 endoleaks, limb occlusion).

Altered blood flow patterns due to severe angulation proximal neck angulation have been found to increased drag forces on endografts, increasing the risk of graft migration.[11] Additionally, the inability of many devices to cope with severe neck angulation resulting in asymmetrical device deployment may render the endograft more susceptible to migration.[12] Consequently, neck angulation has been associated with an increased risk of adverse aneurysm-related events in the short and midterm.[13] Moreover, owing to these concerns, patients with severe proximal anatomy were excluded from several major trials and, consequently, outcomes in this particular subgroup have not been easily assessable. In a EUROSTAR-based report from Hobo et al. with a mean (SD) follow-up of 19.9 (17.9) months (n = 1,152), patients with severe proximal angulation were at increased risk of presenting a proximal type 1 endoleak (HR 1.80, 95% CI 1.25–2.58). [14]

Recent devices have been specially designed to broaden EVAR applicability particularly in more challenging proximal neck anatomies. Weale et al. reported their prospective experience with the use of the Aorfix (Lombard Medical, Didcot, UK),[15] a US Food and Drugs Administration-approved device for the treatment of patients with AAA with up to 90° angulated necks. In a group of 30 patients with a mean infrarenal angle of −81.2° [range 63°–110°], two (6.7%) cases of primary proximal type 1 endoleaks were found to persist at the 6-month follow-up, despite intraoperative ballooning of the proximal stent. The Anaconda AAA stent graft system (Vascutek, Terumo, Inchinnan, UK) has also claimed a role in the management of patients with AAA with angulated proximal anatomy. Rödel et al. reported recently on the 4-year outcomes of this device in a group of 36 patients with proximal neck angulation >60°.[16] Primary clinical success had been sustained in 25 (69%) patients. Two endograft occlusions were reported along with five limb occlusions, particularly, according to the authors, in the presence of increased neck angulation. Additionally, one patient presented a migration of the device with proximal type 1 endoleak. In a retrospective analysis of 519 patients treated with the Endologix graft (Endologix, Irvine, CA, USA), Qu et al. reported,[17] in a subgroup of 36 patients with neck angulation >60°, one (2.8%) secondary proximal type 1 endoleak during an overall mean follow-up of 2.6 years (range 4.0 months to 5.0 years). Nevertheless, 25 (69.0%) of these patients had required additional proximal cuffs or Palmaz stents during the primary intervention. In the sample in the present study, only one (2.2%) patient in the study group required an additional proximal extension intraoperatively.[4]

Morphological neck changes and proximal device fixation of the Endurant Stent Graft were evaluated in the sample presented herein. Barb detachment may result from the inability of the barb to follow the lesser aortic curvature in very angulated necks. In the current sample, patients with severe neck angulation presented a 3.7-fold increased risk of single barb detachment. However, multiple barb detachment was not identified and barb detachment did not increase over time. Moreover, this finding does not represent device failure, as significant migration was not identified among the present population.

Increased device oversizing has been used to ensure adequate proximal seal, particularly in situations prone to eccentric deployment, such as in the presence of severe proximal neck angulation, which was also identified among the present study group. However, other morphologic features also differentiated significantly the study group: neck length was shorter ($p = .05$; Table 1), aneurysms were larger ($p < .01$), and, as reported previously, patients in the study group presented a greater variability in neck conformation, assuming more frequently a noncylindrical form. [4] It is hypothesized that in patients with cylindrical proximal aneurysm necks, increased oversizing may not be warranted as unlike devices with columnar strength, the high conformability of the Endurant Stent Graft enables it to follow intimately the aneurysm neck curvature in severely angulated anatomy. EVAR has been found to induce dynamic morphologic remodeling of the neck, as reported by van Keulen et al, [17] particularly with the deployment of endografts with columnar strength. Hoshina et al found that in a group of 46 patients with proximal neck angulation >60°, [18] 41 (89.0%) presented significant and straightening immediately after endograft deployment. Moreover, the rate of further straightening during follow-up was graft-dependent. Statistically significant reductions were also identified in both suprarenal and infrarenal neck angles, which were more pronounced in the angulated group, despite the high flexibility of the device deployed. However, when comparing suprarenal and infrarenal angle variation on the last available CTA to the first postoperative one, the present data suggest that significant angle reduction occurred only immediately after device deployment and did not modify, as the Endurant Stent Graft remained adapted to the underlying anatomy. The authors hypothesize that the increased flexibility of this device, which leads to a more concentric deployment of the endograft and enduring conformation to an unstrained aortic neck in the mid-term, may result in decreased morphologic neck modification, which, in turn, may contribute to a decreased risk of neck dilatation, proximal type 1 endoleak, or device migration.

Noticeable limitations to the present study include its retrospective design, which is subject to selection and reporting bias, thus contributing to the significantly different mean follow-up time among groups. Nevertheless, all patients were treated in a consecutive fashion with the same endograft, followed prospectively, and life-table analysis was performed showing no difference in any of the endpoints. Additionally, case volume may limit the reproducibility of the findings at other centers. However, as all patients

received the same endograft, the conclusions may be clinically relevant to many centers where this device is currently available. Finally, the sample size may limit revealing of more subtle differences between groups. However, this report represents the largest study to date reporting on clinical outcomes following EVAR in patients with severe proximal neck angulation during a median follow-up of 4 years.

CONCLUSION

EVAR with the Endurant Stent Graft System is safe in patients with severe proximal neck angulation provided that a suitable proximal seal length is obtained. Mid-term outcome and freedom from neck-related secondary interventions were not influenced by the severity of proximal neck angulation. Aortic neck remodeling occurred more significantly in patients with adverse neck anatomy but angulation changes were not marked and did not modify significantly during follow-up, confirming the enduring ability of this device to conform to challenging anatomies over time.

CONFLICT OF INTEREST

J. M. de Vries, F.L. Moll, J.A. van Herwaaden, and H.J.M. Verhagen act as consultants for Medtronic. The other authors have no conflicts of interest to declare.

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Chapter 8

The influence of neck thrombus on clinical outcome and aneurysm morphology after endovascular aneurysm repair

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ABSTRACT

Objective

This study investigated the influence of significant aneurysm neck thrombus in clinical and morphologic outcomes after endovascular aneurysm repair (EVAR).

Methods

The patient population was derived from a prospective EVAR database from two university institutions in The Netherlands from 2004 to 2008. Patients with significant thrombus in the neck (>2 mm in thickness in at least >25% of circumference) were identified as the thrombus group and were compared with the remaining patients without neck thrombus (no-thrombus group), treated within the same period. The primary end point was clinical success. Secondary end points included technical success and rates of decline in renal function. Detailed morphologic analysis of the aortic neck was serially performed for the thrombus group patients to assess changes in thrombus volume.

Results

The study included 389 patients: 43 (39 men; mean age of 72.3 years) met the criteria for the thrombus group; of these, 31 (72%) had significant thrombus in >50% of the aortic neck circumference, and 8 (19%) had circumferential thrombus >2-mm thick. Median follow-up was 3.34 years (interquartile range, 2.67-4.72). The estimated 5-year clinical success rate was 74% for the thrombus group and 62% for the no-thrombus group (P = .23). Endograft migration was more frequent in the thrombus group (P = .02). Multivariable Cox regression analysis showed a significant association between migration and use of a device without active fixation (hazard ratio, 4.9; 95% confidence interval, 1.31-18.23; P = .018) but not with the presence of neck thrombus (P = .063). No differences were found in the rates of decline in estimated glomerular filtration rate at 30 days and during follow-up between the thrombus and no-thrombus groups. The thrombus volume in the first 10 mm of aortic neck was progressively reduced over time until it was not measurable in most patients, resulting in complete circular attachment of the endograft to the vessel wall.

Conclusions

Our findings suggest that the presence of aneurysm neck thrombus has no significant influence on short-term and midterm EVAR results.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is a valid alternative to open repair for abdominal aortic aneurysms (AAA), with advantages regarding perioperative morbidity and mortality.[1,2] However, several morphologic aneurysm characteristics limit its use, particularly at the level of the proximal aneurysm neck. This anatomic site is essential for the proper fixation and sealing of endovascular devices, and consequently, it is the most frequent constraint for EVAR.[3] Neck length, diameter, pulsatile distension,[4] angulation, and presence of calcification or thrombus have all been considered important determinants for outcome after EVAR.

In the presence of neck thrombus, most manufacturers advise against EVAR, mostly due to concerns regarding embolization to the renal arteries, migration, or proximal type Ia endoleaks. All major trials studying EVAR have excluded patients with significant neck thrombus, and consequently, its adverse influence is scarcely supported by evidence.[5] Of interest and against current opinion, two small studies have suggested that thrombus may not influence clinical outcome after EVAR.[6,7]

This study compared clinical success after EVAR in patients with and without significant neck thrombus and also analyzed the technical success, rates of change in renal function, and morphologic neck changes over time. Our hypothesis was that significant thrombus in the aneurysm neck would not significantly affect the outcome of AAA patients treated by EVAR.

METHODS

Study design

We performed a retrospective comparative study of EVAR patients with or without significant neck thrombus. This study used data from a prospectively kept joint database from two university hospitals (Erasmus University Medical Center, Rotterdam, and the University Medical Center, Utrecht) in The Netherlands.

Patient population

EVAR was used to treat 401 AAA patients in these two institutions from 2004 to 2008. From this group, 43 patients with significant neck thrombus (thrombus group) were selected by reviewing preoperative computed tomography angiography (CTA) images and identifying patients with thrombus lining the first 10 mm of aortic neck with a thickness >2 mm in >25% of the neck circumference in at least three consecutive 3-mm axial CTA slices. Patients without aortic aneurysms (ie, isolated iliac aneurysms) or patients with previous aortic surgery were excluded. The remaining 346 patients formed the

no-thrombus group. For homogeneity, patients treated with an endoprosthesis other than those used in the thrombus group were excluded (five with Lifepath [Edwards Life Sciences, Irvine, Calif], one with Powerlink [Endologix Inc, Irvine, Calif], and six with Anaconda [Vascutek, Terumo, Inchinnan, UK]).

The choice to treat patients with neck thrombus by EVAR was individualized and accounted for the patient's calculated open surgical risk, anatomic suitability for EVAR, and informed consent. According to the institutional protocol for patients with neck thrombus, sizing for endoprosthesis selection was performed adventitia-to-adventitia, oversizing was greater than generally recommended (20%-30%), and proximal graft ballooning was not performed unless required to resolve an intraoperative type Ia endoleak.

Image acquisition and postprocessing

CTA image acquisition was performed according to institutional protocols for EVAR using a 16-slice or 64-slice Brilliance CT scanner (Philips Medical Systems, Best, The Netherlands). Two expert observers (K.C., F.B.G.), blinded to patient data, performed all measurements. Preoperative, 30-day, and yearly postoperative CTAs were analyzed.

Aneurysm maximal transverse diameter and proximal neck diameter and length were measured using dedicated 3Mensio Vascular 4.2 software with center lumen line reconstruction (3Mensio Medical Imaging BV, Bilthoven, The Netherlands). Neck length was defined as the length from the lowermost renal artery to the first discernible level where the aortic diameter increases by 10%.[8] Aneurysm volume was calculated according to a previously published protocol.[9] All diameter measurements in the aneurysm neck were performed from adventitia to adventitia. Additional center lumen line–based measurements on postoperative CTAs were performed to assess the distance from the lowermost renal artery to the start of the first covered stent.

To objectively demonstrate changes in the neck thrombus over time, the volume of thrombus was measured by manually segmenting each axial CTA slice in the first 10 mm of proximal neck. A three-dimensional model of thrombus was created and the volume was computer-generated (Figure 1). Thrombus volume was serially measured in all preoperative and postoperative CTAs for patients in the thrombus group.

Definitions

Technical success was defined as successful access and deployment of the endoprosthesis, without need for conversion to open repair or the presence of type I or III endoleak, significant kinking, or obstruction of flow, and includes the first 24 hours after the procedure.

Clinical success was defined as successful deployment at the intended position, without death as a result of AAA treatment, postimplantation rupture, conversion to open repair, type I or III endoleak, device infection or thrombosis, migration, sac growth, or device integrity failure.

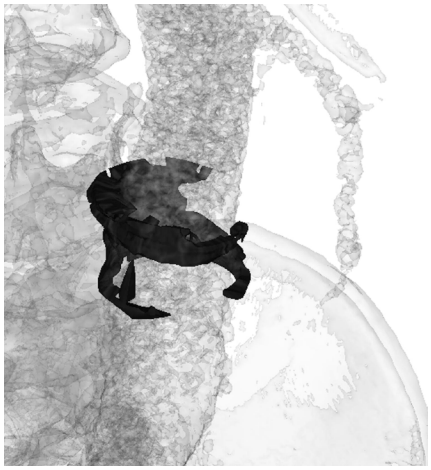

Figure 1. In this thrombus volume model, thrombus is manually segmented in all axial computed tomography angiography (CTA) slices within the first 10 mm of the aortic neck.

Migration was defined as downward displacement of the device by >10 mm, although a lower threshold of 5 mm was also considered separately. The position of the endograft at the first postoperative CTA, performed 24 to 48 hours after the index procedure, was used as baseline for migration measurements.

Sac growth was defined as a diameter increase >5 mm, although an increase in sac volume >5% was also considered separately.

Neck dilatation was defined if the difference between the preoperative and the postoperative neck diameter was >1 mm. All definitions are according to the reporting standards for EVAR.[10]

The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease formula.[11]

End points

The primary study end point was clinical success. In addition, technical success and individual criteria of clinical success were analyzed. Preoperative and postoperative (30-day) creatinine measurements were obtained for all patients, and changes in eGFR were tested. Serial creatinine measurements (at yearly follow-up visits) were only available for patients treated at Eramsus University Medical Center. The measurement obtained at the last follow-up visit was used, and the rates of change in eGFR were compared between groups.

Additional analysis performed exclusively in the thrombus group: Detailed descriptions of complications, secondary interventions, and causes of death were obtained. Changes in neck morphology were analyzed, including thrombus volume in the first 10 mm below the lowest renal artery.

Table 1 Baseline characteristics

Variable[a]	Thrombus (n = 43)	No thrombus (n = 346)	*P*
Age, years	72.3 ± 7.0	72.8 ± 7.6	.88
Male gender	39 (90.7)	313 (90.5)	>.99
ASA III or IV	25 (58.1)	172 (49.7)	.33
eGFR, mL/min/1.73 m^2	69.0 (54.4-81.6)	72.7 (25.0)	.34
Neck length, mm	34.0 (26-42)	30.5 (21-45)	.28
Neck diameter, mm	26.0 (24-28)	24.0 (23-26)	.004
AAA diameter, mm	60 (55-68)	60 (54-70)	.83
Neck thrombus, %			
25%-50%	12 (27.9)	…	…
50%-75%	23 (53.5)	…	…
>75%	8 (18.6)	…	…
Endograft used			
Excluder	11 (25.6)	145 (41.9)	.047
Talent	19 (44.2)	138 (39.1)	.62
Zenith	1 (2.3)	9 (2.5)	>.99
Endurant	12 (27.9)	54 (15.6)	.052

Legend*: AAA*, Abdominal aortic aneurysm; *ASA*, American Society of Anesthesiologists physical status classification; *eGFR*, estimated glomerular filtration rate. a) Continuous data are expressed as mean ± standard deviation or median (interquartile range) and dichotomous data as count (percentage).

Statistical methods

Normally distributed continuous variables were compared using the Student *t*-test or one-way analysis of variance tests, as applicable, and are presented as mean ± standard deviation. Nonparametric continuous variables were compared using Mann-Whitney or Kruskal-Wallis tests, as applicable, and are reported as median and interquartile range (IQR). Related samples were analyzed with paired Student *t*-tests or the Wilcoxon signed rank test, depending on their distribution. Dichotomous variables were compared between groups using Pearson χ^2 statistics and are presented as counts and percentages. Confidence intervals (CIs) for proportions were calculated using the Wilson procedure, correcting for continuity.[12]

Kaplan-Meier survival tables were used to estimate clinical success and freedom from migration. Equality between groups was assessed with the Mantel-Cox log-rank test. Cox-regression analysis was used to obtain the hazard ratio (HR) and 95% CI for variables associated with migration. All statistical tests were two-sided and considered statistically significant at $P < .05$. All analyses were performed using SPSS 19 software (SPSS Inc, Chicago, Ill).

Table 2. Clinical outcomes after endovascular aneurysm repair

	Thrombus		No thrombus		
Variable	No. (%)	95% CI[a]	No. (%)	95% CI[a]	*P*
Technical success	43 (100)	89.8-100	344 (99.4)	97.7-99.9	>.99
30-day death	2 (4.6)	0.8-17.0	16 (4.6)	2.7-7.5	>.99
Clinical success	32 (74.4)	58.5-85.9	258 (74.6)	69.6-79.0	>.99
Secondary intervention	5 (11.6)	4.3-25.9	70 (20.2)	16.2-24.9	.22
Conversion to open repair	0 (0)	0.0-10.2	13 (3.8)	2.1-6.5	.38
Sac growth	4 (9.3)	3.0-23.0	38 (11.0)	8.0-14.9	>.99
Migration	4 (9.3)	3.0-23.0	8 (2.3)	10.8-4.7	.033
Limb thrombosis	3 (7.0)	1.8-20.1	11 (3.2)	1.7-5.8	.19
Endograft infection	0 (0)	0.0-10.2	3 (0.9)	0.2-2.7	>.99
Postimplant rupture	1 (2.3)	0.1-13.8	3 (0.9)	0.2-2.7	.51
AAA-related death	3 (7.0)	0.02-0.20	19	0.03-0.09	.72

Legend: *AAA*, Abdominal aortic aneurysm; *CI*, confidence interval. a) The 95% CIs are presented for the proportions.

RESULTS

Patient characteristics

From 2004 to 2008, 396 patients were treated by EVAR using the following endoprostheses: Talent (Medtronic, Santa Rosa, Calif) in 157, Excluder (W. L. Gore and Associates, Flagstaff, Ariz) in 161, Zenith (Cook Medical Inc, Bloomington, Ind) in 10, and Endurant (Medtronic) in 68. Baseline characteristics of these patients are described in Table 1.

Technical success and 30-day mortality

Technical success was high and similar between groups (Table 2). One patient in the thrombus group required intraoperative placement of a transrenal giant Palmaz stent (Cordis, Miami Lakes, Fla) to resolve a type Ia endoleak. This patient had a reverse-tapered, 26-mm-long neck that was 24-mm to 28-mm in diameter, with circumferential thrombus, irregular calcified plaques, and no significant angulation. The selected endoprosthesis was a 28-mm Excluder, which was insufficiently oversized. The device was placed just below the lower-most renal artery but failed to achieve adequate seal. After transrenal stent placement, the endoleak was no longer visible. No further complications occurred during 5.8 years of follow-up.

One patient required placement of an intraoperative renal stent. This patient had a very long but wide (34-mm) neck with thrombus lining 50% to 75% of the circumference. A 36-mm Endurant endograft was selected. The implantation was uneventful, but the completion angiogram showed a slow-flow signal in the renal artery. The position of the radiopaque markers suggested that the graft was partially covering the renal ostium,

and a balloon-expandable stent was placed with success. No signs of renal embolization were present at the postoperative examinations, and no complications occurred during 2.6 years of follow-up.

Mortality at 30 days was similar in both groups, and no deaths occurred as a result of graft-related complications. Two deaths in the thrombus group occurred in acute patients. In the thrombus group, two polar renal infarctions were observed on the first postoperative CTA. This resulted in mild and transitory deterioration of renal function in one patient. In both cases, an accessory renal artery was intentionally covered to provide adequate seal, so these cannot be attributed to dislodgment of thrombus. There was no evidence of macroembolization of the renal arteries or its main branches.

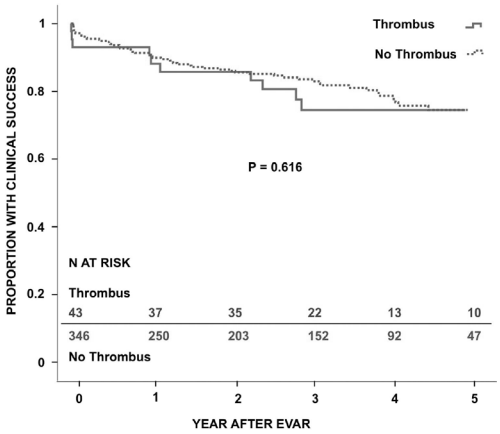

Figure 2. Kaplan-Meier curves show clinical success in the thrombus and no-thrombus group out to 5 years.
Legend: The standard error is <0.10 for the displayed curves. *EVAR*, Endovascular aneurysm repair.

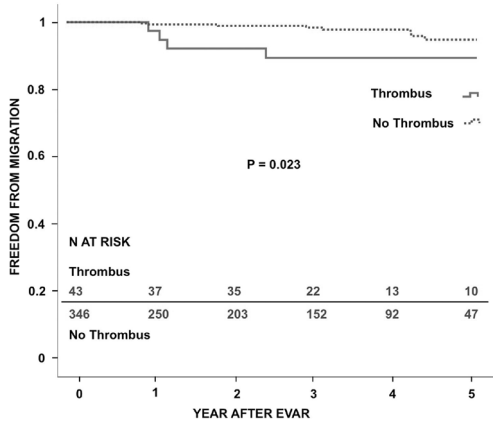

Figure 3. Kaplan-Meier curves show freedom from migration in the thrombus and no-thrombus group out to 5 years.
Legend: The standard error is <0.10 for the displayed curves. *EVAR*, Endovascular aneurysm repair.

Clinical success

Median follow-up was 3.34 years (IQR, 2.67-4.72 years) for the thrombus group and 3.10 years (IQR, 1.9-4.7 years) for the no-thrombus group ($P = .11$). The estimated 5-year clinical success rate was 74% for the thrombus group and 61% for the no-thrombus group, without a statistically significant difference (Figure 2).

Outcomes of the individual components of clinical success were tested for differences and are reported in Table 2. Significance was only found for migration (Figure 3). The 5-year rate of freedom from migration was estimated at 89.6% for the thrombus group and 95.0% for the no-thrombus group. Univariable Cox regression analysis showed the presence of neck thrombus was associated with a stent migration (HR, 3.6; 95% CI, 1.11-12.25; $P = .033$). However, this association became nonsignificant after correcting for the type of graft ($P = .063$). In contrast, a significant association with migration was observed for the use of a device without active fixation (HR, 4.9; 95% CI, 1.31-18.23; $P = .018$; Table 3). No significant differences between groups were found in secondary intervention, sac growth, or need for conversion to open repair (Table 4).

One patient in the thrombus group died with abdominal pain and hypotension 2.4 years after EVAR, suggesting rupture as a probable cause. This was an 86-year-old patient with a preoperative AAA diameter of 62 mm, neck length of 35 mm, and neck diameter of 26 mm. Thrombus covered less than half of the neck circumference. The patient had prohibitive open surgical risk and was treated endovascularly using a Talent 32-mm endoprosthesis. The implantation was uneventful, but migration (11 mm) was noted at the 2-year CTA. No endoleak or increase in sac diameter was detected. Retrospectively, sac volume analysis revealed an increase in volume by 7%. By the time migration was diagnosed, the patient's general and mental condition had worsened and was considered

Table 3. Multivariate Cox regression for variables associated with migration

Variable	HR (95% CI)	*P*
Neck thrombus	3.1 (0.94-10.50)	.063
Endograft with no active fixation	4.9 (1.31-18.23)	.018

Legend: *CI*, Confidence interval; *HR*, hazard ratio.

Table 4. Estimates for secondary intervention, sac growth, and conversion to open repair at 3 and 5 years[a]

	3-year estimate			5-year estimate		
Variable	Thrombus	No thrombus	*P* [b]	Thrombus	No thrombus	*P* [b]
Secondary intervention	0.10	0.17	.26	0.10	0.28	.09
Sac growth	0.12	0.08	.75	0.12	0.21	.56
Conversion to open repair	0.00	0.03	.29	0.00	0.05	.22

Legend: a) Estimates were derived from Kaplan-Meier survival tables. Standard error was <5% in all cases. b) Obtained through the Mantel-Cox log-rank test.

a poor candidate for any secondary intervention. Unfortunately, the postimplantation rupture could not be objectively confirmed because no CTA was performed at the time of symptoms nor was an autopsy requested.

During follow-up, only one type I endoleak was found in the thrombus group, and that was a distal endoleak treated successfully by implantation of an extension limb. Causes of death, secondary complications, and secondary interventions in the thrombus group are detailed in Table 5.

Renal function after EVAR

The rates of change in the eGFR at 30 days and at the last follow-up are presented in Figure 4. The graphic distribution of patients in the thrombus and no-thrombus groups

Table 5. Detailed clinical outcomes after endovascular aneurysm repair for the thrombus group

Outcome	No. (%)	95% CI[a]
Death ≤30 days		
Myocardial infarction	1 (2.3)	0.1-13.8
Bowel ischemia	1 (2.3)	0.1-13.8
Death >30 days		
Myocardial infarction	2 (4.6)	0.8-17.0
Stroke	1 (2.3)	0.1-13.8
Respiratory sepsis	1 (2.3)	0.1-13.8
Gastrointestinal malignancy	1 (2.3)	0.1-13.8
Postimplant rupture	1 (2.3)	0.1-13.8
Secondary complications		
Type I/III endoleak	1 (2.3)	0.1-13.8
Migration >10 mm	4 (9.3)	3.0-23.0
Migration >5 mm	8 (18.6)	8.9-33.9
Sac growth		
>5 mm in diameter	3 (7.0)	18.2-20.1
>5% in volume	8 (18.6)	8.9-33.9
Neck dilatation >5%	2 (4.6)	0.8-17.0
Limb thrombosis	3 (7.0)	18.2-20.1
Conversion to aortouniiliac	1 (2.3)	0.1-13.8
Secondary interventions		
Limb extension	1 (2.3)	0.1-13.8
Thrombectomy + PTA	2 (4.6)	0.8-17.0
Femorofemoral crossover	1 (2.3)	0.1-13.8
Axillobifemoral bypass	1 (2.3)	0.1-13.8

Legend: *CI*, Confidence intervals; *PTA*, percutaneous transluminal angioplasty. a) 95% CIs are provided for the proportions.

was similar. At 30 days, the changes in eGFR were −2.62 ± 8.03 mL/min/1.73 m^2 for the thrombus group and −3.36 ± 15.17 mL/min/1.73 m^2 for the no-thrombus group (*P* = .77). At the last follow-up visit, the changes were −7.71 ± 18.04 mL/min/1.73 m^2 for the thrombus group and −3.73 ± 21.21 mL/min/1.73 m^2 for the no-thrombus groups, respectively (*P* = .39). No patients in the thrombus group progressed to end-stage renal disease or required dialysis in the perioperative period or during follow-up.

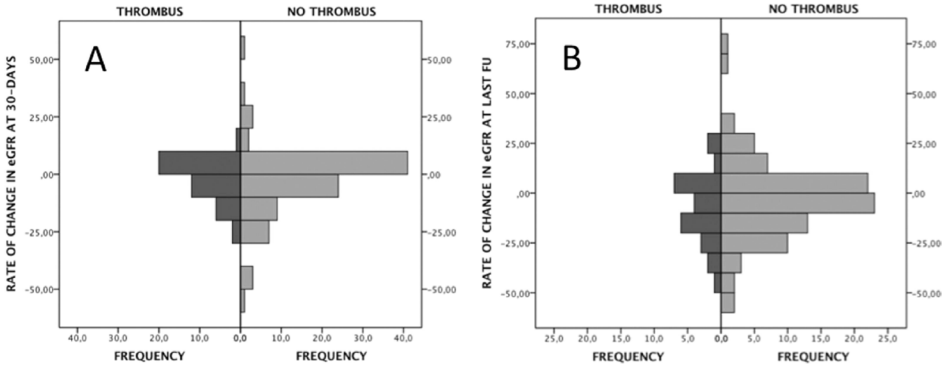

Figure 4. A, Rate of change is shown in estimated glomerular filtration rate (*eGFR;* mL/min/1.73 m^2) ≤30 days of surgery. B, Rate of change in eGFR is shown at the last follow-up visit for patients from one institution only (Erasmus University Medical Center, Rotterdam, The Netherlands).

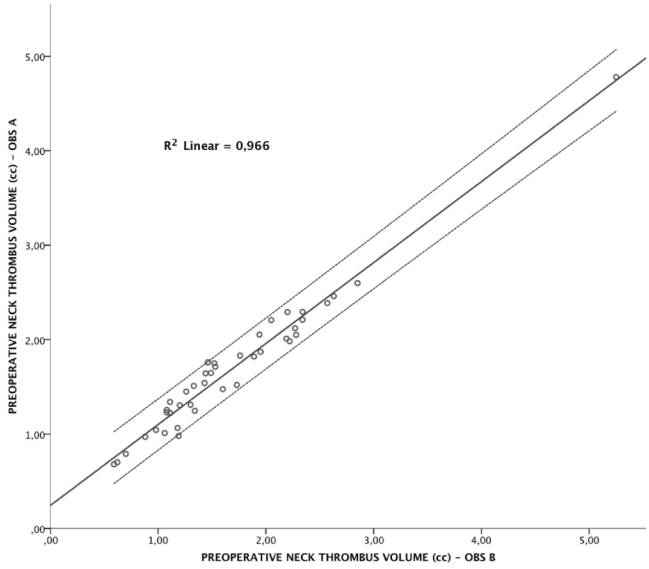

Figure 5. Intraobserver variability is shown for thrombus volume in the first 10 mm of aortic neck. Legend: The *outside lines* represent the 95% confidence interval.

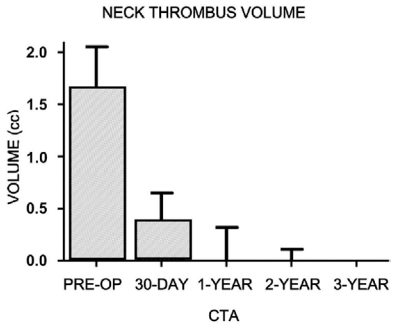

Figure 6. Neck thrombus volume is shown in the first 10 mm of aortic neck.
Legend: The *bars* represent the mean volume, and the *error bars* show the standard deviation. *CTA*, Computed tomography angiography.

Morphologic neck changes in the thrombus group

For validation of thrombus volume measurements, intraobserver variability was tested on all preoperative examinations, with good agreement between observations (Figure 5). Mean thrombus volume in the neck was 1.61 ± 0.51 cm^3 preoperatively and 0.20 ± 0.31 cm^3 at 1 year. This was a mean reduction of 1.40 ± 0.09 cm^3 ($P < .001$). All patients demonstrated significant decrease in neck thrombus volume over time: 23 of 41 (63.4%) had unquantifiable volume of thrombus in the last CTA, and only 11 (27%) had volumes >0.3 cm^3 (Figure 6).

Dilatation of the infrarenal neck was common in the thrombus group, occurring in 23 of 43 patients (53.4%). The mean increase in diameter was 2.1 ± 1.89 mm during the follow-up. No correlation was found between neck dilatation and the quantity of thrombus in the neck or with migration. Dilatation was only observed up to the main-body diameter of the originally implanted endograft.

DISCUSSION

Current opinion associates thrombus in the proximal AAA neck with greater risk of proximal type I endoleak, endotension, stent graft migration, and renal embolic complications, thus considering it a relative contraindication for EVAR.[6] However, no concrete scientific evidence to date supports this concept: it is essentially based on concerns expressed by experts and manufacturers. In this study, we could not find any significant differences in outcome in patients with or without neck thrombus nor could we identify any clinical, imaging, or laboratory adverse effect resulting from the presence of neck thrombus at the time of implantation.

The optimal method to quantify neck thrombus remains a matter of debate. Most clinical studies have used percentages of thrombus-covered neck diameter for cat-

egorization.[3,6,13,14,15,16] This method is not ideal, because it is fairly subjective and does not account for the thickness of thrombus nor for its longitudinal extent. However, the method is acceptable for a broad selection of patients. We chose to select patients in this manner, making our results comparable to most of the existing literature. Alternative quantitative methods, such as the volumetric technique proposed by Wyss et al,[17] are less suitable for patient selection because they provide an overall quantification of the proportion of thrombus in the neck but say nothing about the thickness at a particular location or circumferential involvement.

The presence of thrombus did not influence the technical success after EVAR. Successful deployment was achieved in all patients, and there was no evidence of renal or peripheral embolization after implantation. Indirect evidence of embolization, by means of a postoperative decline in eGFR, was also absent, as discussed subsequently. However, another publication reported one renal infarction in 19 EVAR patients with neck thrombus.[6] Our policy regarding implantation is that proximal ballooning should not be performed when using current (self-expandable) endoprostheses, unless strictly necessary. Although we have no data to support this policy, it may explain why no renal embolization occurred in our series of 45 patients. We also note that open repair in these patients is also potentially hazardous because clamp placement might fracture and dislodge thrombus and suprarenal clamping adds complexity and risk to the procedure.

Endograft migration was frequent in the thrombus group, especially when considering the lower threshold of 5 mm. Unfortunately, only migration >10 mm was available for the no-thrombus group and comparison is restricted to this definition. Despite the more frequent occurrence of migration in the thrombus group, multivariable correction for graft type resulted in a nonsignificant association. However, using an endograft without active fixation increased the risk of migration by more than fourfold. Endografts without active fixation (ie, Talent) are more prone to migrate, as previously demonstrated.[18] The presence of thrombus may facilitate migration when radial force is the sole means of fixation. Although we cannot provide or find any robust data in the literature to support it, we currently select devices with suprarenal active fixation when neck thrombus is present and have not observed any migration in these patients.

A recent publication reported the influence of neck thrombus (among other neck characteristics) on the occurrence of graft-related complications after EVAR.[17] In accordance with our study, they found no detrimental effect of neck thrombus to adverse events during follow-up. In fact, their results suggested a protective role, which is most likely due to confounders, as the authors appropriately acknowledge. Their study used data from the EVAR trials, and therefore, all patients had favorable anatomy, including little neck thrombus, which makes these results less comparable to ours. In an older study in which homemade devices were used in 19 AAA patients with aortic neck thrombus, no serious adverse events were detected after a mean follow-up of 23 months.[6]

In the thrombus group, one rupture occurred after implantation. This patient was known to have a migrated endograft, which emphasizes the importance of secondary intervention to maintain success in the face of this complication. Despite this event, the postimplantation rupture rates in both groups were similar and compared favorably with the crude annual rupture risk of 0.7% recently reported from the EVAR studies.[18] No other AAA-related deaths or conversions to open repair were registered, and although the sample was small, it compares to the findings of larger randomized and observational studies.[2,19,20,21] The median neck length of the thrombus group was, however, greater than generally observed in EVAR series, and that may explain why our higher migration rate did not result in a greater number of adverse clinical events.

As mentioned, the percentage of thrombus-lined neck circumference is a relatively crude and subjective means of quantifying the actual thrombus present. Stent implantation may compress thrombus and extend it radially on the aortic wall, which could erroneously lead to the conclusion that thrombus is increased after implantation. We chose to manually segment the thrombus in the first 10 mm of aortic neck to demonstrate changes in volume after implantation. Because endograft placement was not accurately below the lowest renal artery in all patients, the results may still be somewhat artificial. Another possibility is that thrombus was "redistributed" to a larger area outside the measured segment after implantation. Despite these limitations, it is clear that the entire circumference of the stent graft becomes more closely attached to the vessel wall as time elapses (Figure 7). This may be the result of radial forces imposed by the self-expanding implanted material and vessel pulsatility. The measurable volume of thrombus in the aneurysm neck decreased significantly over time in all patients, and complete graft apposition to the vessel wall was achieved.

Neck dilatation was observed in more than half of our patients. Although this occurs commonly in EVAR patients, the proportion in the thrombus group was higher than expected. There may be three explanations for this:

- Neck diameters in the thrombus group were unusually large, which have been demonstrated to dilate more than small necks.[22]
- Because a threshold of >1 mm was used, this is proportionally less significant in a large vs a small neck diameter.
- Our policy on oversizing for patients with neck thrombus may result in greater dilatation up to the diameter of the endoprosthesis, as demonstrated previously.[23,24]

Despite this observation, the maximal neck diameter did not surpass the proximal diameter of the implanted endoprosthesis, and therefore, seal was uncompromised in all affected patients.

Decline of renal function after EVAR may have devastating consequences for the quality of life after treatment, especially when dialysis is necessary.[25] A possible cause for this complication is manipulation with wires and sheaths and deployment or ballooning,

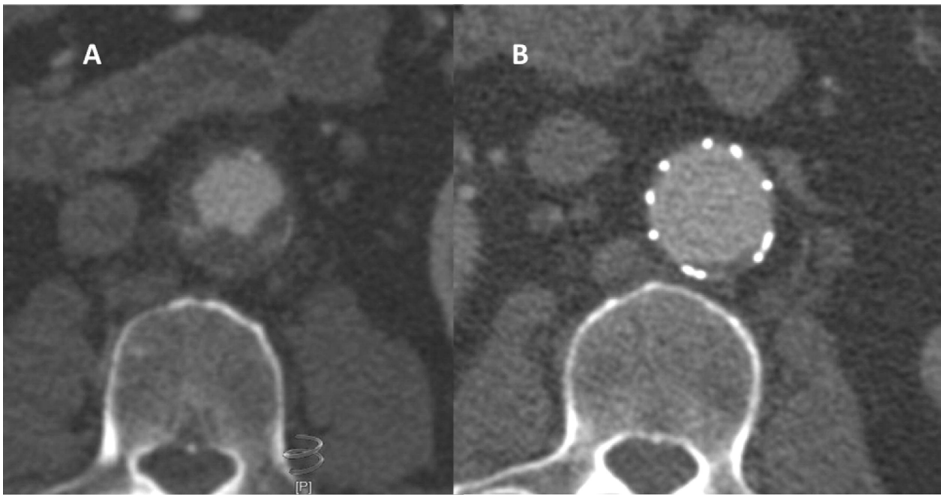

Figure 7. A, A preoperative computed tomography angiography (CTA) shows thick, circular thrombus of the aortic neck. **B,** At 1 year after endograft implantation, the pre-existing thrombus can no longer be identified. The endograft circumference is in contact with the full diameter of the aortic neck. A thin layer of in-graft thrombus can be identified.

which may dislodge thrombus to the renal arteries. Contrast nephropathy, fixation of the endoprosthesis, and other unrelated causes could also contribute significantly. Although there was no evidence of macroembolization, smaller particles could also cause serious glomerular dysfunction. We were not able to demonstrate, however, any difference in the early and late rates of decline in eGFR when comparing with patients without neck thrombus. More important, the amount of thrombus or percentage of the aortic circumference with thrombus did not correlate to the decline in renal function.

Degradation of renal function after EVAR was also reported by Greenberg et al,[26] who found a continuous decline in eGFR over the first year up to a maximum of 7.5% from baseline. Although neck thrombus was not quantified in that study, the presence of significant or circular thrombus in the neck was an exclusion criterion.[26] Similarly, Alsac et al[27] reported a 10% decline in eGFR 1 year after EVAR, also in patients without significant neck thrombus, a finding similar to ours. These rates of decline in eGFR are superior to those reported in a large substudy of the UK-EVAR trials investigating renal function after aneurysm repair. However, these were mainly derived from the EVAR-1 trial and, therefore, a "healthier" cohort.

Some limitations of this study warrant mentioning. First, treatment allocation was individualized, without a previously defined formal inclusion or exclusion criteria. The retrospective nature of this study, although based on a prospectively kept database, is subject to bias. Furthermore, we do not have data on patients with similar anatomic characteristics treated by open repair. In addition, the sample size is relatively small,

despite being the largest published series on patients with aortic neck thrombus. Also, the population on which the study is based comprised a large majority of northern European white subjects, perhaps not representative of other ethnic groups.

The significant number of missing values for eGFR at 1 year may result in a significant bias. Although selection was not random, it is a result of differences in follow-up schemes between institutions. Even so, the renal function outcomes during follow-up should be analyzed with precaution. Lastly, bias in referral of patients and the institutional expertise with EVAR may have weighted the results.

CONCLUSIONS

The present study demonstrates similar midterm clinical success for patients with and without neck thrombus treated by EVAR. In patients with (severe) neck thrombus, technical success was 100%, without any clinical, laboratory, or imaging evidence of renal or peripheral embolization. Over time, graft apposition to the neck wall is improved, with progressive reduction in thrombus volume over the first 10 mm of neck. A comparison with patients without neck thrombus found no differences in postoperative or late renal function. Our results suggest that with careful planning and execution, EVAR in patients with neck thrombus can result in outcomes within those expected for a general EVAR-treated population.

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Chapter 9

Familial abdominal aortic aneurysm is associated with more complications after endovascular aneurysm repair

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ABSTRACT

Objective

A familial predisposition to abdominal aortic aneurysms (AAAs) is present in approximately one-fifth of patients. Nevertheless, the clinical implications of a positive family history are not known. We investigated the risk of aneurysm-related complications after endovascular aneurysm repair (EVAR) for patients with and without a positive family history of AAA.

Methods

Patients treated with EVAR for intact AAAs in the Erasmus University Medical Center between 2000 and 2012 were included in the study. Family history was obtained by written questionnaire. Familial AAA (fAAA) was defined as patients having at least one first-degree relative affected with aortic aneurysm. The remaining patients were considered sporadic AAA. Cardiovascular risk factors, aneurysm morphology (aneurysm neck, aneurysm sac, and iliac measurements), and follow-up were obtained prospectively. The primary end point was complications after EVAR, a composite of endoleaks, need for secondary interventions, aneurysm sac growth, acute limb ischemia, and postimplantation rupture. Secondary end points were specific components of the primary end point (presence of endoleak, need for secondary intervention, and aneurysm sac growth), aneurysm neck growth, and overall survival. Kaplan-Meier estimates for the primary end point were calculated and compared using log-rank (Mantel-Cox) test of equality. A Cox-regression model was used to calculate the independent risk of complications associated with fAAA.

Results

A total of 255 patients were included in the study (88.6% men; age 72 ± 7 years, median follow-up 3.3 years; interquartile range, 2.2-6.1). A total of 51 patients (20.0%) were classified as fAAA. Patients with fAAA were younger (69 vs 72 years; $P = .015$) and were less likely to have ever smoked (58.8% vs 73.5%; $P = .039$). Preoperative aneurysm morphology was similar in both groups. Patients with fAAA had significantly more complications after EVAR (35.3% vs 19.1%; $P = .013$), with a twofold increased risk (adjusted hazard ratio, 2.1; 95% confidence interval, 1.2-3.7). Secondary interventions (39.2% vs 20.1%; $P = .004$) and aneurysm sac growth (20.8% vs 9.5%; $P = .030$) were the most important elements accounting for the difference. Furthermore, a trend toward more type I endoleaks during follow-up was observed (15.6% vs 7.4%; $P = .063$) and no difference in overall survival.

Conclusions

The current study shows that patients with a familial form of AAA develop more aneurysm-related complications after EVAR, despite similar AAA morphology at baseline. These findings suggest that patients with fAAA form a specific subpopulation and create awareness for a possible increase in the risk of complications after EVAR.

INTRODUCTION

Approximately 20% of the abdominal aortic aneurysm (AAA) patients have a positive family history for aneurysms, with a prevalence ranging largely from 6% to 35%, depending on ethnicity and method of data collection.[1,2,3,4] This suggests that in these families there is a genetic predisposition to AAA and that patients can be classified as familial AAA (fAAA), whereas patients without a clear inherited risk can be classified as sporadic AAA (spAAA). Despite the apparent familial tendency toward AAA formation and results from some genetic studies, the exact underlying genetic defects and their contribution to the development, growth, and severity of complications are unknown.[5] The molecular and clinical well-delineated genetic aortic aneurysm syndromes, including Marfan, Loeys-Dietz, the vascular Ehlers-Danlos syndrome, and defects in the smooth muscle cell genes *MYH11* and *ACTA2*, are mostly associated with thoracic aortic aneurysms, but occasionally AAA may be observed in the affected families.[6,7,8,9,10] Like in most known syndromes, in AAA, there are recognized defects both in the connective tissue components and in cellular elements affecting all layers of the aortic wall.[5]

In the last decade, endovascular aneurysm repair (EVAR) has proven to be a valid treatment modality for AAA and the majority of elective patients are now treated endovascularly.[11] Generally, endovascular repair in patients with known genetic aortic aneurysm syndromes is not advised, since patients have a higher chance of complications.[12,13] At present, little is known on clinical outcome after EVAR for patients with an inherited risk for AAA, and no data on aneurysm morphology of this particular group are available to date. One may hypothesize that AAA patients with a positive family history may develop more seal and fixation problems, and also postimplantation sac growth because of inherited aortic wall defects. Furthermore, differences in aneurysm morphology for fAAA patients, if present, could also influence outcome. In the present study, we evaluated aneurysm-related complications after EVAR for patients with fAAA and spAAA and explored possible differences in aneurysm morphology in these groups.

METHODS

The study population was derived from a prospective database including all EVAR procedures performed at the Erasmus University Medical Center in Rotterdam, The Netherlands. From January 2000 until March 2012, 473 patients were treated with EVAR at our institution. Exclusion criteria for this study were isolated iliac artery aneurysm, traumatic aneurysm, anastomotic aneurysm, infectious aneurysm, and ruptured aneurysm. Between 2009 and 2012, all AAA patients at our institution were contacted when visiting the outpatient clinic or by mail and asked to fill out a semistructured questionnaire to collect personal data and family histories. Patients who did not respond after one reminder were contacted and interviewed by telephone (K.V.). In families with multiple AAA patients, only one index patient (ie, first family member diagnosed with AAA) was included in the study. Patients previously diagnosed with a genetic aortic aneurysm syndrome (eg, Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndrome) were excluded, but no specific genetic testing was routinely performed. A flow diagram of patient inclusion is presented in Figure 1. The study complied with the declaration of Helsinki and was approved by the Institutional Review Board.

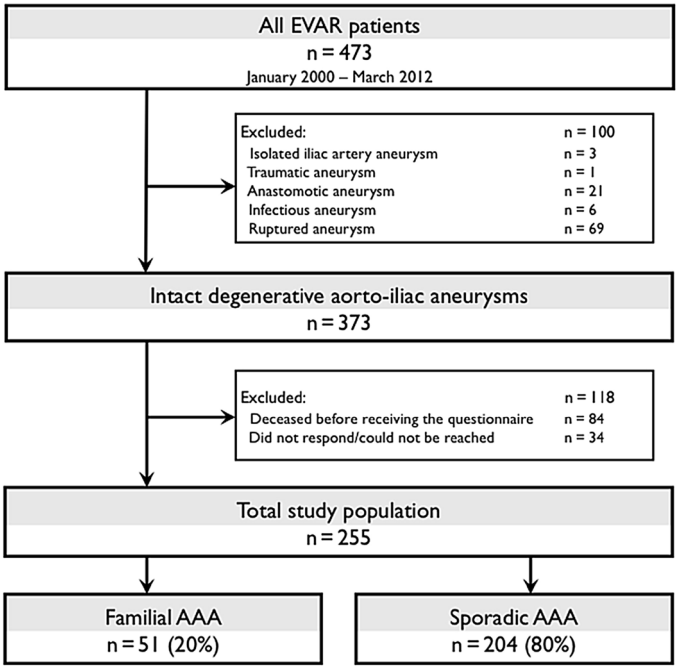


Figure 1. Flow diagram of patient inclusion.
Legend: *AAA,* Abdominal aortic aneurysm; *EVAR,* endovascular aneurysm repair.

Questionnaire and classification of familial AAA

The questionnaire requested information on demographics and the medical history of the index patient. Furthermore, structured questions were included on the occurrence of aortic aneurysms and cardiovascular disease for all known relatives of the index patient. Patients were classified as fAAA when at least one first-degree relative (parents, siblings, or children) was reported to have an aortic aneurysm.[1] Patients who did not report a first-degree relative affected with AAA were classified as spAAA. Patients reporting only second- or third-degree relatives were also classified as spAAA because the reporting of medical information of second- or third-degree relatives was considered less reliable.

Image processing

All patients were preoperatively assessed using computed tomography angiography (CTA) and entered the institutional surveillance protocol that included an early post-operative CTA (typically before hospital discharge), a CTA at 6 months and 1 year, and then CTA scans yearly after. Since 2007, the 6-month examination has been waived, and CTA surveillance replaced by duplex ultrasound (DUS) examinations in selected patients considered a lower risk according to the treating physician's experience in concurrence with Clinical Practice Guidelines of the European society for Vascular Surgery. Also, DUS examinations or noncontrast CT scans were performed as an alternative to CTA in patients with impaired renal function.

CTA was performed according to standardized institutional protocols. Morphologic analyses and measurements were performed using dedicated software with center lumen line (CLL) reconstruction (3Mensio, Vascular 4.2 software; 3Mensio Medical Imaging BV, Bilthoven, The Netherlands). CLLs were semiautomatically constructed and followed the center of the aortic and iliac permeable lumen.

The preoperative, early (<30 days) postoperative, and last follow-up CTA scans were analyzed in all patients. In patients with complications after EVAR, all CTA scans were analyzed.

Interobserver variability was previously assessed and agreement was high for AAA diameter (*R2* linear = 0.996), neck length (*R2* linear = 0.991), and neck diameter (*R2* linear = 0.935).[14]

Definitions

Aneurysm related definitions used in the study were derived from the reported standards for EVAR and/or were previously described.[11,14,15,16,17] Briefly, aneurysm and neck diameters were determined after CLL reconstructions. Aneurysm neck length was defined as the length of the lowermost renal artery to the level where the aortic diameter increases with at least 10%. Aneurysm angulation (suprarenal and infrarenal) were defined after CLL reconstruction. Aneurysm neck thrombus and calcification were defined as having

more than 25% of the cross-sectional area of the neck being affected. Iliac stenosis was defined as having at least one focal stenosis in the one of the iliac arteries. Iliac tortuosity was defined as absent, minor, or major by one experienced observer (F.B.G.) using three-dimensional reconstruction. Iliac aneurysm was defined as having an iliac diameter over 3 cm measured after CLL reconstructions. Aneurysm sac behavior and proximal neck dilatation during follow-up were calculated for patients with at least two suitable imaging surveillance exams. Aneurysm neck growth was defined as an increase of ≥2 mm between the maximum neck diameter at first postoperative and last available CTA scan during follow-up. Aneurysm sac growth was defined as an increase of in diameter ≥5 mm and aneurysm sac shrinkage as a decrease in diameter ≥5 mm between the maximal aneurysm diameter at first postoperative and last available imaging (ie, two available CTA scans or two available DUS examinations) during follow-up.

End points

The primary study end point was freedom from complications after EVAR. Complications after EVAR was defined as a composite of one of the following: endoleak during follow-up (ie, type Ia, type Ib, type III, or undetermined type endoleaks on postoperative examinations), secondary intervention (ie, proximal stent/cuff, limb extension, coil/glue embolization, open ligation of collaterals, conversion to aorto-uni-iliac device, conversion to open repair and relining), aneurysm sac growth, acute limb ischemia, or postimplantation aneurysm rupture. Type II endoleak was not included as a complication after EVAR because we consider intervention for type II endoleak only when in combination with aneurysm sac growth, which is included as complication after EVAR.[11] In case the primary end point was met by multiple criteria, the date of the first event was considered for the purpose of survival analysis.

The secondary end points were individual components of the primary end point (endoleak during follow-up, secondary interventions, and aneurysm sac growth), aneurysm neck growth, and overall survival after EVAR.

Clinical characteristics

The medical histories of the patients were obtained from medical files. The demographic characteristics included sex and age. The cardiovascular comorbidities included ischemic heart disease (history of myocardial infarction, coronary revascularization, or pathologic Q-waves on the electrocardiogram), cerebrovascular disease (history of ischemic/hemorrhagic stroke or transient ischemic attack), and cardiac arrhythmia. The cardiovascular risk factors included kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), diabetes mellitus (fasting plasma glucose ≥7.0 mmol/L, nonfasting glucose ≥11.1 mmol/L, or use of antidiabetic medication), hypertension (blood pressure ≥140/90 mm Hg in nondiabetics, ≥130/80 mmHg in diabetics, or use of antihypertensive

medication), and chronic obstructive pulmonary disease (history of chronic obstructive pulmonary disease or stage ≥1 according to the Global Initiative for Chronic Obstructive Lung Disease classification). Smoking status was obtained and included current smoking and ever smoking (ie, patients who are currently smoking OR patients with a history of smoking). Prescription medications were recorded and included the use of statins, beta-blockers, antiplatelets, and anticoagulant therapy.

Statistical analysis

Dichotomous data are described as counts and percentages. Continuous variables are described as mean (standard deviation) or median with interquartile range (IQR) when not normally distributed. Categorical data were analyzed with χ^2 tests and continuous variables with analysis of variance or Kruskal-Wallis tests, as appropriate. A multivariable Cox regression was used to assess the hazard ratio (HR), along with the 95% confidence interval, for complications after EVAR between fAAA and spAAA. Variables entered into the multivariate Cox regression model were selected on basis of univariable significant differences at baseline between fAAA and spAAA (ie, age and ever smoking). Kaplan-

Table 1. Clinical characteristics at baseline

Variable[a]	Familial AAA (n = 51)	Sporadic AAA (n = 204)	*P* value
Male sex	44 (86.3)	182 (89.2)	.554
Age at diagnosis, years	69.3 ± 8.1	72.1 ± 7.1	.015
Age ≤65 years at diagnosis	14 (27.5)	31 (15.2)	.040
Cardiovascular comorbidities			
Ischemic heart disease	20 (39.2)	72 (35.3)	.619
Cerebrovascular disease	6 (11.8)	25 (12.3)	.905
Cardiac arrhythmia	7 (13.7)	17 (8.3)	.243
Cardiovascular risk factors			
Kidney disease	8 (15.7)	51 (25.0)	.186
Diabetes mellitus	10 (19.6)	39 (19.1)	.961
Hypertension	31 (60.8)	138 (67.6)	.285
COPD	18 (35.3)	83 (40.7)	.435
Smoking – current	17 (33.3)	81 (39.7)	.403
Smoking – ever	30 (58.8)	150 (73.5)	.039
Medication			
Statins	40 (78.4)	148 (72.5)	.393
Beta-blockers	42 (82.4)	152 (74.5)	.240
Antiplatelets	43 (84.3)	150 (73.5)	.108
Anticoagulants	5 (9.8)	27 (13.2)	.508

Legend: *COPD,* Chronic obstructive pulmonary disease. a) Continuous data are presented as the mean ± standard deviation and categorical data as number (%).

Meier estimates were calculated for freedom from complications after EVAR. Estimates for fAAA and spAAA were compared using log-rank (Mantel-Cox) test of equality. To assess a possible selection bias, we tested for differences in complications after EVAR, for included and excluded patients of the complete EVAR database, using χ^2 tests. For all tests, a *P* value <.05 (two-sided) was considered significant. All analyses were performed using IBM SPSS Statistics v. 20.0 (SPSS Inc, Chicago, Ill).

RESULTS

A total of 373 patients were treated with EVAR for intact degenerative aorto-iliac aneurysms (Figure 1). Since 84 patients died before receiving the questionnaire and 34 patients did not respond to the questionnaire and could not be reached, the total study population consisted of 255 patients. No patients were identified with a genetic aortic aneurysm syndrome. The mean age of the population was 71.5 (±7.4) years and 226 patients (88.6%) were of male sex.

Clinical characteristics and aneurysm morphology at baseline

Of the 255 included patients, 51 (20.0%) had at least one affected first-degree relative and were classified as fAAA. The remaining 204 patients (80.0%) had no affected first-degree relative and were classified as spAAA. All clinical characteristics at baseline are presented in Table 1. Patients with fAAA were younger compared with spAAA patients (69 vs 72 years; *P* = .015) and were less likely to have ever smoked (58.8% vs 73.5%;

Table 2. Aneurysm morphology at baseline

Variable[a,b]	Familial AAA (n = 51)	Sporadic AAA (n = 204)	*P* value
Neck diameter, mm	26.2 ± 4.2	25.4 ± 3.5	.194
Neck length, mm	31.2 ± 17.5	31.5 ± 13.9	.982
AAA diameter, mm	61.6 ± 12.8	60.3 ± 13.3	.533
Aneurysm angulation			
Suprarenal, degrees of angulation	22.3 ± 17.7	24.0 ± 18.1	.723
Infrarenal, degrees of angulation	37.5 ± 20.3	40.6 ± 24.8	.415
Neck thrombus	14 (27.5)	70 (34.3)	.263
Neck calcification	11 (21.6)	50 (24.5)	.558
Iliac stenosis	8 (15.7)	38 (18.6)	.553
Iliac tortuosity	28 (54.9)	110 (53.9)	.985
Iliac aneurysms	15 (29.4)	65 (31.9)	.736

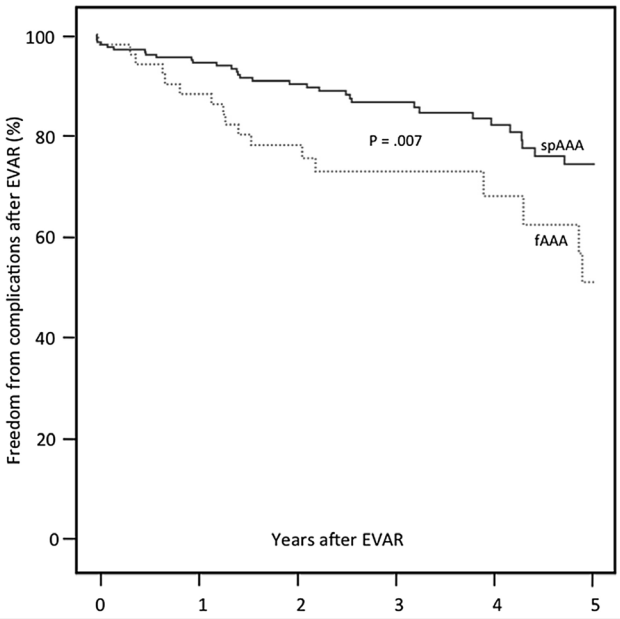
Legend: *AAA,* Abdominal aortic aneurysm; *CTA,* computed tomography angiography. a) Continuous data are presented as the mean ± standard deviation and categorical data as number (%). b) Preoperative CTA scans were available for 242 patients.

P = .039). There were no differences in aneurysm morphology between the two groups (Table 2). Preoperative neck and aneurysm diameter were similar, as well as the presence of iliac stenosis, iliac tortuosity, and iliac aneurysms.

Complications after EVAR

The median duration of follow-up was similar for fAAA and spAAA patients (3.9 years [IQR, 2.4-6.9] and 3.3 years [IQR, 2.1-5.5]; *P* = .163). During this period, a total of 57 patients (22.4%) had complications after EVAR; 18 fAAA patients and 39 spAAA patients (35.3% vs 19.1%; *P* = .013; Table 3). Kaplan-Meier estimates for freedom of complications after EVAR were significantly different between both groups, with a 5-year estimate of 51% in fAAA and 74% in spAAA (*P* =.007; Figure 2).

A total of 19 patients (37.3% of fAAA) had two or more affected relatives. Patients with two or more affected relatives had more complications after EVAR compared with those with only one affected relative (42.1% vs 31.2%, respectively), although it did not reach statistical significance (*P* = .443)



fAAA						
Number at risk	51	44	33	23	14	9
% with events	-	88%	78%	73%	68%	51%
Standard error	(-)	.045	.058	.065	.077	.103
spAAA						
Number at risk	204	172	145	102	68	46
% with events	-	94%	90%	87%	83%	74%
Standard error	(-)	.015	.022	.026	.031	.045

Figure 2 .Kaplan-Meier estimates are shown for complications after endovascular aneurysm repair (*EVAR*) between familial abdominal aortic aneurysm (*AAA*) (*dashed red line*) and sporadic AAA (*solid blue line*). Legend: *fAAA,* Familial AAA; *spAAA,* sporadic AAA.

Table 3. Complications after endovascular aneurysm repair (*EVAR*)

Variable[a]	Familial AAA (n = 51)	Sporadic AAA (n = 204)	*P* value
Complications after EVAR, patients	18 (35.3)	39 (19.1)	.013
Endoleak during follow-up, events	8 (15.7)	18 (8.8)	.147
Type Ia	5	9	
Type Ib	3	6	
Type III	0	1	
Type undetermined	0	2	
Secondary intervention	20 (39.2)	41 (20.1)	.004
Proximal stent/cuff	4	10	
Limb extension	5	18	
Coil/glue embolization	2	2	
Open ligation of collaterals	3	4	
Conversion to AUI	1	0	
Conversion to open repair	2	5	
Relining	3	2	
Aneurysm sac growth[b]	10 (20.8)	18 (9.5)	.030
Acute limb ischemia	0	4	.313
Postimplantation aneurysm rupture	0	0	…

Legend: *AAA,* Abdominal aortic aneurysm; *AUI,* aorto-uni-iliac device; *CTA,* computed tomography angiography; *DUS,* duplex ultrasound. a) Categorical data are presented as number (%). b) Aneurysm sac measurements were available for 237 patients with ≥ two postoperative imaging examinations (ie, two CTA scans or two DUS examinations).

Patients with fAAA had a 2.1-fold increased risk of complications after EVAR compared with spAAA patients after adjustment for age and ever smoking (HR, 2.1; 95% confidence interval [CI], 1.2-3.7; Table 4). Age (HR, 0.99; 95% CI, 0.95-1.02; *P* = .405) and ever smoking (HR, 0.84; 95% CI, 0.49-1.45; *P* = .538) did not predict for complications after EVAR in the multivariable model.

Endoleaks during follow-up

Patients with fAAA had more endoleaks during follow-up (15.7% vs 8.8%), although it did not reach statistical significance (*P* = .147). The difference appeared to be caused mainly by more type Ia and Ib endoleaks (15.6% vs 7.4%; *P* = .063).

Secondary interventions during follow-up

Patients with fAAA had a significantly higher secondary intervention rate after EVAR than spAAA patients (39.2% vs 20.1%; *P* = .004). Proximal stent/cuff, coil/glue embolization, open ligation of collaterals, and relining were more common in patients with fAAA. Detailed data regarding elements of secondary interventions are presented in Table 3.

Table 4. Uni- and multivariable analysis for complications after endovascular aneurysm repair (EVAR)-associated with familial abdominal aortic aneurysm (*AAA*)

	Univariable			Multivariable[a]		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sporadic AAA	Ref			Ref		
Familial AAA	2.15	1.22-3.81	.008	2.05	1.15-3.66	.015

Legend: *CI,* Confidence interval; *HR,* hazard ratio. a) Adjusted for age and ever smoking.

Table 5. Aneurysm sac behavior and proximal neck dilatation during follow-up

Variable[a]	Familial AAA	Sporadic AAA	*P* value
Aneurysm neck diameter[b]			
Growth	25 (59.5)	103 (63.2)	.662
Aneurysm sac diameter[c]			
Growth	10 (20.8)	18 (9.5)	.030
Stability	15 (31.2)	52 (27.5)	.608
Shrinkage	23 (47.9)	119 (63.0)	.057

Legend: *AAA,* Abdominal aortic aneurysm; *CTA,* computed tomography angiography; *DUS,* duplex ultrasound. a) Categorical data are presented as number (%). b) Aneurysm neck measurements were available for 205 patients with ≥ two postoperative CTA scans. c) Aneurysm sac measurements were available for 237 patients with ≥ two postoperative imaging examinations (ie, two available CTA scans or two available DUS examinations).

Aneurysm sac behavior and proximal neck dilatation during follow-up

Aneurysm sac growth was more common in patients with fAAA than those with spAAA (20.8% vs 9.5%; *P* = .030; Table 5). Notably, this was independent of type II endoleaks, which occurred in 13.7% of the fAAA patients and 11.8% of the spAAA patients (*P* = .713). Patients with fAAA also tended to have less aneurysm sac shrinkage (47.9% vs 63.0%; *P* = .057). There was no difference in aneurysm neck growth, which occurred in 59.5% of the fAAA patients and 63.2% in patients with spAAA (*P* = .662).

Overall long-term survival

During follow-up, 41 patients died; seven (13.7%) in the fAAA group and 34 (16.7%) in the spAAA group (*P* = .609).

Assessment of selection bias

As mentioned above, no difference in survival was observed between the two groups. However, we observed a difference in complications after EVAR for patients included and excluded from analysis (22.4% vs 15.1%, respectively; *P* = .046).

DISCUSSION

The main finding of the study was that patients with fAAA have a twofold higher risk of developing aneurysm-related complications after EVAR than patients with spAAA, despite similar AAA morphology. Although Brewster et al showed several years ago a trend toward more aneurysm-related mortality in patients with a history of aneurysmal disease,[18] this is the first report focusing on the association between family history and complications after EVAR.

In this study, we chose not to include patients with isolated iliac, traumatic, anastomotic, or infectious aneurysms because they either have different EVAR related complication risk or have other pathophysiological mechanisms leading to aneurysm formation compared with "typical" AAA. In addition, we excluded the ruptured aneurysms because they have a high rate of nonresponders because of high mortality, which could be an important source of bias. Also, the purpose of this study was primarily to determine the contribution of family history to preoperative risk assessment and modification, which is essentially directed at elective (preventive) situations. For ruptured aneurysms, family history of AAA is most likely not going to change the immediate attitude, which is to offer a life-saving procedure.

We found that 20% of our AAA population had a positive family history, which is similar to other studies reporting on the prevalence of fAAA.[1,19,20,21] Furthermore, patients with fAAA were younger and were less likely to have a history of smoking compared with patients with spAAA in our population. Previous studies similarly suggested that fAAA patients are slightly younger but studies on the effect of smoking are scarce.[1, 20 and 22]

Since it is well known that adverse AAA morphology may result in increased number of adjunctive procedures,[23] and it is also known that some genetic aortic aneurysm syndromes are associated with specific anatomic features like arterial elongation and tortuosity,[24,25,26] we determined aneurysm morphology before stent implantation. Maximum AAA diameter and presence of iliac tortuosity or stenosis were comparable between the two groups. Similarly, aneurysm neck characteristics such as diameter, length, angulation as well as the presence of thrombus and calcification were not different for fAAA and spAAA patients. Consequently, the observed disparities in complications cannot be attributed to morphologic differences between the groups.

Secondary interventions and aneurysm sac growth were the most important elements accounting for the difference in the composite primary end point of complications after EVAR. Although patients with fAAA also tended to have more endoleaks, in particular proximal and distal type I endoleaks, this difference failed to reach statistical significance because of limited patient numbers in the two groups. Patients with fAAA displayed more aneurysm sac growth, independent of the presence of type II endoleaks and less aneurysm sac shrinkage than patients with spAAA. It may be hypothesized that

an intrinsic weakness of the aortic wall results in more rapid progression of aneurysm disease and contributes to a higher need for secondary interventions in fAAA patients. These observations suggest that—as yet unknown—inherited connective tissue disorders may underlie aneurysm formation in patients with familial AAA.

Over the median follow-up period of 3 years, aneurysm neck growth was quite common (about 60%) in both groups. This high rate results from a low threshold definition and is comparable to other reports on contemporary stent grafts.[27,28]

In patients with known connective tissue disorders, endovascular therapies have been shown to result in much higher failure rates due to rapid dilatation or dissection of the aorta and are generally unadvised.[12,13] Nevertheless, we still believe that EVAR is a valid treatment alternative over open repair in patients with a positive family history because most complications observed in our study in fAAA patients could be treated with minimally invasive techniques. Also, low morbidity and the early survival advantage of EVAR appears to be unchanged in the fAAA group. Although standard postoperative surveillance is still recommended, our study should create awareness for the fact that patients with fAAA may develop more complications after EVAR. New prospective studies are needed for clarification of our findings and should determine which postoperative surveillance program suits fAAA patients best. Apart from the surveillance program, all fAAA patients in our institute receive genetic counseling to provide information on the hereditary of aortic aneurysms and are offered screening for all first-degree relatives.

There are several limitations that need to be considered. First, the single-center nature of this study limits the generalization of the results. A second limitation is the classification of familial AAA based on self-reported family history alone. The chance of having affected relatives is lower in small families compared with large families. Also, since objective screening of relatives was not performed, under-reporting of fAAA is likely. Third, no systematic molecular screening was performed for the known genetic aortic aneurysm syndromes. However, since these syndromes are rare causes for AAAs and generally present at a younger age, their contribution to the study population is probably negligible. In addition, the relative short follow-up of 3.3 years should be taken into account because it is known that endoleaks may develop in a later stage. Long-term follow-up is therefore warranted. Lastly, our study is also limited by its retrospective design, therefore, we evaluated possible selection bias. The mortality of fAAA and spAAA patients was similar for both groups, which suggests homogeneity between the two included groups, but we observed small difference in complications after EVAR for included and excluded patients. This was probably explained by the fact that patients treated for ruptured aneurysms died more frequently in the perioperative period and consequently could not develop a complication. Also, patients with a small anastomotic aneurysm treated with a covered stent are less likely to develop an EVAR-related complication as defined in the study. Therefore, we believe that bias might be present due

to the study design but was minimized by the chosen inclusion criteria and does not invalidate the main findings of the study.

In conclusion, the current study shows that patients with a familial form of AAA develop more aneurysm-related complications after EVAR, despite similar AAA morphology at baseline. Although the limitations of this study suggest caution in interpretation of the results, the twofold higher aneurysm-related complication rate after EVAR should create awareness for a possible incremental risk in this subgroup. Our findings emphasize the need for further research on genetic causes and underlying molecular mechanisms of AAA.

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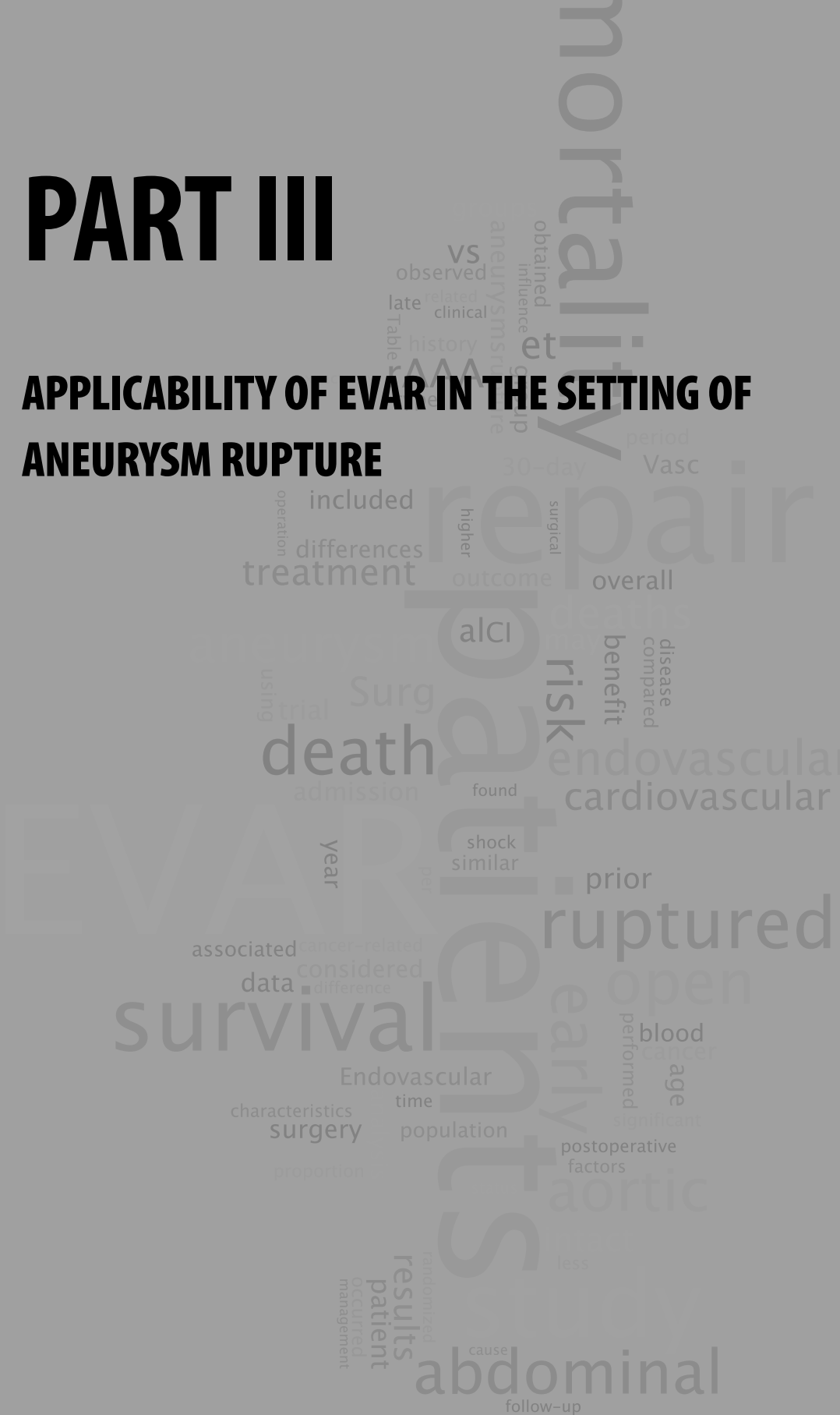
PART III

APPLICABILITY OF EVAR IN THE SETTING OF ANEURYSM RUPTURE



Chapter 10

Differences in mortality, risk factors, and complications after open and endovascular repair of ruptured abdominal aortic aneurysms

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ABSTRACT

Objective/background

Endovascular aneurysm repair (EVAR) for ruptured abdominal aortic aneurysm (rAAA) has faced resistance owing to the marginal evidence of benefit over open surgical repair (OSR). This study aims to determine the impact of treatment modality on early mortality after rAAA, and to assess differences in postoperative complications and long-term survival.

Methods

Patients treated between January 2000 and June 2013 were identified. The primary endpoint was early mortality. Secondary endpoints were postoperative complications and long-term survival. Independent risk factors for early mortality were calculated using multivariate logistic regression. Survival estimates were obtained by means of Kaplan–Meier curves.

Results

Two hundred and twenty-one patients were treated (age 72 ± 8 years, 90% male), 83 (38%) by EVAR and 138 (62%) by OSR. There were no differences between groups at the time of admission. Early mortality was significantly lower for EVAR compared with OSR (odds ratio [OR]: 0.45, 95% confidence interval [CI]: 0.21–0.97). Similarly, EVAR was associated with a threefold risk reduction in major complications (OR: 0.33, 95%CI: 0.15–0.71). Hemoglobin level <11 mg/dL was predictive of early death for patients in both groups. Age greater than 75 years and the presence of shock were significant risk factors for early death after OSR, but not after EVAR. The early survival benefit of EVAR over OSR persisted for up to 3 years.

Conclusion

This study shows an early mortality benefit after EVAR, which persists over the mid-term. It also suggests different prognostic significance for preoperative variables according to the type of repair. Age and the presence of shock were risk factors for early death after OSR, while hemoglobin level on admission was a risk factor for both groups. This information may contribute to repair-specific risk prediction and improved patient selection.

INTRODUCTION

Since the introduction of endovascular aneurysm repair (EVAR) in 1991 by Volodos et al.[1] and Parodi et al.,[2] the use of this less invasive treatment for infra-renal aortic aneurysms has expanded significantly. Nowadays, >60–70% of all elective abdominal aortic aneurysm (AAA) repairs are performed with EVAR.[3,4] This is not the case for ruptured AAA (rAAA), for which the use of EVAR has not yet achieved generalized acceptance.[5,6] In general, rAAA are frequently fatal with a mortality of up to 80%,[7] but patients surviving until they receive hospital care, might expect to benefit from a minimally invasive technique.

For elective surgery, randomized trials have demonstrated a nearly uniform threefold reduction in peri-operative mortality and prolonged survival benefit for EVAR over open surgical repair (OSR), which is maintained for at least 2 years.[8,9] These results, also confirmed by large registries and national audits,[10] have justified a shift towards a preferential use of EVAR. For rupture, however, evidence of a similar advantage is still lacking.

The aim of this study was to determine the impact of treatment modality on early mortality after rAAA repair, and to evaluate the differences in the prognostic capacity of preoperative variables in determining early survival for EVAR and OSR. Additionally, we investigated the differences in major postoperative complications and assessed any survival advantage related to treatment modality during follow-up.

METHODS

The study complied with the Declaration of Helsinki. According to our institutional guidelines, no formal ethical approval was required.

Patients

The study population consisted of all consecutive patients who underwent AAA repair between January 2000 and June 2013 at a single, tertiary institution. For this study, only patients with confirmed rAAA were included. Some of these patients have previously been included in a published 20-year overview of institutional trends in the management of rAAA.[7] Patients with infected aneurysms and those having had prior aneurysm repair were excluded from the analysis.

Data collection

All possible operation codes and surgical reports were retrospectively retrieved, and hospital charts and computed tomography angiographies (CTAs) were checked for the presence of rupture. If confirmed, patient demographics, clinical baseline characteristics, intraoperative details, and clinical and laboratory outcome were obtained. Baseline char-

acteristics on admission included age, gender, state of consciousness, blood pressure, and pulse rate. Duration from the emergency room (ER) to the operating theatre, operation duration, body temperature, blood pressure and pulse rate during operation, type of anesthesia, blood loss, and usage of blood products and fluids were derived from operative and anesthesia reports. Laboratory results on admission were also obtained. Postoperative complications and events were retrieved from hospital registries. Survival status and the exact date of death of treated patients were obtained via the national civil registry.

Missing data

Baseline data that were not retrievable were analyzed for differences between the OSR and EVAR groups. There were no significant differences in the number of missing data in either group, except for blood loss and the volume of intraoperative transfusion, owing to a lack of documentation about minimal blood loss and transfusions needed with an EVAR procedure. Only variables with <3% missing data were included in multivariate models.

Institutional management of rAAA

The Erasmus University Medical Center is a tertiary teaching institution with full capacity for endovascular and open vascular surgery (24 hours a day/7 days a week), serving about 1.5 million people living in the Rotterdam and surrounding area. Owing to the characteristics of the institution, a relatively high proportion of AAA repairs are done for rupture. Although the logistics involved in EVAR have been adapted and improved over time, the capacity to offer both treatment options was present throughout the entire study period. This made EVAR available for any anatomically suitable patient on any day and at any time. The choice of treatment is individualized, but preference is generally given to EVAR in older patients.

If a patient presents at the ER with a suspected rAAA, the on-call surgical team is informed. On arrival of the patient in the ER, an ultrasound of the abdominal aorta is done to confirm the presence of an aortic aneurysm if the patient is not known to have an AAA. Otherwise, a CTA can be performed immediately. Patients are managed by permissive hypotension in the ER, and resuscitation is started only if the patient becomes unconscious.

According to protocol, a multi-slice CT scanner is used for rAAA CTA. The patient is scanned from nipple to pubic symphysis with a collimation of 118*0.6, and plain and contrast series are acquired after administering 120 mL of Visipaque 320 contrast. Anatomical suitability for EVAR is determined by the surgeon's expectations and experience. In anatomically complex cases, or whenever time allows, a dedicated post-processing workstation (3Mensio Vascular 4.2 software; 3Mensio Medical Imaging, Bilthoven, the

Netherlands) is available for sizing and planning. After diagnosis, informed consent is obtained whenever possible.

Aneurysm repair is performed either by consultant vascular surgeons or by residents during their vascular sub-specialization under the direct supervision of a consultant vascular surgeon. For EVAR, repair is performed in the operating theatre using a mobile C-arm. Preference is given to local anesthesia for EVAR, although the decision depends on the individual case.

For OSR, a midline transperitoneal approach is preferred, and aorto-aortic or aorto-bi-iliac reconstruction is performed depending on the presence of concomitant iliac aneurysms. Postoperatively, intra-abdominal pressure using a vesical pressure probe is only checked when there is clinical suspicion of abdominal compartment syndrome.

Definitions

Rupture was defined by either direct visualization of fresh blood in the retroperitoneal or peritoneal compartments during OSR, or visualization of peri-aortic hematoma on the immediate preoperative CTA.[11] Early mortality was defined by in-hospital mortality or death within 30 days of surgery. Major complications were defined as one of the following: respiratory; cardiac; cerebrovascular; renal failure (estimated glomerular filtration rate [eGFR] < 30); abdominal; wound; bleeding-related; lower limb ischemia; graft-related. Endovascular complications and EVAR-related adverse events were classified according to the reporting standards for EVAR by Chaikof et al.[12] The shock index was calculated by dividing the heart rate by systolic blood pressure, and was calculated from the first heart rate and blood pressure recorded on arrival in the ER.[13]

Endpoints

The primary study endpoint was early mortality. Secondary endpoints were early major complications and overall survival during follow-up.

Statistical analysis

Categorical variables are presented as counts and percentages, and compared with chi-square tests. Continuous variables are presented as means ± standard deviation and compared with Student *t* tests; or as median and interquartile range, and compared with Mann–Whitney *U* tests if the distribution was non-parametric. The influence of missing data on results was tested by comparing the outcome of patients with missing data to those with complete data sets. A logistic regression model was used to assess the proportional outcome risk associated with EVAR. Variables associated with 30-day in-hospital mortality were tested in univariate analysis by type of repair, and significant variables were introduced in a multivariate logistic regression model to determine independent significance. From the beginning of the study period the implementation

of EVAR evolved and the number of patients undergoing the procedure increased. As a result, the year of operation was used as a co-variable to adjust for the growth in patients treated with EVAR every year. A graph of the proportion of the groups per year and the mortality rates per year of both groups is shown to illustrate the changes in both groups during the study period. Overall survival during follow-up was estimated using Kaplan–Meier tables, and survival after EVAR versus open repair was compared using the log-rank (Mantel–Cox) statistical test.

Table 1. Preoperative baseline characteristics on admission.

Variable	OSR *n* = 138	EVAR *n* = 83	*p*
Age			
Mean ± SD	71.9 ± 7.8	72.1 ± 8.2	.89
>75 y, *n* (%)	46 (33)	29 (35)	.81
Male gender, *n* (%)	123 (89)	68 (93)	.37
Unconsciousness, *n* (%)	4 (3)	1 (1)	.65
Cardiopulmonary resuscitation before OR, *n* (%)	1 (1)	0 (0)	1
Hemodynamic status[a]			
Systolic blood pressure, mean ± SD	114 ± 37	115 ± 37	.81
Diastolic blood pressure, mean ± SD	69 ± 26	67 ± 21	.55
Heart rate (bpm), mean ± SD	85 ± 22	88 ± 25	.37
Shock index > 1[b]	31 (24)	29 (36)	.05
Hemoglobin (g/dL)			
Median (IQR)	11.1 (9.4–12.6)	11.8 (9.6–13.3)	.10
<11, *n* (%)	60 (46)	31 (42)	.59
Coagulation			
INR ≥ 1.5, *n* (%) [c]	33 (28)	24 (33)	.52
Platelet count ($\times 10^3$/μL), median (IQR)[a]	177 (135–235)	196 (154–256)	.008
eGFR			
Median (IQR)	61 (45–77)	63 (46–75)	.96
< 60, *n* (%)	68 (53)	37 (51)	.86
Leukocytes ($\times 10^3$/μL), median (IQR)[c]	12.0 (9.0–16.3)	12.5 (8.5–16.3)	.69
CRP (mg/dL), median (IQR)[c]	11 (5–47)	14 (4–70)	.58
Time from ER to OR (mins)[d]	50	36	.023

Legend: OSR = open surgical repair; EVAR = endovascular aneurysm repair; OR = operating room; BPM = beats per minute; IQR = interquartile range; INR = international normalized ratio; eGFR = estimated glomerular filtration rate; CRP = C reactive protein; ER = emergency room. A) Missing 1–3% of baseline data. b) Heart rate/systolic blood pressure. c) Missing 3–15% of baseline data. d) Missing >15% of baseline data.

RESULTS

From January 2000 to June 2013, 878 patients underwent AAA repair at our institution. The study sample of rAAA included 221 patients with a mean age of 72 ± 8 years (90% of whom were men). Of these 221 patients, 138 were treated with OSR and 83 with EVAR. The demographics and clinical characteristics of patients on admission did not differ significantly between groups (Table 1).

Intraoperative details

Within the OSR group, 13 (9%) intraoperative deaths occurred, while in the EVAR group four (5%) deaths occurred (p = .21; Table 2). Most deaths occurred as a result of severe hemorrhagic shock. Intraoperative complications were observed in 15 (11%) and 10 (13%) patients after OSR and EVAR, respectively (p = .48). These complications differed significantly between groups. Thrombosis (n = 7) and iatrogenic arterial lesions or dissection (n = 6) were the most frequent intraoperative complications for the OSR group; in the EVAR group, the main intraoperative complications were type I/III endoleaks (n = 6). Large differences were observed between the two treatment groups regarding the duration of operation, estimated intraoperative blood loss, and the intraoperative consumption of blood products and fluids (p < .001; Table 2).

Table 2. Intraoperative characteristics.

Variable	OSR	EVAR	p
Duration of surgery (h), median (IQR)[a]	3.42 (3.07–4.46)	2.46 (2.20–3.57)	<.001
Blood loss (mL), median (IQR)[b]	4,500 (2,050–8,875)	200 (0–500)	<.001
Red blood cell concentrates, median (IQR)[b]	6 (3–11)	2 (0–4.5)	<.001
Plasma units, median (IQR)[b]	6 (2–10)	0 (0–2)	<.001
Platelet units, median (IQR)[b]	1 (0–5)	0 (0–0)	<.001
Crystalloids, median (IQR)[b]	4,000 (2,500–7,000)	1,500 (1,000–2,125)	<.001
Colloids, median (IQR)[b]	1,500 (1,000–2,000)	500 (0–1,000)	<.001
Body temperature at end of surgery, °C, median (IQR)[b]	35.9 (35.0–36.5)	36.00 (35.50–36.25)	.21
Intraoperative death, n (%) [a]	13 (9)	4 (5)	.21
Intraoperative complications, n (%) [a]	15 (11)	12 (14)	.48
Endoleaks (type I/III), n (%)	—	6 (7)	
Graft occlusion	2 (1)	1 (1)	
Peripheral embolization/thrombosis	7 (5)	0 (0)	
Iatrogenic dissection	3 (2)	0 (0)	
Arterial disruption with bleeding	3 (2)	2 (2)	
Unintentional renal artery occlusion	0 (0)	2 (2)	

Legend: OSR = open surgical repair; EVAR = endovascular aneurysm repair; IQR = interquartile range. a) Missing 1–3% of baseline data. b) Missing 3–15% of baseline data.

Table 3. Thirty-day/in-hospital outcome after ruptured abdominal aortic aneurysm repair.

Variable	OSR	EVAR	OR[a]	95%CI
Mortality	55 (40)	20 (24)	**0.45**	0.21–0.97
Major complications	95 (76)	46 (58)	**0.33**	0.15–0.71
Systemic complications	80 (64)	42 (53)	0.69	0.34–1.38
Local complications	38 (30)	15 (19)	**0.37**	0.16–0.83
Fatal complications	37 (30)	13 (16)	**0.39**	0.17–0.90
Multiple complications	52 (42)	21 (27)	0.53	0.26–1.08

Legend: ORs are given for EVAR compared with OSR. Significant values are presented in bold. OSR = open surgical repair; EVAR = endovascular aneurysm repair; OR = odds ratio; CI = confidence interval. a) Logistic regression is performed for each outcome measure, adjusting for age, gender, estimated glomerular filtration rate, preoperative hemoglobin level, hemodynamic status (shock index), and year of operation.

Early survival

Early death occurred in 55 patients (40%) and 20 patients (24%) for OSR and EVAR, respectively. After adjusting for age, gender, eGFR, hemoglobin (Hgb) and hemodynamic status, and year of operation, EVAR was associated with a twofold risk reduction of early death compared with OSR (odds ratio [OR]: 0.45; 95% confidence interval [CI]: 0.21–0.97; Table 3). In multivariate analysis of risk factors for early mortality (Figure 1), significant differences were observed between groups. Only a low Hgb level was an independent risk factor for both types of repair. Being older than 75 years and the presence of shock were risk factors for OSR only and not for EVAR. Univariate analysis suggested coagulopathy on admission as a risk factor for EVAR (OR: 4.60, 95%CI: 1.49–14.18) instead of OSR (OR: 1.69, 95%CI: 0.79–3.66), but the high number of missing values (12%) did not allow for inclusion of this variable in the multivariate model. Type of anesthesia (local vs. general) had no effect on mortality for EVAR patients (OR: 1.19, 95%CI: 0.67–2.04). Figure 2 shows the proportion per year of EVAR- or OSR-treated patients, as well as the 30-day mortality per year per treatment.

Major postoperative complications

Median stay in the intensive care unit (ICU) was 4 (1–11) days for OSR and 1 (1–5) days for EVAR ($p = .001$). Median hospital stay was 14 (6–33) days for OSR and 8.5 (4–21) days for EVAR ($p = .001$). More major complications occurred after OSR than after EVAR (76% vs. 58%, $p = .007$). Furthermore, OSR patients were more likely to suffer from more than one complication (42% vs. 24%, $p = .047$) and have more frequent fatal complications (30% vs. 16%, $p = .033$). The distribution of complications is shown in Table 4. More abdominal, wound, and bleeding complications occurred after OSR, and more graft-related problems occurred after EVAR. Compared with OSR, EVAR was associated with a threefold risk reduction for major complications (OR: 0.33, 95%CI: 0.15–0.71), after adjusting for age, gender, Hgb, eGFR, hemodynamic status on admission, and year of surgery (Table 3).

Late survival

The survival benefit after EVAR on early outcome was maintained during the mid-term follow-up. The estimated survival after 2 years was 52% for OSR versus 65% for EVAR ($p < .001$; Figure 3). After 3 years, the survival benefit after treatment with EVAR was no longer present.

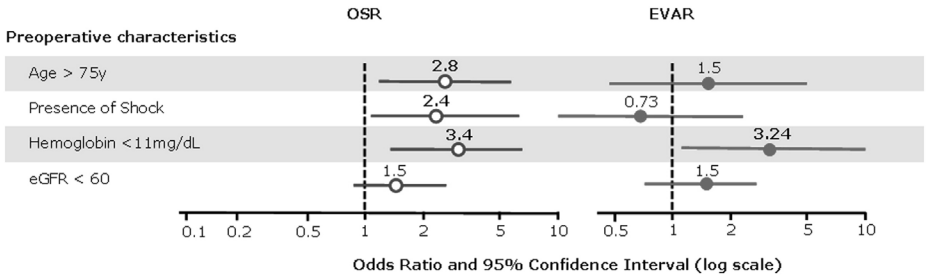

Figure 1. Multivariate logistic regression analysis of risk factors for early mortality, by type of repair (only including variables with <3% missing data).
Note. eGFR = estimated glomerular filtration rate; OSR = open surgical repair; EVAR = endovascular aneurysm repair.

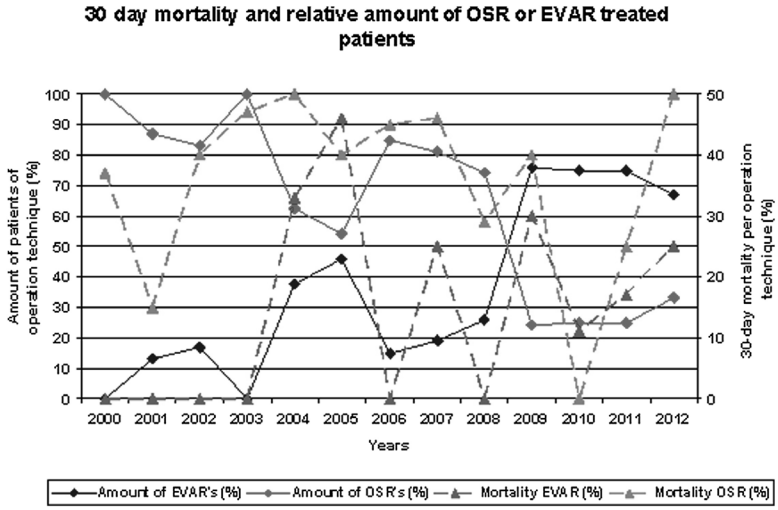

Figure 2. Thirty-day mortality and relative amount of open surgical repair (OSR)- or endovascular aneurysm repair (EVAR)-treated patients.

Table 4. Postoperative complications.

Variable	OSR	EVAR	*p*
Days in ICU, median (IQR)	4 (1–11)	1 (1–5)	.001
Total days of admission, median (IQR)	14 (6–33)	8.5 (4–21)	.001
Major complications	95 (76)	46 (58)	.007
Systemic complications	80 (64)	42 (53)	.124
Cardiac	20 (16)	8 (10)	
Cerebrovascular	6 (5)	3 (4)	
Renal	49 (39)	25 (32)	
Pulmonary	33 (26)	18 (23)	
Local complications	38 (30)	12 (19)	.070
Bowel ischemia	13 (10)	2 (3)	
Abdominal compartment syndrome	10 (8)	4 (5)	
Bleeding	7 (6)	1 (1)	
Distal embolization/thrombosis	5 (4)	1 (1)	
Wound infection	9 (7)	1 (1)	
Graft-related	3 (2)	5 (6)	
Multiple complications	52 (42)	19 (24)	.047
Fatal complications	37 (30)	11 (16)	.033

Legend: OSR = open surgical repair; EVAR = endovascular aneurysm repair; ICU = intensive care unit; IQR = interquartile range.

DISCUSSION

In this study, EVAR was associated with a twofold reduction in early mortality after rAAA, after correcting for possible confounders. This benefit persisted for up to 3 years after the index event. Moreover, risk factors for early mortality varied in type and importance according to which treatment modality was selected. These risk factors could have a potential impact on current clinical practice.

In contrast to elective EVAR, which is widely accepted, EVAR for rAAA is far from accepted owing to a significant lack of level A evidence.[5,6] To date, only two randomized controlled trials have been published on the subject. The Nottingham trial, which was only a pilot study, had difficulties with enrollment and was not able to show any differences in early mortality or complications. Recently, the results of the AJAX trial have been published.[14,15] In this study, no difference in 30-day mortality and severe complications between EVAR and OSR were found. This could be explained, in part, by the unexpectedly good results from OSR, arguably difficult to achieve in most settings. With regard to the secondary endpoints of the AJAX study, EVAR generally performed better: mean ICU stay, mean hospital stay, mean blood loss, and the need for mechanical ventilation all fa-

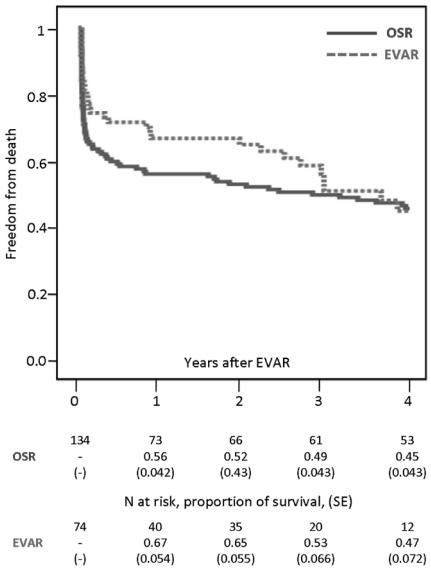

Figure 3. Kaplan–Meier curve of survival after ruptured abdominal aortic aneurysm repair, by type of repair (log rank $p = .52$).

Note. OSR = open surgical repair; EVAR = endovascular aneurysm repair.

vored the EVAR group. Both of the aforementioned studies were limited by low inclusion rates, which may result in significant bias, and are both considered to be underpowered.

Two other randomized trials are still in progress (IMPROVE[16] and ECAR[17]). While the results of the ECAR trial are awaited, the IMPROVE investigators recently presented preliminary data.[18] They were able to recruit 613 patients (about two-thirds of all eligible patients) with a clinical diagnosis of ruptured aneurysm. Based on intention-to-treat analysis, no significant difference was found between the EVAR and OSR groups for 30-day mortality (35.4% and 37.4%, respectively), but there was a significant number of protocol variations (11%). In the endovascular first strategy group, patients who were actually treated by EVAR ($n = 150$) had a 30-day mortality of 25% compared with 37% for those treated in the OSR first strategy group ($n = 220$), results similar to those obtained in our study (24% and 40%, respectively). Subgroup analysis revealed a survival benefit for women treated with EVAR. After EVAR, patients had a shorter stay in hospital than OSR patients, and the costs related to both groups of patients after 30 days was comparable. They also found that the lowest measured systolic blood pressure was an independent risk factor for 30-day mortality, and that the use of local anesthesia during EVAR reduced the 30-day mortality. In this study shock and use of local anesthesia had no effect on mortality after EVAR.

In contrast to published randomized trials, retrospective data are generally more favorable for EVAR. Inclusion of symptomatic non-ruptured aneurysms in retrospective

series could contribute to this difference between trials and retrospective studies. To avoid such a bias in our study, we individually assessed the presence of true rupture in all cases. Veith[19] has published collected data from 49 institutions that routinely use EVAR for the treatment of rAAA. One thousand and thirty-seven patients treated by EVAR and 763 patients treated by OSR were included in the review. The study showed a significant reduction in early mortality favoring EVAR (21% vs. 36%, $p < .001$). The author concluded that EVAR is superior to OSR for patients with suitable anatomy, especially those who are more hemodynamically unstable, which is in line with the findings in this study. A population-based study by Mandawat et al.[20] showed that EVAR is superior to OSR in regard to short-term clinical outcomes (36% vs. 18%, $p < .01$). Nedeau et al.[21] published a retrospective study comparing EVAR with OSR. Although their patient sample was smaller than in this study (19 EVAR and 55 OSR patients), their conclusions were very similar, with EVAR conferring an early and mid-term survival benefit. A recent publication by Mehta et al.[22] also compared early mortality for EVAR versus OSR in rAAA patients.[22] In a sample of 283 patients, of whom 120 underwent EVAR, the authors reached a similar conclusion regarding an early mortality benefit for EVAR, which was maintained over time. However, the study by Mehta et al.[22] found a higher risk for EVAR in elderly patients, which was only present for OSR in this study. In addition to survival analysis, more insight is provided into the complications after rAAA, suggesting important differences on the number and type of complications found after OSR and EVAR.

A low Hgb level on admission was associated with adverse early prognosis after rAAA. This seems logical, as it suggests more extensive bleeding and a more prolonged evolution, increasing the chance of cardiac ischemia due to inadequate oxygen delivery. This is potentially aggravated by the fact that OSR is associated with greater blood loss. Age more than 75 years was associated with a higher risk of early death after OSR, but not after EVAR. This could be the result of reduced physiological reserve in elderly patients, which is insufficient to withstand the added insult of open surgery. Similarly, the presence of shock on admission was an independent predictor for early outcome after OSR, but not after EVAR. This interesting observation may be explained by the less invasive nature of EVAR and the maintenance of higher peripheral resistance during endovascular operations. Another interesting observation is that coagulopathy on admission was associated with increased mortality after EVAR, but not after OSR. Although this could not be tested for confounders, it may be explained by persistent bleeding followed by abdominal compartment syndrome, and by a higher threshold for transfusion after EVAR.

The difference in early survival could also be explained by patient selection prior to the operation.[22] A common argument is that the most unstable patients would not undergo a CTA and, as a consequence, not be offered EVAR. In our population, however, admission hemodynamic status was similar for both groups, and the presence of shock

was only found to influence outcome after OSR. It could be argued that the difference of admission time suggests that OSR patients are more unstable as theirs is shorter. We think that this difference is mainly due to the need for CTA in EVAR patients and not directly to patients' hemodynamic status. Furthermore, admission information was missing 16.7% of the data, which makes it less reliable than the shock index (<3%). These findings support the prior suggestion by Hinchliffe et al.[6] that the most unstable patients may be the ones to obtain the greatest benefit from EVAR. Also, it is possible that anatomically suitable patients for EVAR have a better outcome than those who are anatomically unsuitable, independent of the type of repair, as suggested by Ioannidis et al.[23] and Dick et al.[24] However, this effect was not observed in a study by Ten Bosch et al.,[25] in which anatomical suitability did not influence results in a cohort of patients who all underwent preoperative CTA irrespective of hemodynamic status. We could not confirm the hypothesis of anatomical suitability because some patients undergoing OSR did not undergo a preoperative CTA, and performing this analysis would inevitably incur bias. However, no supra-renal or type IV thoraco-abdominal aneurysm patients were included in our series.

Postoperatively, the total admission period and ICU period for patients treated with EVAR was significantly lower than that of OSR-treated patients. This suggests a quicker recovery and less severe postoperative complications for EVAR. In parallel with mortality, EVAR was associated with a threefold reduction in the risk of major complications, and the occurrence of multiple and fatal complications were more frequent after OSR, contributing to better early survival rates for EVAR.

Over time, the prognosis of patients treated with EVAR gradually converged with that of OSR patients. In this series, the benefit of EVAR was maintained up to 3 years; beyond this point, the survival of the two groups was similar. No clear explanation for this effect could be found, but it is hypothesized that it may reflect the less aggressive nature of EVAR, therefore minimizing the "second hit" after rupture. In patients with severe comorbidities, the additional surgical aggression of OSR could result in early death. Similarly, frail patients may survive the acute period after EVAR, but succumb to their comorbidities at mid-term. We found no evidence that EVAR-related complications could explain the observed pattern.

The results of this study are limited by the retrospective design and individualized treatment selection, which could result in bias. Also, the time span of the study may have influenced results, with inevitable management and referral modifications occurring over time. For the outcome analysis, year of operation was used as a co-variable, therefore adjusting for this potential confounder. Because of the relatively small sample, and because many patients died very early after the start of follow-up owing to the rupture, there was not sufficient statistical power to determine differences in long-term survival, and restricted the analysis to 4 years after repair. Finally, accurate turn-down

rates for repair, which are known to significantly influence the overall survival after rAAA, could not be provided. This important limitation probably has less impact on direct comparison between treatment modalities than on the overall results of rAAA repair.

In conclusion, this study shows a twofold early mortality risk reduction for rAAA patients undergoing EVAR, which is maintained over the mid-term. Old age and the presence of shock were significant predictors of early mortality for OSR only, suggesting that EVAR may be particularly beneficial for patients presenting with these factors.[26] Also, OSR patients were at higher risk of major postoperative complications, required longer ICU and hospital stays, and appeared more likely to suffer from multiple and fatal complications after surgery. These results support the preferential use of EVAR for rAAA, and suggest a potential improvement in risk prediction by introducing the type of repair into the equation.

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Chapter 11

Contemporary life expectancy and causes of death after repair of intact and ruptured abdominal aortic aneurysms

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Submitted

ABSTRACT

Background

Contemporary prognosis after abdominal aortic aneurysm (AAA) repair is largely unknown. We designed a retrospective cohort study to determine the prognosis, causes of death and differences in outcome after intact (iAAA) and ruptured AAA (rAAA).

Methods and Results

All AAA patients treated from 2003-2011 at a single university institution in The Netherlands were analysed. Survival status derived from civil registry data. Causes of death were obtained from death certificates. Primary endpoints were overall early and late mortality. Secondary endpoints were cardiovascular, cancer-related and AAA-related mortality. Predictors for perioperative and late survival were obtained using logistic regression and Cox-regression models, respectively.

Results

619 consecutive AAA patients (12% female, mean age 72) were included, of which 152 (24.5%) were rAAA. Endovascular repair was performed in 390 (63%). Age (OR: 1.08 per year, 95% CI: 1.09-1.15), renal insufficiency (OR: 2.94, 1.51-3.46), rupture (OR: 10.63, 4.80-23.5) and open repair (OR: 3.59, 1.69-7.62) were predictors of 30-day death. Five-year survival expectancy was 65% for iAAA and 41% for rAAA. Cardiovascular deaths occurred in 35% of patients, and cancer-related deaths in 29%. Predictors for late mortality were age (HR: 1.08 per year, 1.05-1.10) and prior malignancy (HR: 2.83, 1.99-4.03). After 30-days, only 6 deaths (1.1%) were AAA-related.

Conclusions

The results suggest improved cardiovascular related survival after AAA repair, with malignancy assuming growing preponderance. Endovascular repair reduced perioperative mortality by 3-fold, but no survival benefit was observed at long-term. After the perioperative period, survival of rAAA and iAAA patients is similar.

INTRODUCTION

The prognosis of abdominal aortic aneurysm (AAA) patients undergoing repair is of major importance for decision-making, both in elective and acute situations. While rupture contributes significantly for the mortality of untreated AAA patients,[1,2] those undergoing successful repair are considered to have a worse life expectancy than the background population. This is thought to be mainly due to a high prevalence of occult or overt atherosclerotic disease (especially coronary artery disease).[3,4] In addition, patients surviving ruptured AAA repair are commonly considered to have an inferior late prognosis, although there is no scientific support for this belief.

The evolution of AAA treatment in the last decades has resulted in improved early outcomes for elective and ruptured situations alike. However, it is unclear if these improvements have been accompanied by a similar improvement in long-term prognosis for AAA patients. The effects of superior secondary prevention for atherosclerosis and modification of environmental and behavioural characteristics may have resulted in better survival and a shift away from cardiovascular deaths. On the other hand, changes in postoperative surveillance brought about by endovascular repair (frequently including repeated radiation exposure and nephrotoxic contrast agents), may have worsened the expected prognosis of this specific population.

The purpose of this study is to determine the contemporary prognosis of patients undergoing AAA repair, focusing on the possible differences between intact and ruptured AAAs and analysing specific risk factors for overall, cardiovascular and cancer-related mortality. Additionally, we explore differences in prognosis after endovascular and open AAA repair.

METHODS

Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki declaration on research ethics.

Study design

Retrospective, single centre cohort study.

Patients

The study sample was derived from the population of patients consecutively treated for AAA at the Erasmus University Medical Centre (EMC), Rotterdam, The Netherlands, from January 2003 to November 2011. These are included were included in a prospective AAA

database, which was inquired. The latest follow-up period considered was December 2011, therefore ensuring all patients had at least an expected follow-up of 30 days. This limit to follow-up was determined by the latest available datasets for causes of death (see below). Patients with infectious aneurysms and patients with a prior history of abdominal aortic repair were excluded.

Definitions

Ruptured aneurysms were defined as either having evidence of retroperitoneal blood on a CTA immediately prior to intervention or clear mention of periaortic hematoma on the operative report. AAAs were otherwise considered intact. Renal insufficiency at admission was considered present if the estimated glomerular fraction (eGFR) – calculated using the MDRD formula[5] – was less than 60. Anaemia at admission was considered if the serum haemoglobin level was less than 13mg/dl (12mg/dl if female), according to the World Health Organization definition.[6]

Institutional management of AAA

The EMC is a tertiary teaching institution performing around 100 abdominal aortic procedures yearly. Elective AAA is routinely performed for AAA with a maximum diameter greater than 5.5cm or growth >5mm in 6 months, or whenever symptoms occur. Selection for EVAR is individualized, considering the patient's co-morbidities, anatomical characteristics and informed consent. In the latter half of the study, preference was generally given for EVAR, both for intact and ruptured AAA.

Survival status

Survival status was derived from inquiry of civil registry database information. Only deaths occurring within the study time frame (2003 to 2011) were considered.

Causes of death

The causes of death were obtained by inquiry of the Dutch Central Bureau of Statistics (CBS) – study ID: 7465. To obtain information on cause of death, a database with all patients deceased within the study interval was anonymised and matched to the official death certificate reports, using ICD-10 codes. According to Dutch privacy legislation, data analysis was only allowed to authorized researchers (KU, FBG) inside a secure environment, and all output was checked by the CBS for privacy violation before it was allowed for publication purposes. Autopsy was not routinely performed, and the expected cause leading to health deterioration prior to death was considered as the underlying cause of death, in parallel to the strategy used for the overall Dutch population. The causes of death were grouped according to the *International Classification of Diseases, 10th Revision* (ICD-10). For cardiovascular death, the following codes were used: I10-I79; for

cancer-related death: C00-C43, C45-C97, D00-D03, and D05–09; for AAA-related death: I71.3, I71.4, I71.8, I71.9 and I72.3.

Endpoints

The primary endpoints are overall early and late mortality. Secondary endpoints are AAA-related, cardiovascular and cancer-related mortality.

Statistical methods

Baseline characteristics were described as counts and percentages (dichotomous variables), or means and standard deviations (continuous variables). Differences at baseline were assessed using Pearson's chi-Square or Student's t-test, where appropriate. Estimates of survival were obtained using Kaplan-Meier plots, and tabulated with the respective 95% confidence intervals at yearly intervals. General population survival estimates were generated after age and gender matching. Independent risk factors for 30-day death after AAA repair were obtained using a logistic regression model, which included age, gender, renal function at admittance, anaemia at admittance, maximum preoperative AAA diameter, indication for treatment (rupture vs. intact) indication, type of anesthesia (general vs. locoregional) and type of repair (open vs EVAR). For long-term outcome, a Cox-regression model was constructed to determine risk factors for all-cause, cardiovascular and cancer-related death. The variables included were: age, gender, prior history of cardiovascular disease (cardiac, cerebrovascular or peripheral ischemic disease), prior history of diabetes mellitus, prior history of cancer, renal insufficiency at admittance, anaemia at admittance, indication for treatment and type of repair. To determine the influence of radiation exposure resulting from postoperative surveillance strategies after endovascular repair, we performed a sub-analysis of patients without a prior history of cancer and compared cancer-related mortality between endovascular and open surgery using a Chi-square test. All tests were two-sided and significance was considered when P value < 0.05. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc., Chicago, IL).

RESULTS

From January 2003 to November 2011, 619 patients underwent primary repair for non-infected AAA at our institution. Survival status was available for all but one patient (due to emigration) who was excluded from further analysis. Mean age was 71.9 ± 7.6, 74 (12%) were female and 152 (25%) were ruptured AAA. Endovascular repair was performed in 390 patients (63%).

Table 1. Baseline characteristics by surgical indication

	Intact AAA	***Ruptured AAA***	***P-value***
	N=466	*N=152*	
Demographics			
Female gender – N (%)	56 (12)	18 (12)	0.954
Age (years, mean ± SD)	71.8 ± 7.5	72.3 ± 7.7	0.553
Prior medical history			
Ischemic heart disease – N (%)	216 (46)	50 (35)*	0.016
Cerebrovascular disease – N (%)	91 (19)	22 (15)*	0.279
Diabetes mellitus – N (%)	72 (15)	12 (8)*	0.036
History of cancer – N (%)	97 (21)	17 (12)*	0.023
PAD – N (%)	87 (19)	16 (11)*	0.040
Preoperative eGFR<60 – N (%)	142 (30)	75 (49)	<0.001
Preoperative anaemia– N (%)	116 (25)	113 (75)	<0.001
AAA characteristics			
Max AAA diameter, mm mean ± SD	62 ± 12	77 ± 17 †	<0.001
Operative details			
Loco-regional anaesthesia – N (%)	97 (21)	25 (16)	0.198
Open surgical repair – N (%)	137 (29)	91 (60)	<0.001

Legend * 11 rAAA patients (2%) missing baseline data; † 20 patients missing baseline diameter; PAD – Peripheral arterial obstructive disease; eGFR – estimated glomerular filtration ratio

Baseline characteristics

A greater proportion of patients undergoing repair for intact AAA had a prior history of ischemic heart disease (46% vs. 35% for ruptured AAA) and diabetes (15% vs. 8%), Table 1. Other demographics and past medical history were not different between these two groups. More patients in the ruptured AAA group had eGFR<60 (49% vs. 30% for intact AAA) and were anaemic (75% vs. 25%) at admittance, as expectable due to their acute presentation. Also, the maximum AAA diameter of ruptured cases was generally greater (77±17mm vs. 62±12mm). The choice of anaesthetic technique did not differ for intact and ruptured AAA patients. Patients with intact AAA, however, were less likely to undergo open surgical repair (29% vs. 60% for ruptured cases). Baseline characteristics are detailed in Table 1.

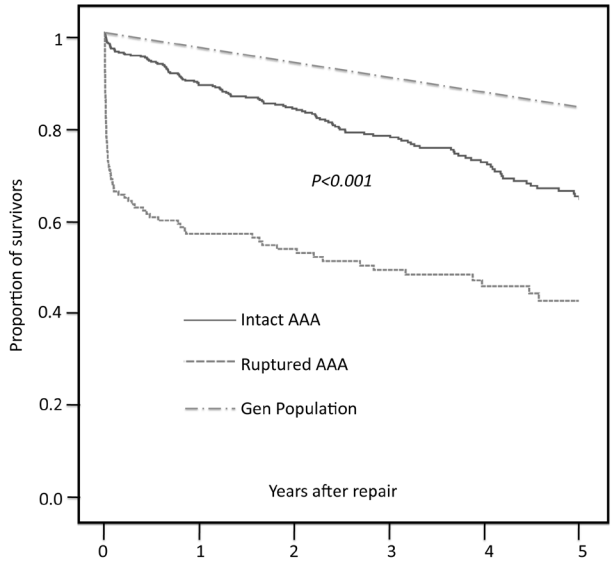
Early postoperative mortality

Overall, there were 66 deaths within 30-days. As expected, patients with ruptured AAA had a higher early mortality rate (N=50, 32.9% vs. N=16, 3.4% for intact aneurysms). Age (OR: 1.08 per year increase, 95% CI: 1.09 to 1.15), renal insufficiency at admittance (OR: 2.94, 95%CI: 1.51 to 3.46), rupture as indication (OR: 10.63, 95% CI: 4.80 to 23.5) and open surgical repair (OR: 3.59, 95% CI: 1.69 to 7.62) were independent predictors of death within 30-days after surgery, Table 2.

Table 2. Risk factors for early mortality (logistic regression)

	Univariable	*Multivariable*
Risk factor	*OR (95% CI)*	*OR (95% CI)*
Age *	1.08 (1.04 to 1.12)	1.09 (1.04 to 1.15)
Female gender	0.93 (0.66 to 2.80)	1.01 (0.39 to 2.62)
Renal insufficiency	3.50 (2.06 to 5.94)	2.94 (1.5 to 5.71)
Anaemia	5.94 (3.33 to 10.61)	1.66 (0.79 to 3.46)
Baseline AAA †	1.02 (1.01 to 1.04)	0.99 (0.96 to 1.01)
Rupture	13.79 (7.55 to 25.2)	10.63 (4.80 to 23.5)
General anaesthesia	3.47 (1.36 to 8.83)	1.48 (0.47 to 4.60)
Open repair	4.68 (2.69 to 8.14)	3.59 (1.69 to 7.62)

Legend: * per unit (year) increase; † per unit (mm) increase. OR: Odds Ratio



	466	376	296	218	148	107
Intact AAA	-	0.89	0.84	0.78	0.72	0.65
	(-)	(0.015)	(0.018)	(0.021)	(0.025)	(0.029)

N at risk, proportion of survivors, (Standard Error)

	152	76	62	49	34	25
Ruptured AAA	-	0.56	0.53	0.48	0.45	0.41
	(-)	(0.041)	(0.042)	(0.043)	(0.044)	(0.046)

General		-	-	-	-	-
Population		0.97	0.94	0.91	0.88	0.84

Figure 1. Kaplan-Meier survival estimates after AAA repair, compared with age and gender matched general population.
Legend: EVAR – endovascular aneurysm repair; OSR – open surgical repair. Gen Population- General Population.

Table 3. Risk factors for late mortality (Cox-regression)

Mortality	Overall		CV related		Cancer related	
	Univariable	*Multivariable*	*Univariable*	*Multivariable*	*Univariable*	*Multivariable*
Risk factor	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Age *	1.08 (1.04 to 1.12)	1.08 (1.05 to 1.10)	1.08 (1.04 to 1.12)	1.08 (1.04 to 1.13)	1.05 (1.01 to 1.10)	1.05 (1.01 to 1.09)
Female gender	0.93 (0.55 to 1.59)	0.90 (0.51 to 1.59)	1.06 (0.46 to 2.49)	1.14 (0.48 to 2.72)	1.33 (0.56 to 3.13)	1.50 (0.39 to 2.78)
Renal insufficiency	1.56 (1.13 to 2.15)	1.23 (0.88 to 1.72)	2.32 (1.37 to 3.94)	1.71 (0.98 to 2.96)	1.94 (1.49 to 1.78)	0.80 (0.41 to 1.56)
Anaemia	1.74 (1.26 to 2.39)	1.42 (0.99 to 2.02)	2.05 (1.20 to 3.49)	1.38 (0.76 to 2.47)	1.67 (0.93 to 3.01)	1.56 (0.79 to 3.05)
CV history	1.39 (1.00 to 1.92)	1.33 (0.94 to 1.89)	1.79 (1.01 to 3.18)	1.71 (0.94 to 3.11)	0.84 (0.47 to 1.50)	0.90 (0.48 to 1.67)
Cancer history	2.73 (1.96 to 3.83)	2.83 (1.99 to 4.03)	1.55 (0.82 to 2.94)	1.67 (0.86 to 3.24)	5.17 (2.89 to 9.24)	5.06 (2.73 to 9.38)
Diabetes history	0.87 (0.54 to 1.41)	0.85 (0.52 to 1.39)	1.22 (0.60 to 2.49)	1.24 (0.60 to 2.56)	0.75 (0.29 to 1.89)	0.70 (0.27 to 1.81)
Rupture	1.24 (0.85 to 1.83)	1.25 (0.80 to 1.98)	1.79 (0.99 to 3.24)	1.69 (0.86 to 3.34)	1.17 (0.56 to 2.43)	1.50 (0.64 to 3.54)
EVAR	0.88 (0.65 to 1.22)	0.81 (0.57 to 1.15)	0.81 (0.47 to 1.39)	0.78 (0.44 to 1.39)	1.18 (0.64 to 2.17)	1.05 (0.53 to 2.08)

Legend: * per unit (year) increase. HR – Odds Ratio; CV – Cardiovascular; EVAR – Endovascular Aneurysm Repair

Late overall mortality

Over a median follow-up of 2.4 years (range: 8.9 years), there were 157 deaths after 30-days. The estimated survival after operation for intact AAA was 78% and 65% at 3- and 5-years, respectively. For ruptured AAA, the estimated survival was 48% and 41%, respectively (Figure 1). The independent predictors for late overall mortality after AAA repair were age (HR: 1.08 per year increase, 95% CI: 1.05 to 1.10) and prior history of cancer (HR: 2.83, 95% CI: 1.99 to 4.03), Table 3. If 30-day deaths were not considered, there would be no difference in prognosis for intact and ruptured AAA patients over the first 5 years (Figure 2).

Late cardiovascular and cancer-related mortality

During follow-up there were 55 (35%) cardiovascular deaths. Only age (HR: 1.08 per year increase, 95% CI: 1.04-1.13) was identified as an independent predictor of cardiovascular death after AAA surgery. Cancer-related deaths occurred in 46 (29%) patients. Lung cancer was the most common type (22/46), followed by neoplasms of the digestive tract (11/46). Age (HR: 1.05 per year increase, 95% CI: 1.01-1.09) and prior history of cancer (HR: 5.06, 95% CI: 2.73-9.38) were independent predictors of cancer-related death. When excluding patients without a prior history of cancer, there was no difference in

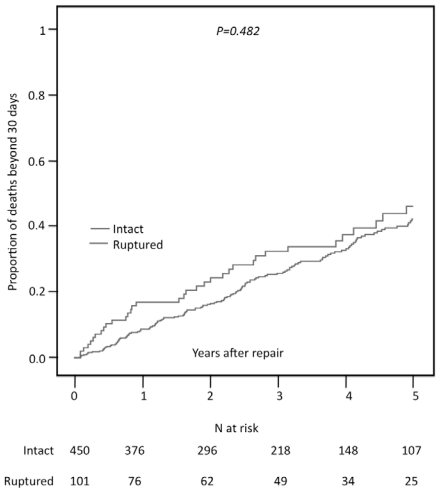


Figure 2. Estimated proportion of deaths beyond 30-days of AAA repair

Table 4. AAA-related late mortality

Patient	*Gender*	*Age*	*Days after surgery*	*Associated causes (ICD-10 codes)*	*Type of repair*	*Indication for repair*	*Place of death*
1	Male	68	34	Sepsis (A41.9)	EVAR	Rupture	Hospital
2	Male	93	73	Postprocedural complications of the circulatory system, unspecified (I97.9) Dementia (F03.0), Renal insufficiency (N18.9)	EVAR	Intact	Nursing home
3	Male	73	90	Sequelae of complications of surgical and medical care (T98.3), Embolism or thrombosis of arteries of the lower extremities (I74.3)	Open	Rupture	Nursing home
4	Male	75	147	Sequelae of complications of surgical and medical care (T98.3), Atherosclerosis of the aorta (I70.0)	Open	Rupture	Nursing home
5	Male	62	223	Sequelae of complications of surgical and medical care (T98.3), Sepsis (A41.9)	EVAR	Intact	Nursing home
6	Male	71	772	Vascular graft infection (T82.7)	EVAR	Intact	Hospital

cancer-related mortality between endovascular and open surgery patients (4.6% vs. 5.6%, respectively; P=0.83), suggesting that the possible influence of repeated radiation exposure following EVAR is inexistent or has little impact on prognosis.

AAA-related late mortality

After 30-days, six (1.1%) deaths were coded as being AAA related, Table 4. Three of these occurred in the intact AAA group (0.7%), and three occurred in the ruptured AAA group (3.0%), P=0.042. Only one of these six events was coded as a direct consequence of rupture, which was a patient on the postoperative day 34 after EVAR for ruptured AAA. One death in the intact AAA group and two deaths in the ruptured AAA group occurred within 3 months of operation, which suggests a possible association with the primary event. There was no difference in AAA related late mortality in patients undergoing open repair (two deaths, 1.1%) or EVAR (four deaths, 1.1%), P=0.951.

DISCUSSION

Determining the vital prognosis of patients after AAA repair is paramount for patient selection and informed consent. Our study demonstrates an improved overall survival and a significant shift in the cause of death (towards less cardiovascular and more cancer-related mortality) for patients after AAA repair, compared to historical series. Also, it suggests that the life expectancy after ruptured AAA is similar to those treated electively, once a patient endures the critical perioperative period. Lastly, our findings confirm the early survival benefit of EVAR (both in ruptured and intact patients), which is lost at long-term.

Comparison of overall survival to previous literature

The benchmark randomized studies and large observational studies comparing EVAR and open surgery have shown us that the survival of AAA patients after repair is worse than survival of the age- and gender-matched background population. In a recent meta-analysis including 4 large randomized trials and data from the Medicare and Swedvasc databases, Stather *et al* reported a 14-15% mortality at 2-years, and 33-34% mortality at 4-years or more for elective AAA repair.[1] In a large Swedvasc-based publication on long-term survival after AAA repair spanning from 1987 to 2005, Mani *et al* have reported a 69% and 42% crude 5-year survival after intact and ruptured AAA repair.[7] The estimated survival in our series was 65% at 5-years for intact AAAs, and 41%,for ruptured AAAs. Although these estimates appear relatively similar, it is important to note that these may not be entirely comparable populations – it is likely that before EVAR was generalized,

patients with less physiological reserve (elderly or higher risk patients) were not offered treatment. In our study, the proportion of EVAR patients is much greater.

Cardiovascular mortality shift

Contemporary epidemiological studies have shown that life expectancy continues to increase, and that there is a proportional trend towards a decrease in cardiovascular deaths in the overall population.[8] Although aortic aneurysmal disease typically co-exists with atherosclerosis,[4] the proportion of our patients dying of any cardiovascular cause was relatively low (35%). A historical study of 1112 AAA patients operated between 1970 and 1975 reported cardiovascular related deaths in over 2/3 of patients, a proportion much greater than observed in this study.[9] In a more contemporary series, dating from 1999 to 2004, Brown *et al* reported 256 cardiovascular deaths out of 524 deaths in patients randomized for the EVAR-1 trial over 5.5 years. This corresponds to 49% cardiovascular mortality, a proportion much greater than we observed.[10] The same group reported 46 (32%) fatal myocardial infarctions or strokes in 145 deaths of patients randomized to EVAR for the EVAR-2 trial and followed for 2-8 years.[11] These results suggest a greater contribution of cardiovascular causes for death in these trial populations, compared to the cohort of our study. The Dutch DREAM trial reported cardiovascular deaths in 32/106 (30.1%), a proportion closer to the one found in this study.[12] These disparities may be explained by geographic differences and recent evolution in secondary prevention for this population, particularly with the generalized use of antiplatelet and statin therapy. Although we could not obtain exact figures on the proportion of patients receiving appropriate secondary prevention, it is likely that most received life-long antiplatelet and statin therapy as part of our local protocol. Naturally, both the DREAM and the EVAR-1 trials only included patients considered fit for prophylactic open repair, and do not reflect the real-life population of AAA patients included in the present study.

Cancer-related mortality in AAA patients

Cancer-related mortality is an important cause of mortality for AAA patients, responsible for almost 1/3 of deaths in our population, and coming second only to cardiovascular disease. If coronary ischemic disease, stroke and PAD were considered separately, malignant disease would be the most frequent cause of death by a large margin. Aside from age, only a prior history of cancer was a strong predictor of overall death, increasing the risk by nearly 3-fold, and of cancer related death, increasing the risk by 5-fold. This suggests that a prior history of cancer has a strong impact on the overall survival of AAA patients, and may need to be considered in the decision process for elective treatment. Despite an apparent decrease in incidence of cancer in western populations,[13] this pathology has a marked impact on the prognosis of patients with AAA.

Cancer related mortality was similar between EVAR and open surgery patients. This remained true after exclusion of patients without a prior history of cancer, suggesting that the effect of cumulative radiation of a typical post-EVAR surveillance protocol did not result in an increase in incidence of cancer during the study period.

AAA-related deaths

Previous publications suggest a yearly risk of AAA-related death of 0.5 to 1%.[1] In a publication by Wyss et al, the authors even suggest that these are responsible for the mid-term survival catch-up effect of endovascular vs. open repair, in a way cancelling the early survival benefit of EVAR.[14] The proportion of patients dying from AAA-related cause is smaller in this study, however. This may be explained by patient selection or by the time period involved (improved planning, procedural skills and device technology). Interestingly, infection was primary event in the majority of AAA-related deaths, a matter that deserves consideration in the future.

Impact of rupture on outcome for AAA patients

The timing of surgery had a strong impact on early survival after AAA repair, with ruptured AAA patients having an expected 10-fold increase in mortality. More importantly, timing had no influence of *late* mortality, as illustrated by the parallel evolution of the survival curves beyond 30-days. This similarity in long-term prognosis may seem counter-intuitive, especially considering that the intact AAA group had a higher incidence of coronary disease, diabetes and PAD at baseline in our study. However, it confirms the similar long-term survival expectancy between intact and ruptured AAA patients, observed by Mani *et al*.[7] This interesting finding suggests that an increment in perioperative survival for rAAA patients is the most influential attitude for improving vital prognosis of AAA patients.

Impact of treatment alternatives on survival

The choice of treatment (endovascular vs. open) had a strong impact on 30-day outcome, as already demonstrated extensively in literature,[1] but no influence on overall or AAA related late mortality. Although endovascular patients are known to require a higher number of secondary interventions and have a persistent (yet small) risk of late ruptures, these appear to have no important influence on survival expectancy. There were six AAA-related deaths in our series. Four of these were after endovascular repair, of which three had septic complications suggesting endograft infection to be the predominant cause of AAA-related death after endovascular repair. These results challenge the suggestion by Wyss et al that post-implant ruptures were mainly responsible for the convergence of survival expectancy between OR and EVAR observed in the EVAR-1 trial.[14] Globally, however, our results show no long-term prognostic difference between

open and endovascular repair, which supports a previous publication by Schermerhorn et al.[15]

Limitations

There are limitations to consider in this study. Firstly, this is a retrospective study of a single institution, therefore subject to reporting bias. Also, *post-mortem* examinations are not routinely done in the Netherlands, limiting the diagnostic acuity of codification. The causes of death reported, however, were obtained via the Central Bureau of Statistics, had an availability of 100% and represent the most accurate way available to acquire information on mortality. Reliability of cause-of-death coding in the Netherlands for major causes of death including cancer and myocardial infarction has been investigated and found to be higher than 90% over the period of this study.[16]

Finally, the study generalizability may be compromised by the predominantly western European origin of included patients, by the level of secondary prevention and incidence of cancer observed in the study setting and by the local expertise in aneurysm treatment. Genetic and environmental modifications may result in different outcome for AAA patients.

CONCLUSIONS

The results of this study suggest a trend towards improved overall and cardiovascular related survival after AAA repair compared to historical series, with malignancy assuming growing preponderance in the long-term. Endovascular repair reduced 30-day mortality by 3-fold, but no survival benefit, nor increased mortality was observed in the long-term. After the early postoperative period, the prognosis of patients after ruptured AAA is favourable and similar to that observed after intact AAA repair.

Based on these observations, an increased awareness for malignancy in this specific population is necessary. Also, efforts should focus on improving perioperative mortality for ruptured AAA.

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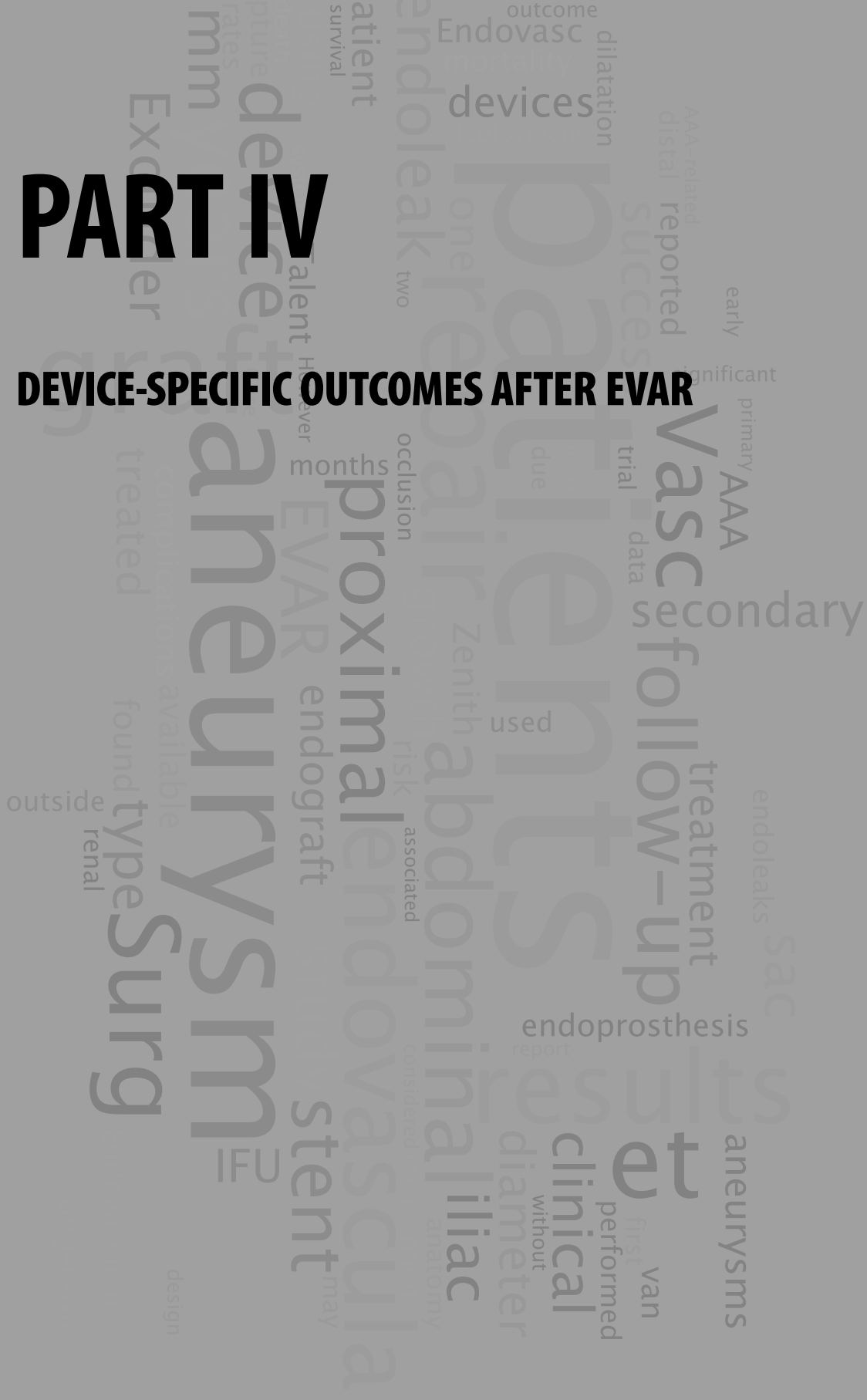
PART IV

DEVICE-SPECIFIC OUTCOMES AFTER EVAR



Chapter 12

Device-specific outcomes after endovascular abdominal aortic aneurysm repair

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ABSTRACT

Over the last decade, endovascular aneurysm repair (EVAR) has been used extensively for elective infra-renal abdominal aneurysm treatment. However, it remains unclear how specific devices perform and how they compare to others. We provide an overview of currently used endografts, and discuss the current evidence regarding device-specific outcomes.

Published literature confirms differences in results according to endograft selection. These differences were more pronounced with older generations of devices, in comparison to newer models. Contemporary results are generally good and one should remember that no randomized data exist regarding individual device performance.

Moreover, by the time there is enough follow-up to draw conclusions, the data is relatively obsolete due to constant improvements in endograft technology and design. Results from EVAR have been steadily improving and individualized device selection has shown to be valuable. It appears that patients with favorable anatomy do well with most modern endografts. Those with challenging anatomies may benefit more from a particular design, delivery and deployment feature requiring greater knowledge and experience for adequate device selection.

INTRODUCTION

Endovascular aneurysm repair (EVAR) has received widespread acceptance as elective treatment for infra-renal abdominal aortic aneurysms (AAA). The first successful procedures in humans report back to 1991, when Volodos, et al.[1] and Parodi, et al.[2] independently demonstrated the feasibility of remotely placing a graft through the femoral arteries in order to exclude the aneurysm sac from circulation.

Both the scientific community and the medical industry showed significant interest in these brake-through reports. It became clear that, while feasible and successful in the short term, these homemade devices were not suitable for widespread use. Rapid developmental research resulted in a number of commercially available devices – at first essentially aorto-aortic tube endografts, than shifting to predominantly bifurcated (aorto-biiliac) or funnel-shaped (aorto-monoiliac) designs.

Technological advancements coupled with extensive clinical research resulted in general acknowledgment of EVAR as a valid alternative to open surgical repair. The technique has been thoroughly validated by several randomized controlled trials[3,4,5,6] and large independent registries.[7,8] The constantly growing number of procedures performed across the world is a clear indicator that this method has gained acceptance from both physicians and patients.

Despite the significant experience to date, it remains unclear how particular EVAR devices compare. Different manufacturers advertise the conceptual advantages of each specific device in relation to others, but this is scarcely supported by solid data. In this evidence-based void, opinions differ according to personal experience or conceptual beliefs. Some trust that currently commercialized models perform equally well in nearly all cases, others feel that a more individualized selection may be more advantageous. In reality, there is no grade I evidence to support either view.

This review aims to provide the reader with an overview of most endovascular devices for AAA treatment: their characteristics, evolution, potential advantages and drawbacks. Current evidence regarding device-specific outcomes is presented and discussed.

CURRENTLY COMMERCIALIZED ENDOGRAFTS (TABLES 1, 2 AND 3)

The first endografts used for EVAR were homemade, relatively crude devices. While usually efficient at excluding the aneurysm sac from circulation, they were associated with a high percentage of technical failure as well as unacceptable rates of early and late complications. Rapidly, industry-driven research and technological advances provided surgeons and interventionists with safe and effective commercial options for EVAR. Through growing experience and research, it gradually became clear that certain

device improvements would facilitate implantation, increase safety, reduce early and late complications and ultimately expand indications. After nearly 20 years, much has changed in endograft technology.

The basic structure of endografts is fairly similar. A prosthetic graft similar in size to the native vessels is introduced via femoral arteries. This graft is completely or partially supported by stents, which provide the structure needed for fixation and to avoid collapse. The proximal and distal edges provide sufficient sealing zone with the contiguous normal-sized vessel to exclude the aneurysm sac from circulation. The configuration is usually bifurcated, extending from the lowest renal artery to a non-aneurismal segment of the iliac arteries. Most manufacturers also provide aorto-uniiliac variants, which usually require a contra-lateral common iliac occlusion device and extra-anatomic femoro-femoral revascularization.

The main body and iliac limbs are provided in a large variety of diameters and lengths, to adapt to specific anatomic restrains. For adequate compliance to the patient's anatomy, different size and diameter extensions may be added, by means of overlapping segments. Delivery systems rely on the same basic features, but profiles, surface materials and deployment systems differ considerably.

Table 1. FDA and CE-approved devices. Details of design, stent structure and fixation

Device	Graft material	Support	Design	Proximal fixation
AneuRx (Medtronic)	Polyester	Complete nitinol mesh exoskeleton	Tri-modular	Infra-renal / friction
Excluder (Gore)	ePTFE	Complete nitinol stent exoskeleton	Bi-modular	Infra-renal / friction + barbs
Talent (Medtronic)	Polyester	Complete nitinol stent endoskeleton	Bi-modular	Supra-renal / friction
Powerlink (Endologix)	ePTFE	Complete elgiloy mesh endoskeleton	Unibody	Optional supra-renal / friction / columnar
Zenith (Cook)	Polyester	Complete stainless steel stent exoskeleton	Tri-modular	Supra-renal / friction + hooks
Anaconda (Vascutek)	Polyester	Body unsupported. Internal nitinol rings structure	Tri-modular	Infra-renal / friction + hooks
Aorfix (Lombard)	Polyester	Complete internal nitinol rings	Bi-modular	Infra-renal / friction + hooks
Endurant (Medtronic)	Polyester	Complete nitinol stent exoskeleton	Bi-modular	Supra-renal / friction + hooks
E-Vita (Jotec)	Polyester	Complete nitinol stent endoskeleton	Bi-modular	Supra-renal / friction

Table 2. Specific device sizes and delivery profile
Legend: OD: outer diameter, MB: main body, CL: contralateral limb

Device	Sizes (proximal/distal)	Deployment profile (OD) MB/CL
AneuRx (Medtronic)	20-28mm / 12-24mm	21F / 16-19F
Excluder (Gore)	23-31mm / 10-20mm	20-22F / 14F
Talent (Medtronic)	22-36mm / 8-24mm	22F / 18F
Powerlink (Endologix)	25-34mm / 16-25mm	21F / 17F
Zenith (Cook)	22-36mm / 8-24mm	18-20F / 14-16F
Anaconda (Vascutek)	19,5-34mm / 10-23mm	20,4-22,5F / 18,3F
Aorfix (Lombard)	24-31mm / 10-20mm	22F / 14F
Endurant (Medtronic)	23-36mm / 10-28mm	18-20F / 14-16F
E-Vita (Jotec)	24-34mm / 14-26mm	20-22F / 16-18F

Table 3. Device-specific recommended Instructions for Use (IFU)

Device IFU	Minimum proximal diameter	Minimum neck length	Maximum neck angulation	Iliac artery diameter range
AneuRx (Medtronic)	10-20% < labelled device diameter	10mm	Not stated	10-20% < labelled device diameter
Excluder (Gore)	19-29mm	15mm	600	8-18,5mm
Talent (Medtronic)	18-32mm	10mm	60	8-22mm
Powerlink (Endologix)	18-32mm	15mm	60	10-23mm
Zenith (Cook)	18-32mm	15mm	60 infrarenal 45 suprarenal	7,5-20mm
Anaconda (Vascutec)	10-20% < labelled device diameter	15mm	Not stated	10-20% < device diameter
Aorfix (Lombard)	2mm < labelled device diameter	20mm	Not stated	1mm smaller < device diameter
Endurant (Medtronic)	19-32mm	10mm	75 infrarenal /60 suprarenal (if neck 10-15mm, 60/45)	8-25mm
E-Vita (Jotec)	10-20% < labelled device diameter	20mm	Not stated	10-20% < labelled device diameter

FDA and CE-approved endografts

AneuRx - Medtronic AVE (Santa Rosa, California, USA) – Figure 1

This is a modular design polyester graft supported by an external nitinol (nickel titanium alloy) woven skeleton. The fixation to the vessel wall depends on friction both proximally and distally. First introduced in 1996, this device received FDA approval in 1999. It has undergone 7 modifications to date, (refining its structural integrity and making

Figure 1. The latest generation AneuRx device.

it progressively more flexible) having the longest longevity of all endografts currently marketed in the USA. The latest generation available (the AAAvantage) features a 21F for main body and 16-19F for iliac delivery system with hydrophilic coating. Aortic diameters range from 20-28mm and iliac diameters range from 12 to 20mm (up to 24mm in flared design).

This device was first associated with mid-term migration in a 2002 study by Conners, et al. This single-center study showed this complication in 15/91 patients within 4 years of follow-up.[10] The issue was further discussed by Zarins, et al. and Sampaio, et al., linking migration with this graft to adverse proximal neck anatomy and sub-optimal deployment (distance from graft to renal arteries), as well as apposition length (distance of graft covered neck seal).[11,12]

Migration is not a specific problem of the AneuRx device, of course. Studies have shown migration to occur with other devices as well, but less frequently (around 2% per year).[13-15] In a 2005 EUROSTAR report, the AneuRx was associated with an annual incidence of 4.3%, higher than any other commercially available graft today.[13] In this report, the higher rate of migration did not translate into significant differences regarding device-related endoleaks, secondary intervention or rupture risk in comparison with the Talent, Excluder and Zenith grafts.

The Positive Impact of endoVascular Options for Treating Aneurysm earLy (PIVOTAL) trial included 332 patients in the EVAR arm. It was funded by Medronic Vascular and included only patients with AneuRx and Talent endografts.[16] Though the exact proportions of each device were not stated, AneuRx devices probably predominated since the Talent endograft only received FDA approval over halfway through the recruitment period. In this trial migration was only present in 0,3%, which is appreciably less than in previous reports. This difference remains to be explained, but possibly changes in the newer generations of the graft and better planning and deployment capacity may be responsible. Further analysis on this is necessary.

Stent fracture was a frequent finding with earlier generations of the AneuRx, Talent and other nitinol-based endografts. This was attributed to the stent material – nitinol – that is known to suffer oxidation after prolonged exposure to blood. This degradation makes it prone to separation and fracture. Electro-polishing and utilization of one-piece stents (without welds) provide better resistance and have been introduced in the subsequent generations of all models. The connecting bar (featured shared by the AneuRx and Talent devices) was also shown to be fragile. Designed to provide stability and rigidity to the device (increasing its columnar strength) this component was frequently found fractured on follow-up imaging. The manufacturer later changed the location of the connecting bar from lateral to medial, which succeeded in preventing fracture.

Rupture risk was a significant problem with the first generation of the AneuRx.[17] The device was responsible for most ruptures in a report from the Lifeline registry.[7] This was attributed to excessive rigidity of the early generation, which was then replaced by a more flexible design. Latter results using subsequent generations did not show a difference in rupture risk when compared to groups with different endografts implanted.

Being widely available since 1999, longevity gives this graft (like others that have been commercialized for a long period) a certain competitive advantage. The reassurance of lasting performance, despite a significant rate of long-term complications, has been well demonstrated by van Herwaarden, et al.[18] They found freedom from secondary interventions to be 48% at 9 years, with proximal fixation issues being the most common cause for re-intervention. Freedom from aneurysm-related death was 90% at 9 years.

Excluder – W. L. Gore & Associates, Inc (Sunnyvale, CA, USA) – Figure 2

The Excluder endoprosthesis is a modular expanded polytetrafluoroethylene and fluorinated ethylene propylene (ePTFE and FEP) graft, fully supported by external nitinol stents. Anchors placed at the proximal edge of the main-body and a proximal sealing cuff enhance fixation and seal. FDA approval for this graft came in 2002, but this graft has been available in the European market since 1997. Since its debut, it has been significantly modified twice (from the Original to Modified, and from Modified to Low Permeability Gore Excluder).

The Excluder is produced in 23-31mm proximal diameters (up to 32 by using aortic extender cuffs) and distal diameters ranging from 10 to 20mm. It requires a separate introducer sheath (not included) with inner diameters of 18 or 20F for main-body deployment. Although this is often interpreted as a very low profile for a main body, it actually corresponds to an outer diameter of about 20-22F, making similar to most available grafts. There is a potential advantage of this separate system in patients with complex access: the graft only needs to be unpacked once access to the deployment site has been achieved with a separate sheath. The expense hazard in the case of access failure is therefore restricted to the cost of the latter.

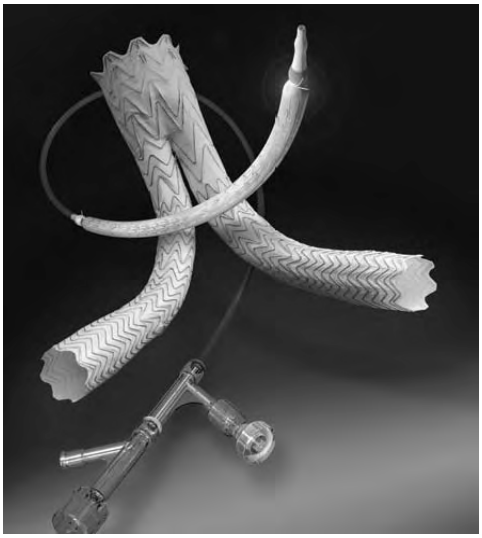

Figure 2. The Excluder device, showing the particular delivery system.

The deployment system of this graft is quite particular. The graft is constrained inside an ePTFE sleeve attached to a delivery catheter. To deploy, one needs only to pull a thread that quickly releases the graft into the intended location. The lack of precise control for proximal placement has been subject of criticism from some, and a "slow release technique" has been described for a more controlled deployment. However, deployment remains relatively imprecise, leading to potential type-I endoleaks, renal artery coverage and higher need of proximal aortic extensions with inherent increased risk of type-III endoleaks.[11] This has lead some clinicians to prefer this graft in longer proximal necks, selecting other grafts with more precise positioning for shorter necks.[19]

In challenging anatomy, the lack of supra-renal fixation has been has been appointed as a risk factor for complications, in particular migration and type-I endoleaks (with subsequent expansion and rupture risk).[11] Hobo, et al.[20] reported on a subgroup of patients with an Excluder endograft (n=901) and found that proximal endoleak at the completion angiogram and long-term proximal neck dilatation (odds ratio of 4.49 and hazard ratio of 1.67, respectively) were more frequently observed in patients with severe neck angulation. In such cases, three techniques have been described to enhance fixation. One is the use of giant Palmaz stents (Palmaz® XL stent - Cordis Corporation, a Johnson & Johnson company; Miami Lakes, Fla), either prior or after the main-body deployment.[21] The second is the "endowedge" technique.[22] This strategy takes advantage of the scalloped proximal edge, fitting the wedge into previously placed renal angioplasty balloons (via a brachial approach). This requires a slow release to allow for proximal mobilization until the intended position is obtained. This theoretically increases about 4mm to the

proximal neck. The last uses a previously placed proximal cuff onto which the main body anchors attach.[22]

Due to the flexible yet kink-resistant nature of the Excluder limbs, performance in face of adverse lilac anatomy is considered superior to that of the Zenith or Talent devices. Data for EUROSTAR and single-centre reports support this, with lower rates of kinking and limb occlusion, despite its preferential use in patients with stenotic, heavily calcified and tortuous iliac arteries.[13,19,23]

There were concerns regarding reduced sac shrinkage and late aneurysm expansion with the first generations of this device.[24] At 4 years, approximately 1/3 of patients treated with the Excluder showed continued increase in aneurysm expansion.[25] When compared to the Zenith and AneuRx devices, the percentage and rate of aneurysm shrinkage differed significantly.[26] In-vitro investigation revealed that this difference in post-implantation behaviour was due to continued pressurization of the aneurysm sac, as a consequence of higher porosity in the graft fabric. Once aware, Gore rapidly addressed the issue by creating and commercializing a modification in the original ePTFE microstructure that significantly reduced transmigration of fluid across the graft.

Results from patients implanted with the latter generation (the Low Permeability Excluder) were subsequently compared with those treated with the previous model. Tanski, et al. found a significant difference in the percentage and rate of aneurysm sac shrinkage at 1 year, favoring the low permeability version.[27] Haider, et al. reported similar findings, and further showed sac regression with the newer model to be comparable to the results using the Zenith device.[28] For patients with an expanding aneurysm, arresting growth by re-lining the original graft with a lower permeability material is a successful treatment strategy.[30] Since it has been demonstrated that sac enlargement may be delayed several years, long term-results with this last generation of the Excluder are still needed.[29]

Despite these concerns regarding post-operative aneurysm expansion, the original Excluder graft was shown to compare favorably with its main competitors in a 2005 EUROSTAR report by van Marrewijk, et al.[13] They found the estimated annual rate of aneurysm expansion to be 4,2%, and rates of device related endoleak, secondary intervention and rupture were 5,0%, 3,5% and 0,1%, respectively. Others have also reported similar results, with a 5-year secondary intervention rate of 13.8%, of which more than 2/3 occur within the first year.[31] In very angulated proximal anatomy (>60º), re-interventions were comparable to the Zenith device and better than those of the Talent device.[20]

Talent – Medtronic AVE (Santa Rosa, California, USA) – Figure 3

The Talent is a modular graft composed of polyester supported by an inner serpentine-like independent stent-ring structure. These stents are sutured to the fabric and attached to each other by connection bars (as mentioned), additionally offering columnar

support. A flared proximal bare stent provides extra fixation (without the aid of anchors or hooks) and an additional short proximal stent is offered in an optional fashion, to further promote adequate seal. Experience with this stent started in 1998, with 4 modifications up to date - mainly related to delivery and deployment systems. Initially introduced with a stiff stent in the aortic body, this was quickly corrected and nearly all implantations were with the subsequent relatively more flexible body.

This endograft is commercialized in a wide array of sizes, ranging from proximal diameters of 22-36mm and distal diameter components ranging from 8-24mm, with possible straight, tapered or flared configuration. The terminal design may also be open or closed web configuration. Aside from the typical bifurcated design, aorto-monoiliac (converter) and aortic and iliac cuff designs are also commercialized. This allows for treatment of a vast majority of aneurysm sizes and configurations. A compliant balloon is pre-mounted in the delivery system for easy use.

Many features of this device were developed to deal with more complex proximal anatomy. Torsello, et al. found adverse anatomy did not adversely influence the aneurysm shrinkage rate, the risk for a secondary procedure, or the clinical success rate in a series of 165 patients with long-term follow-up.[32] The potential for handling complex anatomy was partially offset by the delivery system (22-24F) of the main body (18-20F for contra-lateral extensions) needed to deploy this graft. The newer delivery system (Low Profile) was reduced only to 22F. These diameters are indeed larger than some other endografts and even more so when compared with newer devices such as the Endurant or the Zenith Flex. The prospect of technical failure or iatrogenic lesion remains an issue in diseased or heavily calcified access vessels and in women, known to have smaller diameter iliac arteries.[33,34]

The role of para-renal/supra-renal fixation in relation to renal events during follow-up has been investigated. There seems to be evidence of a higher risk of peri-procedural embolization, translated by peri-operative small segmental renal infarctions without influence on glomerular filtration rates. Similarly, no influence on mid and long-term deterioration of renal function was noted (both infra-renal and trans-renal fixation groups show similar rates of decline).[35,36,37,38]

The Talent and Zenith devices are the most frequently used devices using supra-renal fixation. Inevitably, comparison between the two is more frequent than with other devices. Despite the relatively small experience with this graft in the USA (FDA approval came only in 2008), the European practice is considerable. The largest sample comes from EUROSTAR, reporting in 2005 a total of 1579 patients with this graft implanted.[13] These investigators found that, compared to the Zenith device, the Talent was more likely to migrate (OR: 3,61; 2.1-6.4) and require conversion to open repair (OR: 3,5; 1,9-6.3). However, there was little statistical significance on most outcomes when comparing all third-generation grafts in this study. Ouriel, et al. reported contrary results: in their se-

ries, the risk of migration for Talent was 0% while it was 8.2% for the Zenith, a difference without statistical significance.[39] The potential disadvantage of the Talent in fixation (no hooks or barbs, unlike the Zenith) remains therefore unproven and differences in series may be simply explained by bias in patient selection.

Brown et al. 40 looked into the relationship between graft selection and outcome for the UK EVAR trials patients. In these trials, primarily Talent or Zenith endografts were implanted and only these were analysed. The rate of secondary intervention was similar on the short-term but subsequently higher for the Talent group for up to 4-years (7.0 and 9.4 per 100 patient years for Zenith and Talent grafts respectively, adjusted hazard ratio 0.77). Also higher was the rate of aneurysm related mortality (1.2 and 1.4 per 100 patient years for Zenith and Talent grafts respectively, adjusted hazard ratio 0.90) reflecting a higher mid-term complication rate. However, these differences were small and both devices performed well. As pointed out by the authors, results such as these must be considered with care. Firstly, despite the trial being randomized, the graft selection was not and this may obviously result in bias. Furthermore, during the trial period (1999-2004) graft improvements and modifications in the capacity to identify and interpret post-operative complications may have influenced results. Lastly, follow-up is restricted to mid-term results.

Regarding aneurysm sac regression, a long-term follow-up study demonstrated treatment with the Talent device to result in shrinking in 64% of patients, while increasing in 8.5% of patients.[32] All patients with growing aneurysms had associated type-I or II endoleaks. In the same study, a 6,3% secondary intervention rate was attributed to limb thrombosis, higher than other FDA approved devices. Cochennec, et al., in a comparative study regarding limb occlusion, found a 14% rate at 2 years, at least twice as much as its main competitors. The limb occlusion rate for first-generation devices (like Vanguard and EVT/Guidant) was strikingly higher, though.[41]

Figure 3. The Talent endograft, with the additional short proximal covered stent for enhanced fixation.

In general, larger aneurysms seem to be associated with higher complications and mortality after EVAR. This seems to be particularly true with the Talent, as demonstrated by Waasdorp, et al. in a subgroup analysis comprised only of patients with implanted Talent from the EUROSTAR registry. They concluded that aneurysm size greater than 6cm in combination with a large diameter proximal neck (greater than 26mm) was significantly associated with unfavourable outcome.[32,42]

Figure 4. The Powerlink device. Notice the significant length of the main body, made of 2 overlapping components. The superior component features the optional supra-renal open stent.

Powerlink – Endologix Inc (Irvine, Calif, USA) – Figure 4

The Powerlink is the only available unibody bifurcated graft in the market. Like the Excluder, the elected graft material is ePTFE. Deployment essentially consists on placing the bifurcated device upon the original iliac bifurcation. This provides a proclaimed "anatomical fixation" that prevents device migration. Usually, a proximal component is necessary to complete the long main body and achieve seal. There is a choice of proximal fixation with or without a supra-renal uncovered stent (without hooks or barbs) meant to enhance proximal fixation. Limb extensions are also provided if needed. Available sizes for the proximal component range from 25-34mm and for the iliac components from 16-25mm, either straight, tapered or stepped.

An inner elgiloy (a cobalt chromium alloy) skeleton provides the supportive structure. It is attached to the graft only at the proximal and distal sites of each component and provides the columnar strength needed. The concept is to allow expansion and retraction of the fabric in response to the pulse wave of the aortic flow, therefore reducing strain on the stent material.

The bifurcated body deployment sheaths are relatively small (21F) and contra-lateral access may be easily done in a percutaneous fashion. However, when contra-lateral extensions are required, a 17F deployment sheath is still needed. Replacing the usual contra-lateral guidewire by a hollow one, capable of accommodating a 0,014 standard wire, facilitates cannulation of the contra-lateral limb. This particularly benefits patients with more complex iliac anatomy, especially if angioplasty or extensions are required. FDA approval came in 2004, but the device has been used since 1999 in Europe. In 2005, a voluntary recall of this device was issued, due to frequent separation of the tip of the device from its delivery catheter during insertion. After correction, no further complications were reported on this.

Two randomized multicenter trials were performed with Powerlink. Wang et al.[43] reported the 6-year results from the US FDA trial, with no aneurysm related deaths reported, a 4,3% migration rate, a 2,1% rate of secundary type-I proximal endoleak and a 1,5% rate of late conversion. The aneurysm was shown to shrink in 82,7% of cases and increase in 10,3%. Strikingly, no type III or IV endoleaks, graft disruptions or stent fractures were noted. The French study 44, though smaller, similarly showed no ruptures, 2/64 conversions to open repair and a 4,7% type-I endoleaks associated with migration at 3 years. Likewise, no graft disruption, stent fracture or type III/IV endoleaks were reported.

Subsequently, Qu, et al. reported on a large single-center series of 612 cases using the Powerlink stentgaft system.[45] Their initial experience, starting in 1999, used a "traditional" deployment starting at the renal level. From 2004 the deployment was performed in the anatomical fixation fashion, subsequently extending the graft proximally when needed. In a mean follow-up of 5,2 years, they found only 1 rupture and 7 migrations, all in the renal fixation group. In this series, 28% of patients were considered to have hostile proximal neck anatomy (<15mm length, >60º angulation). These were found to have slightly higher rates of Type I endoleak at 5 years (4,1% vs. 1,2%). Like in previous studies, no stent fractures, graft disruptions or type III/IV endoleaks were found. Furthermore, only 4% of patients exhibited aneurysm sac growth, and the authors speculated that this endoprosthesis is associated to more effective aortic remodelling than modular devices.

The results from published trials using the Powerlink endograft are notable. However, the worldwide experience with this device is relatively small. There remains doubt as to the reproducibility of these results in large population-based series.

Zenith – Cook, Inc (Bloomington, IN, USA) – Figure 5

The Zenith device is a three-piece modular polyester graft with an outer stainless steel stent structure (the most proximal and distal covered stents are internal). These Gianturco-type Z-shaped independent stents are sewn to the fabric with polypropylene monofilament sutures. A supra-renal flared bare stent is designed for extra fixation, and

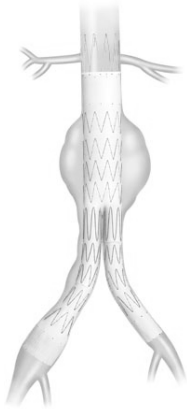

Figure 5. The Zenith Flex. Body stents have been shortened and the gap between them enlarged for greater flexibility.

includes barbs at 3mm increments. In the latest generation of this endograft, stents were shortened and the gaps between them became longer, adding flexibility to the system.

The manufacturers offer the vastest array of sizes and configurations, ranging from main body proximal diameters of 22-36mm, 4 different main-body lengths, and iliac extensions raging from 8-24mm in various shapes and configurations. These can be tailored to fit just about any anatomy. On the other hand, having all the stock off-the-shelf can be quite expensive.

The delivery system has also undergone a recent upgrade. Most main-body devices can be deployed through an 18-20F hydrophilic sheath (only the 36mm diameter graft requires a 22F). Iliac extensions are deployed through a 14-16F sheath. This is a major improvement from their initial 24F delivery system. Before its improvements, the Zenith device had undergone only minor design modifications since introduced in 1997. FDA approval came in 2003, after an already significant worldwide experience.

Greenberg, et al. published on mid and long-term follow-up from the Zenith US pivotal study. Technical success was at 99.5% and procedural success (including any major complication, type-I or type-III endoleaks at 30-days) was 95%.[46] They found aneurysm related death or late rupture to be very rare at 5 years, in both standard risk patients (2% and 0%, respectively) and in high-risk patients (4% and 0,4%, respectively). Only one rupture was reported. Also, the composite rate of conversion, migration and component separation was very low (<3%). It is important to note that, in this study, migration was only considered when a >10mm difference was noted (0,27% of patients). If a 5mm threshold were used (as in most studies), 2,58% would have been considered to migrate, which is still low 47. Other published series support these results, confirming a generally respectable performance with this device.[48-50]

Comparative studies have generally shown the Zenith endograft to perform well. When compared to the Talent device, both did globally well (please refer to the section on Talent for details). While some found a small superiority for the Zenith groups 13 40, others failed to show any significant difference.[39,51] Tonnassen, et al. found freedom from migration to be 67.4% of AneuRx and 90.1% of Zenith patients free from migration at 4 years of follow-up.[52]

Due to its characteristics, the Zenith graft is often used outside the IFU, potentially skewing results when compared to other grafts. In their single-center report, Abbruzzese, et al. found the opposite to be true. In fact, despite being used in more adverse anatomies, the 5-year results were marginally better than those of the Excluder and the AneuRx 53. Wales, et al. reported similar results marginally favouring the Zenith device from their single-center comparison with the Talent endograft despite an adverse bias in patient selection.[51]

The Zenith endograft has been around for well over a decade and subject to minor changes over time, meaning that the first generations were comparable to more recent ones. It has proven efficacy in short and long term, often being used as a reference to evaluate results from others. It is also the platform for a large experience on fenestrated and branched techniques, which remain out of the scope of this review bur are likely to play a significant role in the future.

CE approved endografts

Anaconda – Vascutek, Terumo (Inchinnan, Scotland) – Figure 6

The Anaconda is a three-piece modular system. The fabric is woven polyester sustained by a nitinol outer-frame. Certain design particularities differentiate this device. The proximal fish-mouth configuration is able to cover as much proximal neck as possible while preserving flow to the renal arteries. However, because neck dilatation over time may flatten the proximal stents, in is recommended that the anterior and posterior edges of the graft be horizontally aligned with the renal arteries. Proximal fixation is achieved through radial force, provided by two concentric nitinol rings and complemented by four pairs of hooks. The short main body is completely unsupported, while the limbs have a corkscrew-type stent made of only one stand of nitinol from top to bottom. According to the manufacturers, this allows maximum flexibility and kink-resistance.

The deployment is unique, in the sense that one can freely reposition the proximal stents until a satisfactory result is achieved. This comes at the cost of some complexity in the delivery system. Another ingenious idea is the magnet-aided catheterization of the contra-lateral limb, obviating (like with the Powerlink device) a step that can be time-consuming and challenging, even more so when the body of the graft is unsupported. The delivery sheaths range from 20,4F to 22,5F and the iliac extensions are delivered through an 18,3F sheath. It is available in proximal diameters of 19,5-34mm and lilac diameters of 10-23mm, both in straight and flared conformation.

Figure 6. The Anaconda device. Note the particular proximal configuration and unsupported body configuration.

Although experimental implantation in humans dates back over a decade, there is relatively little experience with this device. Stella, et al.[54] reported on 100 patients treated in a single institution and followed for an average of 23 months. These were patients with relatively short proximal necks (mean 26mm) and 1/3 had >60º angulation. Technical success was 100% with no aneurysm-related mortality during follow-up. There were, however, 4% limb thrombosis and 1 renal artery thrombosis due to dislocation of the proximal stent. Only 2 patients showed growth of the aneurysm >5mm at 24 months, and freedom from secondary intervention was 88% in that period. In another series of anatomically favourable patients (n=51) and even shorter follow-up (16 months), results were similar, with only 1 case of late type-I endoleak and 1 case of migration.[55] Other small studies have been published, all with comparable results on short and mid-term.[56,57] So far, no group presented results over 2 years with the Anaconda device. The question therefore remains regarding durability.

Aorfix – Lombard Medical Technologies (Didcot, UK) – Figure 7

This endograft was specifically designed to handle demanding anatomy and thus provide effective treatment for these patients. The result was a two-piece modular device made of polyester fabric fully supported by helical rings made from a single nitinol wire, similar to the Anaconda device. The proximal end also resembles the Anaconda, with a fish-mouth shape and 4 pairs of hooks to enhance proximal fixation. This graft, however, does not permit repositioning once deployed.

Proximal diameters range from 24-31mm, all available in 4 different body lengths. Distal diameters vary from 10 to 20mm, in straight or tapered design. The main-body is delivered in a pre-mounted 22F sheath. Two lateral push rods hold the graft in place

Figure 7. The Aorfix device. The particular ring-type structure is designed for extra flexibility.

while deploying and are used to precisely position and dilate the proximal stents. The contra-lateral limb is deployed in a 14F sheath.

There are very few published series with this device. Hinchiffe, et al. reported in 2004 on short-term results from 24 patients from the European Multicenter Study. These were fairly good, with one technical failure and no procedure related mortality or complications at 30-days. There was, however, unintentional coverage of an internal iliac artery in 25% of patients, suggesting that in vivo behaviour of the endograft limbs can be somewhat unpredictable. Subsequently, in 2006, a sub-study analysis was published, looking only at 29 patients with >45º proximal neck angulation (of which 79% had >60º angulation).[58] Technical success was 96% with no early device-related deaths or conversions. During follow-up there was one proximal type-I endoleak and one late death from rupture (at 4 years post-operatively) in a patient known to have a fractured stent. Strangely, no further data was published from this study.

Perdikides, et al. recently reported on a single-center experience of 20 patients.[59] Many of these patients had severe angulation of the proximal neck (70% had >60º angulation) and significant iliac tortuosity. The early results were excellent and reflect the current trend towards a very low complication rate using minimal hospital resources with EVAR. In this series, unintentional coverage of the internal iliac artery happened only one, which may be due to the inclusion of planning with 3-D reconstruction software in the study protocol. At a mean follow-up of 34 months, only one late proximal endoleak with an expanding aneurysm (>5mm) was noted. No other complications were reported and there was no aneurysm related mortality. Unfortunately, this was a rather small sample and no other reports confirm these good results.

Despite being commercially available in Europe since 2004, the Aorfix has not yet gained widespread acceptance and the experience with this endograft is very small. An FDA approved study is underway to provide approval for the US market, but results are still unknown.

Endurant – Medtronic AVE (Santa Rosa, California, USA) – Figure 8

The latest CE marked endograft (approved in 2008) was designed to perform equally well in patients with straightforward and very challenging anatomy. It is a bifurcated modular 2-piece polyester graft supported by a nitinol stent outer skeleton. An aorto-

monoiliac configuration is also available. Stents are relatively short and designed in an M-shape in the graft body, which confers great flexibility and conformability while making it resistant to compression and kinking. Fixation in enhanced by a supra-renal stent with anchoring pins, laser-cut from a single nitinol tube to provide greater fatigue resistance.

Sizes range from 23 to 36mm at the proximal end and 10 to 28mm at the distal end, in a straight, tapered or flared composition. A universal docking gate for the contra-lateral extension provides a simplified sizing matrix. The hydrophilic delivery system is 18-20F wide for the main body and 14-16F for the contra-lateral limb. The deployment system features a tip-capture mechanism that ensures a very controlled and precise release of the suprarenal stent. Retraction of the sheath allows for depressurization of the graft before finally securing it in place by releasing the top-cap, thus avoiding the windsock effect. Once deployed, this device nicely adapts to the pre-existing anatomy rather than forcing its shape upon it. On occasion, closure of the top-cap mechanism for retraction may interfere with the proximal bare stent and difficult withdrawal of the delivery system.

Results from two studies have been published so far. The first referred to preliminary results from a multicenter study performed in 40 patients.[59] Six (15%) of these patients had a proximal neck angulation >60º. No device-related complications were reported at 30-days, but longer follow-up was unavailable. A second report, from another European multicenter study, has recently presented one-year results from 45 patients.[60] From these, 84% were considered hostile proximal necks (mean angulation was 55º and mean lengh was 16mm). Technical and clinical success at 30-days were

Figure 8. The Endurant device. The flexibility of the device is illustrated in the picture, reflecting a 90º proximal neck angulation.

97,8% and 95,6%, respectively. They found one case of early type I endoleak, which was successfully corrected at 3-months with an aortic extension, one limb thrombosis treated by thrombectomy and stenting without further complications and one femoral pseudo-aneurysm. Freedom from graft-related endoleaks at one year was 97,8%, and no secondary interventions were required. No aneurysm-related mortality was noted at 1-year.

We have also looked at the performance of the Endurant stent graft in severely angulated necks, comparing a group of 45 patients with > 75º infra-renal angulation or >60º supra-renal angulation (or >60º infra-renal and 45º supra-renal angulation if neck length was <15mm). Still unpublished work from three centers in The Netherlands has shown that severe proximal neck angulation, measured using a well standardized method,[6;] had no influence on technical success, operative details and clinical outcome at 30-days when compared to a control group using the same endograft (Figure 9).

In our experience, trackability and pushability with this device is excellent and we have not encountered difficulties in crossing highly tortuous and stenotic iliac segments. Also, adaptation to the patient's anatomy seems more "physiological", as happens with the previously two endografts discussed. Meanwhile, experience with the Endurant is small and long-term results need to surface to confirm that this device performs at least similarly to other highly scrutinized devices.

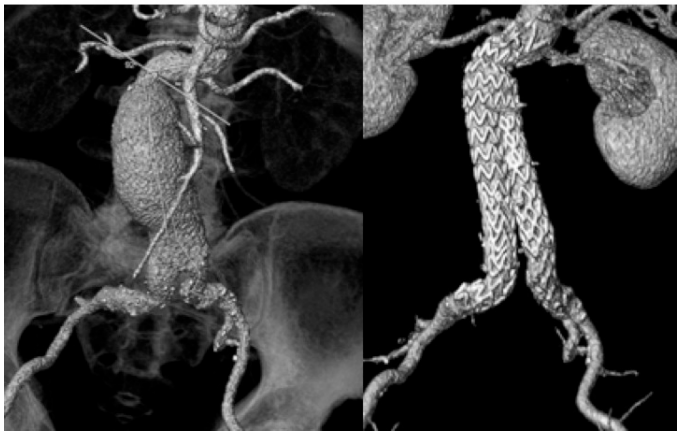

Figure 9. Pre and post-operative reconstruction of a severely angulated aneurysm treated with the Endurant device – Notice the in-vivo compliance to native anatomy, as a result of great flexibility and conformability

E-Vita – Jotec (Hechingen, Germany) – Figure 10

The E-Vita endograft is a bi-modular system using a polyester graft supported internally by nitinol stent-rings sewn to the endograft. The stents are aligned in a tip-to-valley

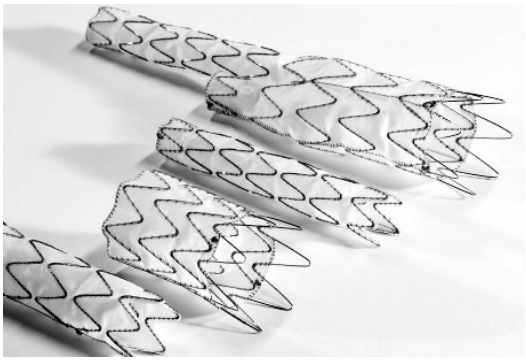

Figure 10. The E-Vita stentgraft.

configuration in the main-body and tip-to-tip in the iliac limbs. Proximal fixation is enhanced by a flared supra-renal open stent without active fixation. Although it shares some similarities with the Talent device, there is no connecting bar – meaning the endograft is more flexible. Proximal sizes vary from 24 to 34mm for the main-body and 14-26 for the iliac extensions, delivered in 20-22F and 16-18F sheaths, respectively. It was also released in the European market in 2008.

Only one publication was found regarding this endograft.[62] It reports on a 19 patient sample, of which 2 patients were secondary interventions due to complications after implantation with other devices; 21% of study-group patients were implanted with tube grafts (the two secondary interventions, one penetrating aortic ulcer of the infra-renal aorta and one false aneurysm). Percutaneous access was used in 83% of all access vessels. The 30-day results were excellent, with 100% technical success and 1 early type-Ib endoleak and 2 secondary renal artery occlusions. At 10-months of follow-up, there was one procedure-related death (due to colon perforation) and one conversion due to complete endograft thrombosis secondary to bilateral limb kinks.

The E-Vita device is fairly new and little data is available. Of the newer commercialized models, it seems to be the most conservative, as in does not introduce any substantial conceptual change in comparison to previous commercialized models. The similarities with previous devices that have proven their efficiency intuitively suggest that results with the E-Vita will not vary significantly, but that remains to be proven by evidence.

DISCONTINUED MODELS

Early devices were generally associated adverse outcome and have gradually all been withdrawn form the market. One should, however, be familiar with their characteristics

and potential complications, since there are still many patients with these grafts implanted.

The short-term efficacy of these early models was seriously compromised by an unacceptable rate of subsequent complications, in particular structural failure and migration. In a EUROSTAR report by Harris, et al. from 2000 the annual rupture risk was 1,0%, but, as acknowledged by the authors, this was probably an underestimate.[63] The cumulative risk of conversion was 2,1%/year and freedom from late conversion among survivors was 90,46% at 4 years. At a mean follow-up of only 12 months, type-I endoleaks occurred in 8,2% (2,6% proximal), type III endoleaks in 3,8%, migration in 2,7% and limb thrombosis in 3,1%. Although this was a mixed sample, it is considered to mainly represent the results from first-generation devices which comprised about half of the sample and had the longest follow-up.

Leurs et al. followed with a long-term follow-up report on 1190 patients treated with a Stentor (Min-Tec, Freeport, Grand Bahama, The Bahamas) or Vanguard (Boston Scientific, Oakland, NJ, U.S.A.) endograft (Figure 11).[64] Despite a 9,3% intra-operative complication rate, 30-day mortality was only 2,9%. However, late results were less favourable. At 4 years, 7% of patients had died of a AAA-related cause, and at 8 years the number doubled. These authors found that patients with larger aneurysms were at a particular risk of complications, with cumulative rates of conversion and rupture-free survival of only 39.6% at 8 years. Vaaramaki, et al. reported similarly an 81% re-intervention rate on 48 patients treated with a Vanguard device, at an average 91 months.[65]

Erosion of the graft polyester fabric was frequently seen with the Stentor device, which was one of the earliest marketed endovascular systems for AAA treatment.[66] In response to generalized safety concerns over this, the manufacturers revised the fabric component of the graft and changed the name to Vanguard. In a relevant manuscript, Jacobs, et al.[67] reported on graft fatigue from their 10-year endovascular experience.

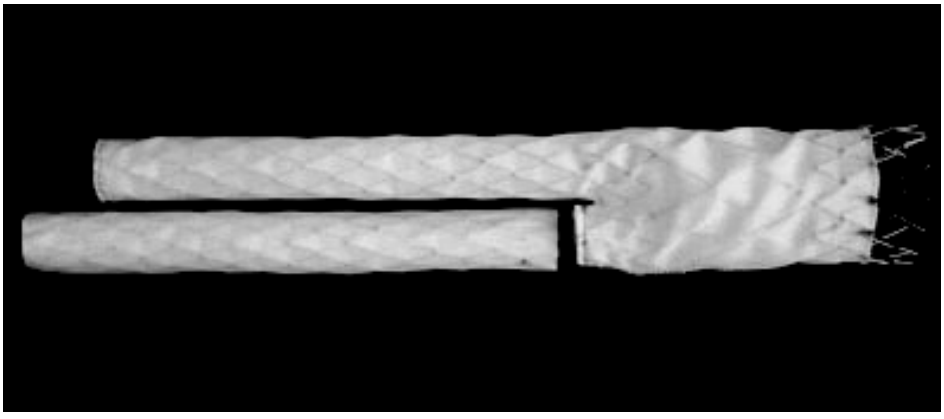

Figure 11. The Vanguard stentgraft, a modular device featuring a supra-renal open stent.

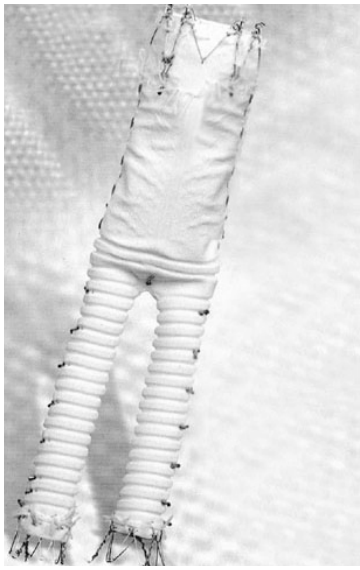

Figure 12. The EVT device. Distal hooks were responsible for many iatrogenic lesions of the iliac arteries.

The Vanguard structure of stents was held together by sutures that frequently disrupted (over 50% of cases at an average of 13 months), leaving the attachment sites fragile and prone to separation. These two major flaws ultimately caused the withdrawal of this device from the market.

Some early devices also revealed alarming rates of stent fractures.[68] The first EVT (Guidant, Menlo Park, California, USA) generation (Figure 12) was prone to stent fracture, which happened in 23% of patients in its Phase I trial.[69] With the subsequent generation – named Ancure/Guidant – there were also fractures reported, in particular at the proximal hooks, but usually without consequences. Metal corrosion and stress fatigue are the appointed causes for stent fracture. These issues have been progressively addressed through advances in design and processing (particularly with nitinol-based structures), generally with success, as demonstrated by detailed analysis of subsequently explanted devices.

The Ancure/Guidant device was withdrawn from the market in 2001, following a mediatic lawsuit involving Endovascular Technologies (the Guidant division responsible for the endograft). The company failed to report on 2628 cases in which 52 emergency operations and 12 device-related deaths occurred.

The LifePath endograft (Edwards Life Sciences, Irvine, California, USA) was a modular polyester graft with elgiloy and stainless steel inner wire structure and no supra-renal fixation but featuring crimps for secure infra-renal fixation (Figure 13). Unlike all other endografts, it was balloon-expandable. This allowed for very precise positioning and high radial force and seemed to avoid subsequent neck dilatation.[70] After concluding

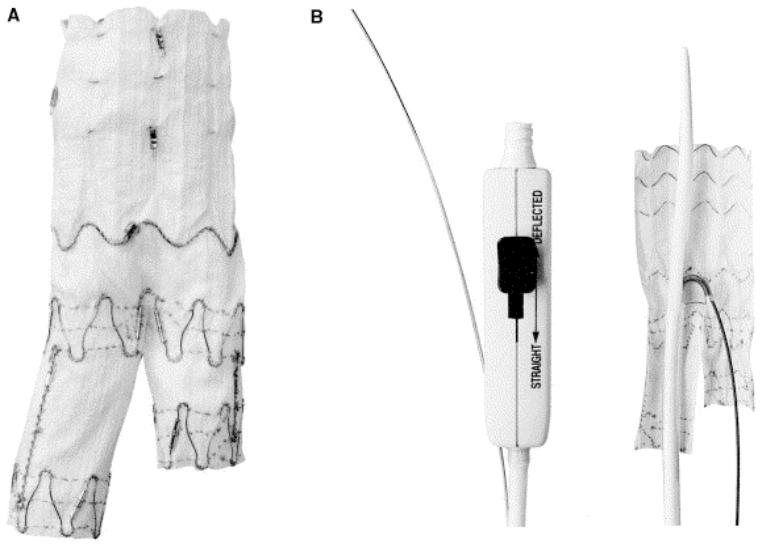

Figure 13. The LifePath device. The balloon-expandable design provided secure and precise positioning.

recruitment for the US clinical trials that would lead to FDA approval, Edwards Life Sciences announced that the LifePath AAA program would be discontinued for financial reasons. After a significant investment that included withdrawal and re-designing the device (due to wireform fracture problems) and just after publishing a report with very good short and mid-term results[71], this came as a surprise.

Ockert, et al. provided long-term follow-up for patients implanted with the LifePath endograft. In their single-center experience they found a very high (28%) rate of wire fracture. This corresponded to 9 patients, of which 4 had either a type-I or a type-III late endoleak. They also found no difference in the occurrence of wireform fracture between generations I and II. The secondary type I endoleak rate was 25%, the type III endoleak rate was 9.5%, and secondary conversion rate of 12.5%. In conclusion, wire form fracture was found to be a major structural problem, resulting in a significant endoleak rate.

DISCUSSION

The first commercialized endovascular devices designed for AAA treatment were very flexible, practically unsupported grafts that very much resembled surgically implanted prosthesis. While fairly efficient in the short term, they demonstrated unacceptable rates of migration and occlusion, and were replaced by much stiffer devices, hence more kink-resistant and less prone to migrate. These were not as adaptable to anatomic restrains and to the hemodynamic stress to which they were subjected after implantation. As a

consequence, device fatigue (stent fracture, disconnection and graft disruption) became more common. Gradually, refinements in fabric, metal and design have provided an array of endografts that are durable, flexible and resistant to collapse. Delivery systems are progressively more accurate and adapted to the complexities of access vessels.

From the data presented in the previous sections, one can conclude that short and mid-term results with all FDA-approved endografts are overall remarkable. Analysing the composite results from the randomized controlled trials, large registries such as the EUROSTAR and hundreds of published studies and case series leaves little room for doubt as to the efficacy and safety of EVAR. Even the most sceptic must agree that evidence supports the non-inferiority of this treatment modality when compared to open repair. Growing numbers of physicians and patients alike are prone to choose the latter option only in particular situations.

Long-term results, although still sparse, also support the idea that EVAR results in a safe and lasting prevention of aneurysm-related death. This is true despite the high (but steadily reducing) secondary intervention rate and significant burden of life-long follow-up. Taking the recently published long-term outcomes from the UK EVAR trials as an example[3,4], one must bear in mind that recruitment for these trials lasted from 1999 to 2004, meaning none of the endografts used then are still commercialized. All have been significantly revised to resolve proven frailties and reduce early and late complications, and some have even been discontinued. A paradigmatic example is that of the Excluder device. A change in the fabric porosity, undertaken in 2004, reduced the rate of aneurysm expansion after treatment, and this has a significant impact on the rate of secondary interventions.[27,28] However, the more permeable generation was used in the UK EVAR trials.

Not only endografts have been changing: the growing experience of individual physicians and institutions has accompanied evolution in materials, making EVAR safer, quicker and more durable. Adequate preparation has shown to influence patient selection and reduce both short and long-term complications. Planning and sizing using dedicated 3-D reconstruction software has a significant and positive influence in results, regardless of graft selection. Moreover, conclusions drawn from results of a specific device in a particular institution may not be representative of global results, due to other variables such as operator experience, individual protocols, access to more modern technology and selection bias.

Patient selection is another important variable for outcome. As peri-operative results continue to improve, more medically high-risk patients will be offered treatment. The advances in endograft technology, with more flexible yet kink-resistant designs, delivery systems with lower profiles and more controlled and precise deployment techniques have significantly reduced the number of patients refused due to anatomical constrains. In fact, the "acceptable" frontiers are constantly being re-assessed (and expanded) both

by physicians and companies. Abbruzzese, et al., in a single institution study of 565 EVAR patients, found that 39,3% of patients were preformed outside the Instructions For Use (IFU) for the selected device.[53] The group outside IFU had higher peri-operative mortality, aneurysm related mortality, re-intervention and graft-related adverse events compared to those treated inside the IFU. Grafts that are thought to be more tolerant (or perform better) in adverse anatomy may be used in these circumstances more often.[58,72,43,45,59,60] Comparing their results with those from patients with very favorable anatomy (or event with a more mixed sample) may falsely induce worse results.

Retrospective studies comparing individual endografts, like those coming from the EUROSTAR reports,[13,63,73,74] the UK EVAR trials[40] and others[53,75,76,26,77,39,78,52,38,51] have contributed to point out specific problems but tend to provide relatively similar outcomes for contemporary devices. Those that provide comparison between generations demonstrate that the more recent are (not surprisingly) associated with less complications, secondary interventions and death.[26, 79]

Amongst so many variables, can we draw any conclusions regarding individual brand performance in comparison to others? Assumptions may be based on conceptual beliefs and (somewhat speculative) interpretation of data, but evidence-based conclusions are hard to depict. No one has ever attempted a randomized comparison between individual models, maybe because most feel device selection should be individualized or because technology would already have changed significantly by the time mid to long-term results were available.

CONCLUSION

Presently, EVAR is current practice for AAA treatment around the world. Yet physicians still struggle with the ultimate decision to select the best treatment for a specific patient. This includes the choice of endograft to implant, from many currently available in the market. Although existing literature does show some small differences in outcome, results are generally good and one should remember that no randomized data exists in this regard. Moreover, by the time there is enough follow-up to draw relevant conclusions the entire market has changed, with constant improvements and new technological advantages.

Reassuringly, overall results from EVAR have been improving at a steady rate and individualized graft selection has globally shown to be an effective solution. It appears that patients with very favorable anatomy do well with most modern devices, whereas those with challenging anatomies may benefit from particular design, delivery and deployment features requiring a greater experience and knowledge for adequate device selection.

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Chapter 13

Clinical outcome and morphologic analysis after endovascular aneurysm repair using the Excluder endograft

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ABSTRACT

Objective

Long-term follow-up after endovascular aneurysm repair (EVAR) is very scarce, and doubt remains regarding the durability of these procedures. We designed a retrospective cohort study to assess long-term clinical outcome and morphologic changes in patients with abdominal aortic aneurysms (AAAs) treated by EVAR using the Excluder endoprosthesis (W. L. Gore and Associates, Flagstaff, Ariz).

Methods

From 2000 to 2007, 179 patients underwent EVAR in a tertiary institution. Clinical data were retrieved from a prospective database. All patients treated with the Excluder endoprosthesis were included. Computed tomography angiography (CTA) scans were retrospectively analyzed preoperatively, at 30 days, and at the last follow-up using dedicated tridimensional reconstruction software. For patients with complications, all remaining CTAs were also analyzed. The primary end point was clinical success. Secondary end points were freedom from reintervention, sac growth, type I and III endoleak, migration, conversion to open repair, and AAA-related death or rupture. Neck dilatation, renal function, and overall survival were also analyzed.

Results

Included were 144 patients (88.2% men; mean age, 71.6 years). Aneurysms were ruptured in 4.9%. American Society of Anesthesiologists classification was III/IV in 61.8%. No patients were lost during a median follow-up of 5.0 years (interquartile range, 3.1-6.4; maximum, 11.2 years). Two patients died of medical complications ≤30 days after EVAR. The estimated primary clinical success rates at 5 and 10 years were 63.5% and 41.1%, and secondary clinical success rates were 78.3% and 58.3%, respectively. Sac growth was observed in 37 of 142 patients (26.1%). Cox regression showed type I endoleak during follow-up (hazard ratio, 3.74; $P = .008$), original design model (hazard ratio, 3.85; $P = .001$), and preoperative neck diameter (1.27 per mm increase, $P = .006$) were determinants of sac growth. Secondary interventions were required in 32 patients (22.5%). The estimated 10-year rate of AAA-related death or rupture was 2.1%. Overall life expectancy after AAA repair was 6.8 years.

Conclusions

EVAR using the Excluder endoprosthesis provides a safe and lasting treatment for AAA, despite the need for maintained surveillance and secondary interventions. At up to 11 years, the risk of AAA-related death or postimplantation rupture is remarkably low. The incidences of postimplantation sac growth and secondary intervention were greatly reduced after the introduction of the low-permeability design in 2004.

INTRODUCTION

Two decades after its introduction,[1] endovascular aneurysm repair (EVAR) is established as a valid treatment option for infrarenal abdominal aortic aneurysms (AAAs). Compared with open repair, there is evidence of an early survival benefit at the expense of a higher late reintervention rate.[2,3,4,5] As long-term data become available, concerns have been raised regarding the durability of EVAR, in particular, regarding the delayed risk of sac growth and rupture after implantation.[6,7]

Several endovascular devices are available for AAA repair. However, evaluation and comparison of individual endoprosthesis is especially difficult due to the lack of device-specific reporting in published studies and to the constant introduction of improvements and new devices. This study aims to analyze long-term results and morphologic changes after EVAR using the Excluder endoprosthesis (W. L. Gore and Associates, Flagstaff, Ariz), a device marketed in Europe since 1997 without major structural modifications, except for the addition of a low-permeability expanded polytetrafluroethylene sleeve to the graft composition in 2004. Our hypothesis is that EVAR can be performed with acceptable complication rates and very low long-term AAA-related mortality using an endoprosthesis that will still be available for the foreseeable future.

METHODS

Patient population

Patient selection and data retrieval were based on a prospectively kept database of vascular surgery patients at Erasmus University Medical Center (Rotterdam, The Netherlands). Inclusion criteria were date of surgery between January 2000 and December 2007, infrarenal AAA treatment, and implantation of an Excluder endoprosthesis. Patients with previous aortic surgery or isolated iliac aneurysms were excluded. Vital status was checked once at the end of follow-up by consult of civil registry data. All causes of death were obtained. Product codes of endografts implanted in 2004 were retrieved to determine which patients received an original design (OD) or a low-permeability (LP) Excluder.

Image acquisition and postprocessing

Computed tomography angiography (CTA) was performed according to standardized institutional protocols. Morphologic analysis and measurements were performed post hoc using dedicated U.S. Food and Drug Administration-approved postprocessing software with center lumen line (CLL) reconstruction (3Mensio Vascular 4.2 software,

3Mensio Medical Imaging BV, Bilthoven, The Netherlands). CLLs were constructed semi-automatically and followed the center of the aortic and iliac permeable lumen.

All CTA scans were analyzed preoperatively, early (<30 days, typically ≤48 hours) postoperatively, and at the last follow-up visit. For patients with complications or sac growth, all other CTAs were also analyzed. No digital records of preoperative and first postoperative CTAs were kept for 28 patients (19.4%), and these measurements were performed on hard copies. Consequently, preoperative and early postoperative sac volumes were not obtainable for these patients.

Two observers (A.J., F.G.) performed all image analysis independently, blinded to patient data. Interobserver variability was assessed in a sample of 30 patients and agreement was high for AAA diameter (R^2 linear = 0.996), neck length (R^2 linear = 0.991), and neck diameter (R^2 linear = 0.935). Aneurysm sac volume was assessed according to a previously published protocol.[8]

Definitions

Neck length was defined as the length from the lowermost renal artery to the level where the aortic diameter increases by at least 10%. Maximum diameter measurements were obtained after CLL reconstruction. Technical success was defined as successful access and deployment of an endoprosthesis, without need for open conversion, type I or III endoleaks, or significant kinking or obstruction of flow. When an unplanned endovascular procedure was necessary to obtain success, during the operation or ≤24 hours, primary assisted technical success was considered. When an unplanned open surgical procedure was necessary, this was considered secondary technical success.

Clinical success was defined as successful deployment at the intended position, without death as a result of treatment, postimplantation rupture, open conversion, type I or III endoleak, device infection or thrombosis, migration, sac growth, or device integrity failure. The distance from the lowermost renal artery to the start of the endoprosthesis was serially measured and migration calculated using the first postoperative measurement as baseline. Migration was defined as downward displacement of the device by >10 mm. A lower threshold of 5 mm was considered separately but not accounted for to determine clinical success. Sac growth was defined as a diameter increase >5 mm or volume increase >5%. Neck dilatation was considered if the difference in neck diameter was ≥2 mm.

Primary clinical success required no additional or secondary procedure. In primary assisted clinical success, a preventive intervention was deemed necessary to maintain clinical success. In secondary clinical success, such a procedure was needed to correct an established complication.

Survival outcomes considered were overall survival and freedom from AAA-related death or postimplantation rupture. Thirty-day morbidity was defined as any complica-

tion that required additional procedures or prolonged hospital stay. All definitions are according to the reporting standards for EVAR.[9]

End points

The primary study end point was clinical success. Individual components of clinical success were used as secondary end points. These were freedom from reintervention, sac growth, types I and III endoleak, migration, conversion to open repair, and AAA-related death or rupture.

Additional analysis

Technical success, early (30-day or in-hospital) outcome, neck morphology changes, and overall survival are analyzed. Serum creatinine levels were obtained before surgery, before hospital discharge, and yearly thereafter. From these, estimated glomerular filtration rates (eGFR) were calculated and compared preoperatively, early postoperatively, and at the last available follow-up.[10]

Statistical methods

Continuous variables are presented as means ± standard deviation or medians and interquartile range, as appropriate. Univariate analysis for normally distributed variables was performed using the Student *t*-tests, and for nonparametric variables, Mann-Whitney *U* tests or Kruskal-Wallis tests were used. Dichotomous variables are presented as counts and percentages and compared between groups using Pearson χ^2 statistics or the Fisher exact test, as applicable. Multivariable logistic regression analysis was used to identify independent risk factors for intraoperative type Ia endoleak, and results reported as odds ratio and 95% confidence intervals (CIs). Kaplan-Meier survival curves were used to estimate clinical success and survival, and equality between groups was compared with the log-rank (Mantel-Cox) test. Univariable and multivariable Cox proportional hazard analysis was used to identify risk factors for sac growth and results reported as hazard ratios and 95% CIs. All statistical tests were two-sided and considered significant when the *P* value was <.05. Analyses were performed using SPSS 19 software (SPSS Inc, Chicago, Ill).

RESULTS

Study population

From 2000 to 2007, 179 patients (88.3% men) underwent EVAR for infrarenal AAAs at the Erasmus University Medical Center. Of these, 144 (80.4%) were implanted with an Excluder endoprosthesis and included in the study. The mean age was 71.6 ± 7.9 years.

Baseline clinical and anatomic characteristics are detailed in Table 1. The following endografts were also used at our institution during the study period: Zenith (Cook Medical Inc, Bloomington, Ind) in 27 (15.1%), Lifepath (Edwards Life Sciences, Irvine, Calif) in four (2.2%), and Talent (Medtronic, Santa Rosa, Calif) in three (1.7%).

Table 1. Baseline characteristics

Variable[a]	Total (n = 144)	OD (n = 61)	LP (n = 83)
Age, years	71.6 ± 8.0	70.5 ± 8.6	72.4 ± 7.5
Male sex	127 (88.2)	55 (90.2)	72 (86.7)
Hypertension	88 (60.7)	39 (63.9)	49 (59.0)
History of CAD	47 (32.6)	15 (24.6)	32 (38.5)
Moderate/severe RD	35 (24.3)	18 (29.0)	17 (20.5)
Smoking history	84 (58.3)	36 (59.0)	48 (57.8)
COPD	35 (24.3)	16 (26.2)	19 (23.0)
CVD	13 (9.0)	7 (11.5)	6 (7.2)
S-PAD	7 (4.9)	4 (6.6)	3 (3.6)
Diabetes	14 (9.7)	7 (11.5)	7 (8.4)
ASA score ≥3	89 (61.8)	37 (60.7)	52 (62.6)
RCR index ≥2	68 (47.2)	25 (41.0)	43 (51.8)
Timing of the procedure			
Elective	122 (84.7)	51 (83.6)	71 (85.5)
Symptomatic	15 (10.4)	7 (11.5)	8 (9.6)
Ruptured	7 (4.9)	3 (4.9)	4 (4.8)
Anesthesia type			
General	54 (37.5)	26 (42.6)	28 (33.7)
Regional	76 (52.8)	29 (47.5)	47 (56.6)
Local	14 (9.7)	6 (9.8)	8 (9.6)
Neck variables			
Length, mm	28.5 (21-42)	26 (18.5-37.5)	32 (21-44)
Diameter, mm	24 (22.2-25)	24 (23-25)	24 (22-25)
Angulation,°	27 (14.2-45.7)	20 (10-37.5)	32 (15-50)
AAA variables			
Diameter, mm	60 (54-70)	59 (52.5-64)	62 (54-72)
Volume, cm^3	185 (150-291)	176 (139-267)	192 (155-292)

Legend*: AAA,* Abdominal aortic aneurysm; *ASA,* American Society of Anesthesiologists; *CAD,* coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *CVD,* cerebrovascular disease; *LP,* low-permeability design; *OD,* original design; *RCR,* revised cardiac risk; *RD,* renal dysfunction; *S-PAD,* symptomatic peripheral arterial disease. a. Continuous data are shown as the mean ± standard deviation or median (interquartile range) and categoric data as number (%).

Technical success

The primary technical success rate of the EVAR procedure was 89.6%, and the primary assisted success rate was 99.3% (Table 2). One conversion to open repair was performed intraoperatively due to inadvertently low deployment. The open procedure and postoperative evolution were uneventful.

Additional intraoperative endovascular procedures were required in 14 of 144 patients (9.7%). These were due to type Ia endoleak in nine, type Ib endoleak in two, and partial occlusion of a renal artery in four. Eight additional patients were found to have intraoperative type Ia endoleak, which resolved with ballooning alone.

A larger preoperative AAA diameter (P = .010) and greater infrarenal neck angulation (P = .024) were identified as risk factors for intraoperative type Ia endoleak. Also, there was a trend toward a higher risk with greater neck diameters (P = .055). Other baseline anatomic characteristics did not increase risk, nor did the timing of surgery (elective vs urgent). In multivariable logistic regression, only neck diameter was significantly associated with intraoperative type Ia endoleak (Table 3). The presence of intraoperative type Ia endoleak or the need for adjunct intraoperative procedures to achieve proximal seal was not associated with a greater risk of secondary intervention, sac growth, or migration. This remained true after correcting for the generation of implanted endoprosthesis.

Table 2. Technical success and 30-day outcome after endovascular aneurysm repair

	No. (%)	
Outcome variable	(N = 144)	95% CI[a]
Technical success		
Primary	129 (89.6)	83.5-93.6
Primary assisted	143 (99.3)	96.2-99.9
Intraoperative conversion to open repair	1 (0.7)	1.2-3.8
Unplanned adjunct procedures[b]	14 (9.7)	5.9-15.7
Proximal balloon-expandable stent	5 (3.5)	1.5-7.9
Proximal cuff	4 (2.8)	1.1-6.9
Renal stenting	4 (2.8)	1.1-6.9
Distal extension	2 (1.4)	0.4-4.9
In-hospital or 30-day death	2 (1.4)	0.4-4.9
Myocardial infarction	1 (0.7)	1.2-3.8
Respiratory infection	1 (0.7)	1.2-3.8
In-hospital or 30-day morbidity	31 (21.5)	15.6-28.9
Graft-related	5 (3.5)	1.5-7.9
Not graft-related	26 (18.1)	12.6-25.1

Legend: a. Confidence intervals (*CI*) are calculated for the proportions. b. Two procedures were performed on the same patient.

Table 3. Multivariable logistic regression analysis of risk factors for intraoperative type Ia endoleak

Variable	HR (95% CI)[a]	*P*
Neck diameter	1.255 (1.013-1.555)	.038
AAA diameter	1.033 (0.990-1.078)	.129
Infrarenal angulation	1.015 (0.989-1.042)	.252

Legend: *AAA,* Abdominal aortic aneurysm; *CI,* confidence interval; *HR,* hazard ratio. a. HRs and the 95% CIs are presented per unit increase.

In-hospital or 30-day mortality and morbidity

In-hospital or 30-day mortality rate was 1.4% as a result of two patient deaths, one on day 4 of acute respiratory failure and one on day 5 of myocardial infarction (Table 2). Both patients were treated in emergency setting due to symptomatic aneurysms.

Five graft-related complications were found in the postoperative period: three type Ia endoleaks requiring reintervention (placement of balloon-expandable stents in two patients and re-ballooning a balloon-expandable stent placed intraoperatively) and two limb occlusions requiring surgical thrombectomy and angioplasty with stent placement. Median hospital stay was 3 days (interquartile range, 2-5 days) and three patients (2.1%) were discharged to another institution.

Clinical success

Median follow-up was 5.0 years (interquartile range, 3.1-6.4; maximum, 11.2 years). No patients were lost for follow-up, and the exact cause of death was obtained for all who died. Notably, 43 patients were available for follow-up more than 6 years after the original procedure (Table 4). The estimated primary clinical success rates were 63.5% and 41.1% at 5 and 10 years, and secondary clinical success rates were 78.3% and 58.3%, respectively (Figure 1).

During the follow-up period, 39 secondary interventions were performed in 32 (22.5%) patients. Problems with the proximal sealing zone were the motif for intervention in 10 patients, comprising seven type Ia endoleaks and three with increasingly short proximal sealing. Whenever possible, the sealing zone was extended by use of a proximal cuff (n = 5) or a partially covered NuMED CP balloon-expandable stent (n = 2; Heart Medical Europe BV, Best, The Netherlands). One patient was converted to aortomonoiliac EVAR after 4 years, and two patients underwent successful open surgical conversion, after 6 months and 10.5 years, due to type Ia endoleak. Nine patients underwent implantation of limb extensions. A type Ib endoleak was identified in four, with imaging evidence in the remaining patients showing increasingly short distal sealing (n = 4) or progression of aneurysmal dilatation distal to the endoprosthesis (n = 1).

Postimplantation sac growth was found in 34 of 142 patients. The generation of implanted endoprosthesis (OD vs LP) was significantly associated with the risk of sac

Table 4. Clinical success and long-term outcome

Outcome variable	No. (%)
Clinical success	
Primary clinical success	93/144 (64.6)
Primary assisted	99/144 (68.7)
Secondary	115/144 (79.9)
Endograft migration	
>5 mm	14/142 (9.9)
>10 mm	5/142 (3.5)
Sac growth	
>5 mm in diameter	34/142 (23.9)
>5% in volume	31/116 (26.7)
Without endoleak	16/142 (11.3)
With endoleak	
Type II	12/142 (8.4)
Type I	6/142 (4.2)
Secondary endoleak	
Type Ia	7/142 (4.9)
Type Ib	4/142 (2.8)
Type II	33/142 (23.2)
Secondary interventions	
Proximal balloon-expandable stent	2/142 (1.4)
Proximal cuff	5/142 (3.5)
Distal extension	11/142 (7.7)
Open/laparoscopic AAA fenestration	5/142 (3.5)
Open/laparoscopic lumbar/IMA ligation	1/142 (0.7)
Percutaneous embolization of IMA/lumbars	4/142 (2.8)
Conversion to aortouniiliac	1/142 (0.7)
Conversion to open repair	
Elective	6/142 (4.2)
Urgent	1/142 (0.7)
Relining	2/142 (1.4)
Iliac PTA	1/142 (0.7)
Mortality (including 30 days)	68/144 (47.2)
AAA-related	3/68 (4.4)
Oncologic	29/68 (42.6)
Cardiovascular	16/68 (23.5)
Other	20/68 (29.4)
Other secondary graft-related complications	
Endograft limb occlusion	2/142 (1.4)
Ischemic colitis	2/142 (1.4)
Buttocks claudication	2/142 (1.4
Postimplantation rupture	1/144 (0.7)

Legend: *AAA,* Abdominal aortic aneurysm; *IMA,* inferior mesenteric artery; *PTA,* percutaneous transluminal angioplasty.

growth (Figure 2). Neck diameter and occurrence of type I endoleak during follow-up were also significant risk factors for sac growth in univariable and multivariable analysis (Table 5. A and Table 5. B).

Elective open surgical conversion was performed in four patients with continued sac growth, despite absence of endoleak, after 1.9, 3.5, 5.5, and 10.3 years. Three of these were implanted with the OD design model. Two patients underwent relining with less permeable endoprosthesis after 4.5 and 5.2 years, for similar reasons. These successfully arrested sac increase. Two patients with endotension underwent endoscopic fenestration, with similar success.

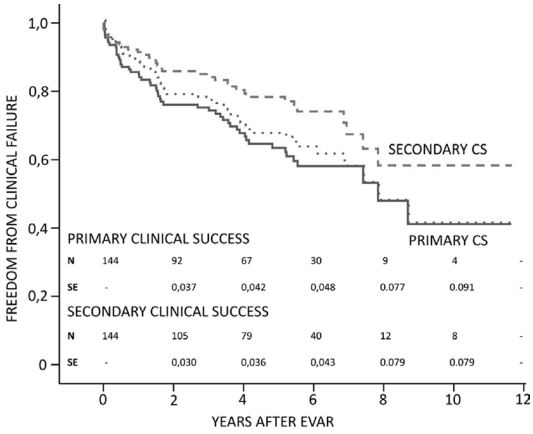

Figure 1. Kaplan-Meier estimates are shown for primary (*solid blue line*), secondary (*dashed red line*), and primary assisted (*dotted blue line*) clinical success (*CS*).
Legend: *N,* Number at risk; *SE,* standard error.

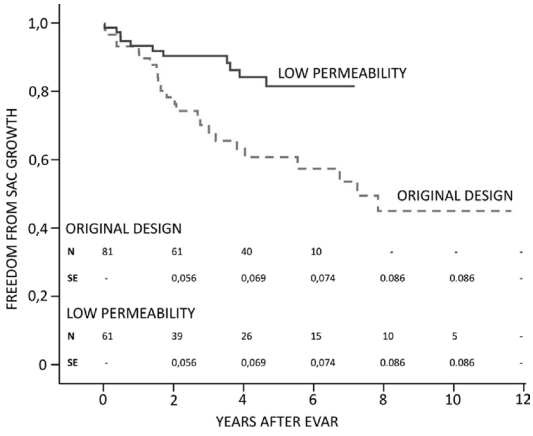

Figure 2. Kaplan-Meier estimates are shown for sac growth according to the low permeability design (*solid blue line*) and original design (*dashed red line*) of implanted endograft. *P* = .005 (log-rank test).
Legend: *N*, Number at risk; *SE*, standard error.

Table 5. A. Cox univariate regression analysis for determinants of sac growth

Variable	HR (95% CI)	*P*
Original design model	5.86 (2.77-12.36)	<.001
Endoleak during follow-up		
Type I	2.66 (1.15-6.13)	.038
Type II	1.82 (0.89-3.72)	.098
Neck angulation[a]	1.003 (0.988-1.018)	.707
Neck diameter[a]	1.185 (1.021-1.374)	.026

Legend: *CI,* Confidence interval; *HR,* hazard ratio. a. Per unit increase in endoleak.

Table 5. B. Cox multivariate regression analysis for determinants of sac growth

Model	Variable	HR (95% CI)	*P*
Type I EL during FU	Type I EL during FU	2.848 (1.170-6.934)	.021
Plus endograft generation	Type I EL during FU	4.899 (1.870-12.830)	.001
	Original design model	3.789 (1.691-8.489)	.001
Plus neck diameter	Type I EL during FU	3.736 (1.405-9.933)	.008
	Original design model	3.849 (1.708-8.673)	.001
	Neck diameter[a]	1.268 (1.070-1.502)	.006

Legend*: CI,* Confidence interval; *EL,* endoleak; *FU,* follow-up; *HR,* hazard ratio. a. Per unit increase in endoleak.

Type II endoleaks were present in 33 of 142 patients (23.2%). Eight were actively treated by means of open (n = 1) or endoscopic (n = 2) AAA sac fenestration, endoscopic lumbar ligation (n = 1), or percutaneous lumbar/inferior mesenteric artery embolization (n = 4). Indication for treatment of type II endoleak was individualized, but association to sac growth was the most common motif for treatment.

Migration ≥10 mm was observed in five patients, of which none had type I endoleak and only one required secondary intervention due to increasingly short proximal seal; however, 15 patients were identified when a lower threshold of ≥5 mm was used. Two (13.3%) of these had a type Ia endoleak and five (33.3%) underwent secondary intervention to extend seal. Univariate analysis found migration increased the risk of secondary type Ia endoleak (*P* = .042) and the need for secondary proximal neck intervention (*P* = .001). Limb occlusion was observed in two patients, of whom one underwent surgical thrombectomy, followed by percutaneous transluminal angioplasty, and the other remained asymptomatic and was managed conservatively.

A mean increase of 1.32 mm (95% CI, 1.05-1.58 mm) was observed between preoperative and last neck diameter, translating into a yearly growth rate of 0.24 mm. Neck dilatation was observed in 52 patients (36.6%). In 29 patients with >7 years of follow-up, neck dilatation was present in 19 (65.5%). Mean oversizing in patients with neck dilatation was 14.6% ± 6.0% vs 11.6% ± 6.6% for those without neck dilatation (*P* = .008). Proximal

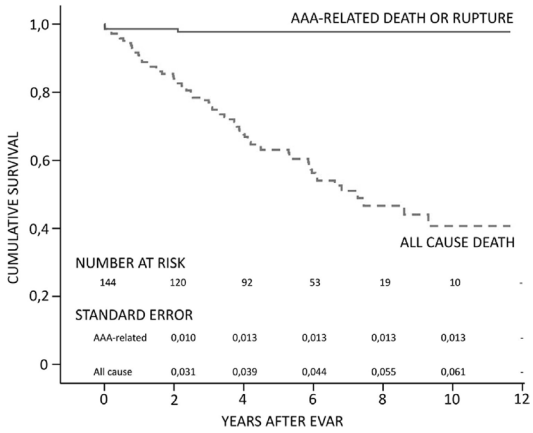

Figure 3. Kaplan-Meier estimates are shown for overall (*dashed red line*) and abdominal aortic aneurysm (*AAA*)-related survival (*solid blue line*). *EVAR*, Endovascular aneurysm repair.

graft diameter did not influence dilatation. The presence of neck dilatation increased the risk of migration ≥5 mm (odds ratio, 5.5; 95% CI, 1.63-18.23), but no increased risk was found for migration ≥10 mm, occurrence of type Ia endoleak, or need for proximal neck secondary intervention. No relationship was observed between neck dilatation and sac growth.

One patient sustained rupture at 2.1 years after implantation. This patient had a shrinking aneurysm, from a 51-mm AAA diameter preoperatively to 42 mm at 2 years, without migration or other complications. At the time of rupture, there was clinical and imaging evidence of graft infection, later confirmed by positive cultures of *Staphylococcus aureus*. The patient underwent open surgery with removal of the infected prosthesis and in situ reconstruction, but died postoperatively. No other postimplantation ruptures occurred. The estimates for AAA-related death or rupture (including 30 days) were 2.4% at 5 years and 2.4% at 10 years (Figure 3).

The mean preoperative eGFR was 74.2 ± 25.9 mL/min/1.73 m^2. After surgery, a decline was observed to a mean eGFR of 69.4 ± 24.5 mL/min/1.73 m^2, which reached statistical significance ($P < .001$). However, at the last follow-up visit, the mean eGFR was 73.7 ± 30.5 mL/min/1.73 m^2, which was not significantly different from the preoperative mean value ($P = .786$).

Long-term survival

Sixty-eight patients died during follow-up. Estimated survival after AAA repair was 6.8 years (95% CI, 6.1-7.5 years; Figure 3). Only three AAA-related deaths occurred: two perioperative deaths and one of infection, as mentioned. The most frequent cause of death was cancer-related, occurring in 29 of 68 (42.6%), followed by myocardial infarction in 10

(14.7%) and stroke in six (8.8%). Overall survival of patients treated urgently was similar to those treated electively, even when 30-day mortality was included (log-rank $P = .117$).

DISCUSSION

Despite evidence of an early advantage over open repair, doubt remains regarding the durability of EVAR.[6,7] More than two decades after the introduction of the technique, solid long-term results remain scarce and limited by the permanent introduction of new devices. The Gore Excluder endoprosthesis was the preferred device in our institution for many years and was used in >80% of patients. Aside from the introduction of the LP design in 2004 and recent developments in the deployment system, this device has been virtually unchanged since its introduction. Therefore, our study provides valuable long-term information with current clinical applicability.

Technical success and early results: Intraoperative adjunct procedures were required in 6.2% of patients to achieve or enhance proximal fixation and seal. Another 2.8% were found to have partial occlusion of a renal artery. These complications were fundamentally associated with inaccurate deployment. This may have led to a bias in patient selection toward use of this device in longer proximal necks. It may also explain why, unlike previously reported,[11] only neck diameter was associated with intraoperative type Ia endoleak.

In-hospital and 30-day mortality was remarkably low (1.4%) for a cohort in which 62% was assessed as American Society of Anesthesiologists classes 3 and 4, including urgent operations. These outcomes compare favorably with those of randomized EVAR trials and may result from selection bias.[5,12,13,14]

Clinical success: Midterm clinical results using the Excluder endoprosthesis have been well characterized,[15,16,17,18,19,20] but long-term clinical outcomes (>4 years) are scarce. Recently, Maleux et al[21] published their 10-year experience with the Excluder device. Overall, their results are similar to ours in regard to early success and late complications. However, their numbers were smaller (n = 121) and included patients with isolated iliac aneurysms (13%), mycotic (5%), and pseudoaneurysms (1.7%), which could bias the overall analysis. Hogg et al[22] analyzed the long-term sac behavior with the Excluder device, but outcomes were compromised by a significant number of patients lost during follow-up: after 1 year, only about two-thirds of patients were available for analysis. To adequately interpret long-term results, completeness of follow-up is an essential prerequisite that our study fulfills.

Long-term results were also recently published for the Talent endoprosthesis.[23] They reported similar primary clinical success rate of 64% at 5 years but a much higher estimated AAA-related mortality of 8% at 7 years and four postimplantation ruptures at a

mean of 40 months, all associated with graft migration and type I endoleak. Another recent publication reported long-term outcomes using the Zenith endoprosthesis in 143 elective patients, of whom four had incomplete imaging data.[24] They found similar intervention-free survival at 5 years of 77%, but six postimplantation ruptures were noted at a mean follow-up of 66 months.

In our study, clinical success was highly dependent on sac growth. As has been previously reported, the generation of the implanted device influenced sac growth—OD grafts increased the risk of sac growth significantly.[15,18,19,25] The large study by Schanzer et al[22] reported an overall 41% risk of sac growth at 5 years; however, no device-specific data were available. In that study, the chance of growth was greater from 2004 to 2008, after introduction of the LP design.

Our results differ, showing a markedly reduced proportion of patients with sac growth after 2004. Accordingly, Hogg et al reported 14.8% sac growth at 4 years for 301 patients treated with the LP. In our study, volume measurements may have introduced a bias, because a larger proportion of patients are classified as having postimplantation sac growth using volume compared with diameter. Because postoperative aneurysm sac volume has been shown to better reflect the efficacy of treatment,[26,27] we believe it provides a more reliable estimate. Importantly, a clear motif for sac growth (eg, type I endoleak or migration) was found in all but one patient treated with the LP endoprosthesis. Conversely, no rupture or AAA-related death was observed in 13 patients with endotension treated conservatively.

Over time, neck dilatation occurred in one-third of patients and was associated with the degree of oversizing. In patients with the longest follow-up, neck dilatation was very common, reflecting the tendency for continued neck dilatation over time when self-expanding nitinol grafts are used. Our data support that long-term dilatation beyond device diameter is rare, and when present, is associated with progression of aneurysmal disease.[28] Reports on neck dilatation differ significantly, perhaps due to institutional policies on oversizing and device-related characteristics. However, others have reported higher dilatation rates in devices with suprarenal fixation, suggesting that as an additional factor promoting dilatation.[29,30,31,32]

Our cohort had few occlusive complications, occurring exclusively in patients with narrow aortic bifurcations, a known risk factor for occlusion.[33] Data for European Collaborators on Stent-Graft Techniques for Aortic Aneurysm Repair (EUROSTAR) and single-center reports further support the good performance of this device in adverse iliac anatomy,[33,34,35] but this was not directly evaluated in our population.

Postimplantation rupture has been recognized as the paradigm of EVAR failure: a report from a large cohort of Medicare beneficiaries noted a rupture risk of 1.8% at 4 years.[36] Subsequently, Wyss et al[6] analyzed postimplantation ruptures from EVAR trial patients and found a rupture rate of 0.7/100 person-years. They suggested this could

explain the loss of early benefit for EVAR compared with open repair. Two ruptures occurred in the EVAR trials after implantation of the Excluder device. In the Veterans Affairs Open versus Endovascular Repair (OVER) trial, with 327 (37.1%) Excluder devices implanted and a mean follow-up of 1.8 years, no late ruptures were documented.[5] The same was observed after a median of 6.0 years in the Dutch Randomised Endovascular Aneurysm Management (DREAM) trial (no device-specific data).[4] Several observational studies analyzing the long-term performance of the Excluder device have reported no late ruptures.[21,22,37,38,39] One patient in our series suffered rupture, although this was caused primarily by endograft infection.

After EVAR, eGFR rates remained stable or slowly declined in most patients, despite an intensive CTA surveillance protocol, with a mean decline of 4.8 mL/min/1.73 m^2 over 5 years. We observed transient worsening of eGFR after EVAR and recovery to near-baseline levels at the end of follow-up. Greenberg et al[40] previously described this U-shaped curve, and we confirm their observation over longer follow-up.

Long-term survival: Our expected survival at 6 years was close to 50%, which is below the expected rate for the same period for the Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) and DREAM trials[3,4] but above the expected survival from the United Kingdom Endovascular Aneurysm Repair 2 (EVAR-2) trial.[2] We report an "every-day" population, perhaps resulting in a more realistic expectation for clinical practice. Interestingly, most deaths were cancer-related. To further improve the long-term survival of AAA patients, a more thorough and multidisciplinary approach to comorbidities and risk is desirable.

Limitations

The observational design and single-center cohort, with inherent selection bias, limit this study; however, unlike most long-term studies, we provide complete follow-up, including cause of death for all patients. As such, we avoid omitted complications that never reach hospital care or get treatment elsewhere. We also acknowledge the relatively small population size.

CONCLUSIONS

This study offers a thorough analysis on clinical outcome and morphologic aneurysm changes up to 11 years after EVAR using the Excluder endoprosthesis. AAA-related mortality was exceptionally low, although clinical success was compromised by a large proportion of sac growth in patients treated with the OD generation endografts. Despite continued need for surveillance and intervention, these results provide reassurance for AAA treatment with a currently commercialized endoprosthesis.

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AUTHOR CONFLICT OF INTEREST

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Chapter 14

Results of endovascular repair of infrarenal aortic aneurysms using the Endurant stent graft

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ABSTRACT

Objective

Recent reports showed that the Endurant stent graft (Medtronic Cardiovascular, Santa Rosa, Calif) is safe and effective for endovascular repair of abdominal aortic aneurysms (AAAs). However, due to its relatively recent introduction, only short-term follow-up data are available. This study presents the 4-year results using this device.

Methods

All clinical data, including detailed anatomic information of the first 100 consecutive patients treated with the Endurant stent graft for an infrarenal AAA in three Dutch high-volume hospitals, were prospectively collected. Computed tomography angiography was routinely performed before the procedure, ≤1 month, and at 1 year post-endovascular aneurysm repair. Thereafter, the imaging modality during yearly follow-up was individualized (duplex ultrasound imaging or computed tomography angiography). Patients were classified as within or outside the instructions for use (IFU) for analysis. Study end points were primary clinical success, overall and AAA-related mortality, and sac morphology changes and endoleak during follow-up. Estimates were obtained using Kaplan-Meier plots.

Results

The study included 100 consecutive patients (88 men) with a median age of 74 years (interquartile range [IQR], 67-79 years) and median AAA diameter of 58 mm (IQR, 55-65 mm), between December 2007 and March 2009. Twenty patients (20%) were treated outside the IFU (18, outside proximal neck IFU, one outside iliac IFU, and one outside both IFUs). Median follow-up was 48 months (IQR, 36-53 months), and no patients were lost. One contained rupture was observed after 1.5 months due to graft infection. No patients had graft migration. Two type Ia endoleaks, 5 type Ib endoleaks, and 15 type II endoleaks were found. Primary clinical success was 97%, 90%, 84% and 77% at 1, 2, 3, and 4 years, respectively. Primary clinical success was comparable for patients treated within or outside IFU (P = .20), although both patients outside iliac IFU needed a secondary iliac intervention. Over time, maximum aneurysm diameter decreased ≥5 mm, remained stable, and increased ≥5 mm in 58%, 32%, and 10% of the patients, respectively. All-cause mortality was 20% at 4 years, with a 3% AAA-related mortality.

Conclusions

The 4-year follow-up data of the Endurant stent graft for AAA treatment shows its use results in a low AAA-related mortality with adequate prevention of rupture or aneurysm growth. Although patients with very challenging anatomy were treated in our series,

primary clinical success rates were comparable for patients treated within and outside the IFU. However, both patients outside the iliac IFU needed a secondary iliac intervention. The knowledge of the present results may aid in improving outcomes in the future.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is increasingly seen as the primary choice of treatment for abdominal aortic aneurysms (AAAs) for patients who are anatomically suitable for endovascular repair.[1] Since the introduction of the latest generation of stent grafts, preliminary EVAR reports on the technical success and safety end points for patients with shorter or more angulated proximal aortic necks or tortuous, small, or calcified iliac arteries showed feasibility of the procedure.[2,3] The Endurant stent graft (Medtronic Cardiovascular, Santa Rosa, Calif) received United States Food and Drug Administration approval in December 2010 and is widely used for EVAR.

Recent results showed that this device is safe and effective in the short term for treatment of patients with AAAs.[3,4,5,6,7] However, due to its relatively recent introduction, only short-term follow-up data are available. Introduction in Europe, however, dates from early 2008, and longer-term results from this geographic region are now starting to appear. These are necessary to assess the durability of treatment with this particular stent graft. Therefore, the purpose of this study was to analyze the 4-year results of our first 100 consecutive patients[7] treated with an Endurant graft for an AAA.

METHODS

Patients

This study is a follow-up study of the cohort described by van Keulen et al[7] in September 2011. Included were the first 100 consecutive patients who were electively treated with the Endurant stent graft for an infrarenal aneurysm in three high-volume, tertiary vascular referral hospitals in The Netherlands (University Medical Center, Utrecht; Erasmus University Medical Center, Rotterdam; and St. Antonius Hospital, Nieuwegein).

Follow-up

All clinical and imaging follow-up data of these first 100 consecutive patients were prospectively collected in a database. Regular follow-up was performed at 1 month and 12 months after EVAR and yearly thereafter. Computed tomography angiography (CTA) was routinely performed ≤1 month after the EVAR procedure and at 1 year after EVAR.

For subsequent annual follow-up visits, the choice of the imaging modality (duplex ultrasound [DUS] imaging or CTA) was individualized according to local protocols.

All available CTA data sets of included patients were transferred to a workstation (3Mensio Medical Imaging BV, Bilthoven, The Netherlands) for analysis, with the support of a three-dimensional reconstruction with central lumen line. Experienced physicians performed the measurements, and pre-EVAR CT scans were also evaluated for baseline aortic anatomy. The characteristics investigated on the CTA scans were AAA diameter, existence of endoleaks, patency of renal arteries, diameter of the AAA neck, and distance from the most distal renal artery to the most proximal stent graft ring. The CTA scans were also checked for any other EVAR-related complications.

DUS imaging was performed by experienced operators, and data on maximum aneurysm diameter, patency of the stent graft, and patency of the native iliac/femoral arteries, as well as any detectable endoleaks, were obtained from the DUS report. In case of doubt or complication at DUS imaging, an additional CT scan was performed.

All complications, secondary interventions, outpatient department visits, readmissions, deaths, and causes of death were documented and analyzed. Causes of death at a location other than the initial treating hospital were investigated by contacting the treating general practitioner or responsible medical specialist.

The primary study end point was primary clinical success, as defined in the reporting standards for EVAR.[8] Secondary end points were overall and AAA-related mortality, sac morphology changes, and the occurrence of endoleak. The morphology of the proximal aneurysm neck of the study patients was classified as within or outside the instructions for use (IFU) criteria of the Endurant stent graft. The proximal neck is considered inside IFU for the Endurant stent graft if the neck diameter is 19 to 32 mm with nonsignificant calcification and thrombus and the neck length is ≥10 mm in combination with a suprarenal angulation ≤45° and an infrarenal angulation of ≤60°. If the neck length is ≥15 mm, then a suprarenal angulation ≤60° and an infrarenal angulation of ≤75° are accepted. We defined <50% calcification and <50% thrombus as nonsignificant. Neck calcification and thrombus were measured 10 mm below the most distal renal artery and defined as the percentage of the circumference calcified or covered with thrombus, respectively. Except for the IFU of the proximal aneurysm neck, patients were also classified as within or without the IFU criteria for the iliac arteries. IFU criteria were an iliac diameter between 8 and 25 mm and a potential distal landing zone of at least 15 mm.

Sac growth was considered if the maximum aneurysm diameter increased by ≥5 mm compared with the first postoperative examination. Sac shrinkage was considered if the maximum diameter was reduced by ≥5 mm. Definitions for complications and secondary interventions were coded and described according to the reporting standards for EVAR.[8]

The decision to treat an endoleak was taken according to the most recent guidelines.[9,10] This resulted in treatment of all potential type I and III endoleaks. Type II endoleaks were only treated if they were associated with aneurysm growth. Type II endoleaks without increased sac diameter were observed. The decision to treat limb occlusion or stenosis was determined by the presence of clinical symptoms.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) for not normally distributed variables. Differences were assessed by nonparametric testing. Categoric variables are presented as number and percentage. The Kaplan-Meier method was used to assess primary clinical success and cumulative rates of survival. The log-rank test was used to compare Kaplan-Meier estimates between patients who were treated within IFU and outside IFU. Significance was assumed at $P \leq .05$. Statistical analysis was performed with SPSS 20 software (IBM Corp, Armonk, NY).

RESULTS

Between December 2007 and March 2009, 100 consecutive elective patients (88 men) were treated with the Endurant stent graft. The median age was 74 years (IQR, 67-79 years). Preoperative screening for comorbidities showed that most of the patients had mild to severe systemic disease by the American Society of Anesthesiologists (ASA) Physical Status Classification (ASA 1, 6%; ASA 2, 45%; ASA 3, 48%; and ASA 4, 1%). The median AAA diameter was 58 mm (IQR, 55-65 mm). All other baseline characteristics are reported in Table 1.

Of the 100 included patients with AAAs, 19 had at least one anatomic characteristic of the proximal aneurysm neck that was considered a violation of the IFU of the Endurant stent graft, and one was outside the iliac IFU as well. For an extensive description of the proximal neck IFU violation, we refer to the previously published 1-year results.[7] In addition, one patient had an iliac anatomy that was outside the IFU of the Endurant stent graft because of a large iliac diameter (27 mm).

The median follow-up was 48 months (IQR, 36-53 months; maximum, 62 months), and no patients were lost to follow-up. Follow-up was >12 months in 88 patients, >24 months in 81 patients, >36 months in 73 patients and >48 months in 48 patients.

The median diameter of the aneurysm sac decreased during follow-up from 58 mm (IQR, 55-65 mm) preoperatively to 51 mm (IQR, 42-60 mm; $P < .001$). In total, 22 endoleaks (2 type Ia, 5 type Ib, and 15 type II endoleaks) were detected during follow-up (Table 2).

Table 1. Baseline characteristics

Parameter	Median (IQR) or No.[a]
Maximum diameter, mm	58 (55-65)
Neck length, mm	34 (22-43)
Neck diameter, mm	27 (25-28)
Neck calcification[b]	
<25%	83
25%-50%	13
50%-75%	4
>75%	0
Neck thrombus[b]	
<25%	64
25%-50%	20
50%-75%	8
>75%	8
Angulation, °	
Suprarenal	23 (8-38)
Infrarenal	41 (25-61)
CIA diameter,[c] mm	
1 cm distal	
Left	13 (16-20)
Right	14 (16-19)
3 cm distal	
Left	14 (16-20)
Right	14 (16-19)
5 cm distal	
Left	14 (16-19)
Right	14 (16-19)
EIA diameter,[d] mm	
Left	10 (9-12)
Right	10 (9-11)
Male sex	88
Hypertension	54
Smoking	45
Diabetes	18
ASA classification	
1	6
2	45
3	48
4	1

Legend: *ASA,* American Society of Anesthesiologists; *CIA,* common iliac artery; *EIA,* external iliac artery; *IQR,* interquartile range. a. Categoric data are presented as the number of patients positive for the variable. b. Neck calcification and thrombus are measured 10 mm below the most distal renal artery and defined as the percentage of the circumference calcified or covered with thrombus, respectively. c. Diameters of the CIAs were measured 1, 3, and 5 cm distally of the aortic bifurcation.d. Diameters of the EIAs were measured 1 cm distally of the iliac bifurcation.

Table 2. Endoleaks during follow-up

Endoleak	Shrinkage ≥5 mm, No.	Stable, No.	Growth ≥5 mm, No.
Type Ia	…	…	2
Type Ib	…	…	5[a]
Type II >30 days	4	5	6

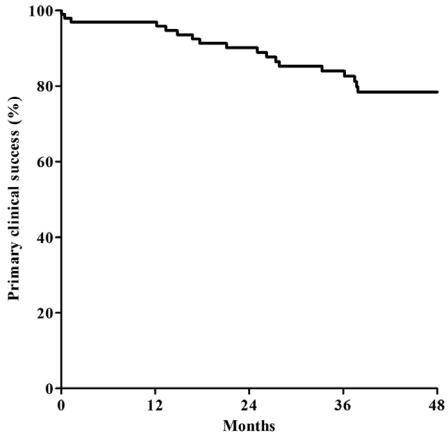
Legend: a. One patient had both a type Ib and a type II endoleak but is shown as type Ib endoleak because was the most likely cause of growth.

Primary clinical success

Primary clinical success (Figure 1) was 97% at 1 year, 90% at 2 years, 84% at 3 years, and 77% at 4 years. When patients treated outside the IFU were compared with patients treated within the IFU (Figure 2), no difference was observed for primary clinical success rates ($P = .20$). However, when only the iliac IFU was taken into account, both patients treated outside the iliac IFU needed an iliac reintervention. During follow-up, secondary procedures were performed in 19 patients (19%). In total, 27 reinterventions were performed, with two patients requiring two reinterventions, and three patients requiring three reinterventions (Table 3). Freedom from secondary interventions was 98%, 91%, 85%, and 80% after 1, 2, 3, and 4 years, respectively.

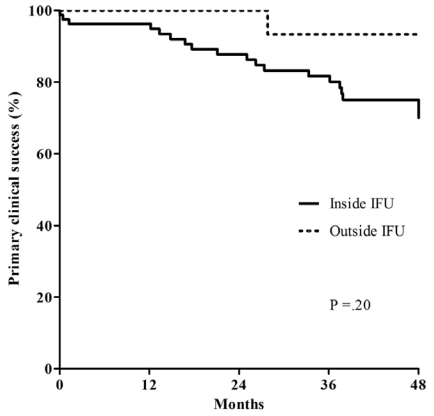
Aneurysm sac growth was observed in 14 patients. A secondary intervention was performed in 13 patients who had aneurysm growth combined with an endoleak. Further growth after the secondary intervention was arrested in eight patients (62%), and shrinkage ≥5 mm occurred in three patients (23%). Enlargement continued in two patients (15%). One patient, with an infected stent graft and a type Ia endoleak requiring placement of a proximal cuff, is discussed in detail below. Another patient underwent embolization of a type II endoleak; however, after the embolization, the aneurysm diameter of this patient increased 5 mm in 18 months. Because no new endoleak was visible and there was an adequate proximal and distal sealing, this patient was kept under strict surveillance. The patient without a detectable endoleak and growth was also kept under strict surveillance.

Proximal cuff placement was performed in three patients (all treated within the proximal neck IFU) after 38 days, 13 months, and 41 months. Initial proximal neck diameters were 21 mm, 32 mm, and 29 mm and increased during follow-up without migration. Aneurysm enlargement after EVAR occurred in all three patients (30 mm, 13 mm, and 10 mm). The patient with 30-mm growth had a large type Ia endoleak combined with a contained AAA rupture. Owing to stent graft infection, the aneurysm had grown with complete disappearance of the infrarenal aneurysm neck. The patient also received intravenous antibiotics, but this could not prevent death from sepsis, 65 days after the initial EVAR. The patient with a 13-mm growth had progressive dilatation of the proximal neck resulting in insufficient seal length, although no type Ia endoleak was found.



No. At risk	100	88	75	62	38
SE.	-	.02	.03	.04	.05

Figure 1. Kaplan-Meier survival curve shows primary clinical success during follow-up after endovascular aneurysm repair (EVAR).
Legend: *SE,* Standard error.



No. At risk inside IFU	80	70	59	51	30
SE.	-	.02	.04	.05	.06
No. At risk outside IFU	20	18	16	11	8
SE.	-	.00	.00	.07	.07

Figure 2. Kaplan-Meier survival curves show primary clinical success in patients treated inside and outside instructions for use (*IFU*) criteria during follow-up after endovascular aneurysm repair (EVAR).
Legend:*SE,* Standard error.

A limb extension procedure was performed in seven patients and was successful in all cases. Five patients (5%) were treated for a type Ib endoleak and two patients (2%) for short distal sealing. Two patients were outside the iliac IFU because the iliac diameter exceeded the recommended 25 mm. Four patients with a type Ib endoleak also had continuing dilatation of the iliac arteries during follow-up, indicating progression of the

Table 3. Secondary procedures performed during follow-up

Type of procedure	Procedures, No.	Time during FU, months
Proximal cuff placement	3	1, 13, 41
Limb extension	8	
Type Ib endoleak	6	21, 28, 33, 40, 54, 57
Short sealing	2	15, 52
Embolization for type II endoleak	6	17, 18, 25, 26, 36, 38
Conversion for infected stent graft	1	21
Treatment for iliac limb occlusion	6	
Embolectomy	2	1 day post-op, 12
Thrombolysis	4	19, 22, 37, 52
Other procedures	3	
Balloon-expandable stent for continuing type Ia endoleak	1	29
Repeat ballooning stent for continuing type Ia endoleak	1	32
Graft limb stenting with a new graft limb because of <50% symptomatic stenosis	1	27

Legend: *FU,* Follow-up.

aneurysmatic disease. Data on sealing lengths and initial iliac diameters for all these patients are reported in Table 4.

Furthermore, a stent graft limb occlusion occurred in four patients (4%) during follow-up at 1 day, and at 12, 37, and 52 months after the initial EVAR. Three of these patients were successfully treated endovascularly, whereas in the remaining patient, endovascular therapy failed. One patient (with an occlusion after 12 months) developed two reocclusions, 7 and 10 months after the first embolectomy. All four patients were treated within IFU for the Endurant stent graft.

Mortality and aneurysm-related death

Nineteen patients (19%) died during follow-up. Causes of death were aneurysm-related in 3, malignancy in 3, sepsis in 3 (1 from respiratory, 1 gastrointestinal, and 1 unknown focus), cardiac disease in 2, gastrointestinal bleeding in 1, preoperatively existent renal insufficiency in 1, and unknown in 6.

The three aneurysm-related deaths occurred within the first year of follow-up. For an extensive description of the AAA-related deaths, we refer to the previously published 1-year results.[7] Overall patient survival rates (Figure 3) were 88% at 1 year, 84% at 2 years, 82% at 3 years, and 80% at 4 years. Mortality rates did not differ between patients who required a secondary intervention and patients without a secondary intervention, with survival rates after 4 years of 86% and 79%, respectively ($P = .59$). Furthermore, survival rates for patients treated within IFU were comparable to survival rates for those treated outside IFU (81% and 79% at 4 years, respectively; $P = .94$).

Table 4. Patients with distal extension[a]

Patient	Indication	Initial iliac diameter R/L, mm	Diameter iliac limb R/L, mm	Potential fixation zone pre-op R/L, mm	Within iliac IFU	Sealing length post-op R/L iliac, mm	Aneurysm growth at the second intervention	Sealing length before second intervention R/L iliac, mm	Side distal extension	Sealing length after second intervention R/L iliac, mm
1	Type Ib endoleak; progressive disease iliac artery	19/18	20/20	≥15/≥15	Yes	39/12	Growth	10/0	L	12/30
2	Type Ib endoleak; progressive disease iliac artery	21/26	24/28	≥15/10	No	0/3	Growth	0/0	Both	24/10
3[b]	Type Ib endoleak left; type Ib endoleak right; progressive disease iliac artery	21/18	24/20	≥15/≥15	Yes	30/28	Growth	15/0 0/38	L R	16/43 N/A[c]
4	Type Ib endoleak	11/14	13/16	≥15/≥15	Yes	16/22	Growth	13/0	Both	34/76
5	Type Ib endoleak; progressive disease iliac artery; retraction of stent graft	27/23	28/28	10/≥15	No	13/25	Growth	0/0	Both	44/58
6	Short iliac seal	20/16	24/20	≥15/≥15	Yes	26/3	Growth	25/0	L	20/23
7	Short iliac seal	18/18	20/20	≥15/≥15	Yes	17/14	Shrinkage	13/2	L	N/A[c]

Legend*: IFU,* Instructions for use; *L,* left; *N/A,* not available; *R,* right. a. The postoperative sealing length was measured on the first postoperative computed tomography angiography (CTA; ≤30 days). The sealing length before secondary intervention represents the sealing length on the last CTA before the iliac extension, and the sealing length after secondary intervention represents the sealing length on the first CTA after the placement of the iliac extension.b. The left limb was extended 40 months after endovascular aneurysm repair (EVAR) and the right limb after 57 months. c. Only a duplex ultrasound (DUS) assessment was performed after the secondary intervention.

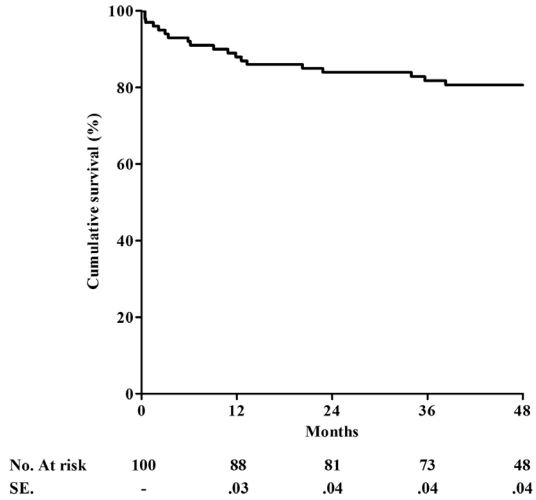


Figure 3. Kaplan-Meier survival curve shows overall survival after endovascular aneurysm repair (EVAR). Legend: *SE,* Standard error.

Aneurysm sac behavior and endoleak

The median diameter of the aneurysm sac decreased from 58 mm (IQR, 55-65 mm) preoperatively to 51 mm (IQR, 42-60 mm; $P < .001$) during follow-up. Fourteen patients (14%) had at any moment during follow-up growth ≥5 mm. Six of these patients (43%) had a type II endoleak and one patient had a type Ib and type II endoleak. A type Ia endoleak was detected in two patients, and four patients had a type Ib endoleak (Table 2). One patient had no detectable endoleak on CTA.

On the last available imaging follow-up, maximum aneurysm diameter decreased ≥5 mm since the initial EVAR in 58% of the patients and remained stable in 32%, whereas 10% of the patients had growth ≥5 mm.

DISCUSSION

The 1-year follow-up results of this study population were published in 2011 when the first 100 consecutive patients of three Dutch high-volume hospitals had their 1-year follow-up visit.[7] In the current report, we analyzed the follow-up results of these patients after a median follow-up of 48 months.

Primary clinical success was 97% at 1 year, 90% at 2 years, 84% at 3 years, and 77% at 4 years. At a median follow-up of 48 months, maximum aneurysm diameter decreased ≥5 mm since the initial EVAR in 58% of the patients and remained stable in 32%, while 10% of the patients had growth ≥5 mm.

It is important to mention that this study also includes patients with a challenging anatomy for endovascular repair of an infrarenal AAA. The Endurant stent graft is the stent graft of primary choice in the cooperating centers because it also offers the possibility of treating patients with a challenging proximal neck due to more angulation or a larger diameter. As we showed in our previous study,[7] up to 48% of the patients would be outside the IFU, depending on which of the commercially available stent grafts at that time would have been implanted: 48% outside the IFU for the Zenith stent graft (Cook Medical, Bloomington, Ind), 40% outside the IFU for the Excluder stent graft (W. L. Gore and Associates, Flagstaff, Ariz), and 27% outside the IFU for the Talent stent graft (Medtronic Cardiovascular).

Even with the generally more liberal IFU of the Endurant stent graft, 20% of patients were outside the recommendation for this device. All patients whose deaths were aneurysm-related were treated within IFU, and primary clinical success was comparable for patients treated within or outside IFU, although both patients treated outside the iliac IFU needed an iliac reintervention. We did not statically compare iliac IFU with iliac non-IFU patients due to sample size.

Considering the possible increase in complication rates resulting from the challenging anatomy presented in this cohort, this study revealed low AAA-related mortality. All-cause mortality was 20% after 4 years, with only a 3% AAA-related mortality at 1 and 4 years, all cases being perioperative deaths or resulting from infection. The all-cause mortality rate, despite being comparable or lower than more historical series,[11,12] can still be considered significant. This is possibly explained by the age and comorbidities of this population, reflected in the ASA classification (48% of the patients were ASA 3). Moreover, most patient deaths occurred during the first year of follow-up (all-cause mortality was 12% after 1 year), and no aneurysm-related deaths occurred thereafter. In the patients who died of unknown causes, aneurysm-related death was unlikely because no patients demonstrated AAA enlargement at their latest follow-up assessment, and only one patient had a demonstrable complication (a type II endoleak without sac enlargement) on the last imaging surveillance examination.

Globally, a significant reduction in median AAA aneurysm diameter was observed over time, from 58 mm to 51 mm ($P < .001$). The diameter remained stable in one-third of patients, and nearly 60% had shrinkage >5 mm, suggesting successful aneurysm exclusion in a high percentage of patients. The rates of sac shrinkage in this cohort appear comparable to previously reported rates of other stent grafts of 60.9% after 3 years, 62.2% after 5 years, and 63% after 5 years.[13,14,15]

In 19 patients, one or multiple secondary procedures were performed. Placement of an iliac extension for treatment of a type Ib endoleak or short distal sealing was the most common secondary procedure (n = 8) in seven patients.

Primary clinical success after 4 years was 77%. This rate is comparable to series with the Talent stent graft, Endurant's predecessor.[14,16,17,18] Because no other 4-year results of the Endurant are available, we could not compare our results with other studies. On one hand, device-specific studies of other currently commercially available stent grafts are scarce but show comparable primary clinical success rate after 3 years.[19,20] On the other hand, Pratesi et al[21] and Baptiste et al[22] reported a freedom of reintervention rate of 94.6% and 92% after 3 years. However, only approximately one-third of patients were available for analysis at this point.

Secondary interventions were generally successful, particularly the interventions for endoleaks combined with growth of the aneurysm. In 85% of the cases, the aneurysm growth was stopped or even shrinkage was shown. This underlines the importance of an adequate follow-up so that problems can be detected and treated.

A stent graft limb occlusion occurred in four patients (4%). This occlusion rate of 4% is comparable with other studies with this particular stent graft[3,4,23] but is still substantial and seems higher compared with other simultaneously available grafts.[20,21,22] However, comparing the results is difficult because of the heterogeneity in patient population and follow-up duration.

We recently specifically looked into the occlusions and suggest that the occlusion rate may be reduced by a more liberal intraoperative and early postoperative (re)intervention strategy.[23] The inclusion of patients with unfavorable anatomy and obstructive disease may probably also contribute to an increased chance of endograft occlusion, even if they are considered within IFU.[23]

Although most stent graft occlusions have been suggested to occur due to technical errors,[23] a review of the first postoperative CTA scans could not identify any anatomic or technical reasons that could have led to the occlusion of a limb during follow-up in one patient. However, a possible explanation for the occlusion was found in the remaining three patients. One occlusion had probably an anatomic reason. This patient had a very small external iliac diameter (7 mm) in relation to the common iliac diameter (21 mm) that potentially limited the flow considerably. The occlusion in one patient, with ventricular tachycardia, was likely caused by the low flow state. One other patient with a limb occlusion presented with several other occlusions at different arteries as well, despite the use of dual antiplatelet therapy, which suggests an unrecognized coagulation disorder.

The number of distal extensions required after implantation was relatively high in this study population and contributed to a large proportion—eight of 27 (30%)—of the secondary interventions. Five patients underwent a secondary intervention for a type Ib endoleak and also two for short distal sealing of the graft. The maximum iliac diameter exceeded the recommended 25 mm of the IFU in two patients. In five of seven patients (71%), the postoperative iliac sealing zone (≥15 mm sealing) was too short, probably due

to the attempt to use as few endovascular components as possible. The distal sealing zone shortened during follow-up, causing in five patients a type Ib endoleak. This was accompanied in four of these five patients by a dilatation of their iliac arteries. Disease progression could possibly have led to further dilatation so that the sealing waned and an endoleak could develop. Another opportunity is that a too liberal interpretation of the IFU for the iliac landing zone or suboptimal placement of the distal graft extensions in the iliac artery resulted in shortening of the distal sealing zone. The patient with no sealing in the right limb at the first postoperative CTA 1 month after EVAR could be considered as technical failure, and this was probably caused by misinterpretation of the fluoroscopy images during the initial EVAR procedure.

On the basis of our experience with loss of distal seal during follow-up, we enhanced the focus on distal fixation and sealing and now try to achieve a distal landing zone of at least 30 mm.

Although all data were prospectively collected in a multicenter cohort, one of the limitations of this study is the relatively small number of patients. In addition, this study describes the first experience with the Endurant stent graft in all three participating hospitals. We expect that results may further improve as experience with this stent graft increases. An example is our extra attention regarding the length of the distal landing zone.

Another limitation is the individualized choice of imaging modality according to local protocols in the different hospitals. Especially for follow-up visits after several years without any imaging complication, DUS was often used. Although this avoids radiation exposure to patients, DUS is less sensitive than CTA for the detection of endoleaks.[21,24]

CONCLUSIONS

This study reveals the 4-year follow up data of the Endurant stent graft for AAA treatment. This stent graft has a more liberal IFU than most other contemporary devices; however, its use results in a low AAA-related mortality, with adequate prevention from rupture or aneurysm growth. Although patients with a challenging proximal neck anatomy were treated in our series, secondary intervention rates were comparable for patients treated within and outside the IFU for the proximal neck. However, the number of distal extensions required after implantation was relatively high in this study population and probably caused by a too liberal interpretation of the IFU for the iliac landing zone or suboptimal placement of the distal graft extensions in the iliac artery. The knowledge of the present results may aid in improving outcomes in the future.

AUTHOR CONFLICT OF INTEREST

J.P.M.V. has a proctor agreement with Medtronic and is a paid consultant; H.J.M.V., F.L.M., and J.A.H. are paid consultants.

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PART V

ENDOVASCULAR-SPECIFIC COMPLICATIONS AFTER EVAR

Chapter 15

Stent graft composition plays a material role in the postimplantation syndrome

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ABSTRACT

Objective

In patients undergoing endovascular aneurysm repair (EVAR), the postimplantation syndrome (PIS), comprising fever and inflammation, occurs frequently. The cause of PIS is unclear, but graft composition and acute thrombus formation may play a role. The objective of this study was to evaluate these possible causes of the inflammatory response after EVAR.

Methods

One hundred forty-nine patients undergoing elective EVAR were included. Implanted stent grafts differed mainly in the type of fabric used: either woven polyester (n = 82) or expanded polytetrafluorethylene (ePTFE; n = 67). Tympanic temperature and C-reactive protein (CRP) were assessed daily during hospitalization. PIS was defined as the composite of a body temperature of ≥38°C coinciding with CRP >10 mg/L. Besides graft composition, the size of the grafts and the volume of new-onset thrombus were calculated using dedicated software, and results were correlated to PIS.

Results

Implantation of grafts made of polyester was associated with higher postoperative temperature ($P < .001$), CRP levels ($P < .001$), and incidence of PIS (56.1% vs 17.9%; $P < .001$) compared to ePFTE. After multivariate analysis, woven polyester stent grafts were independently associated with an increased risk of PIS (hazard ratio, 5.6; 95% confidence interval, 1.6-19.4; $P = .007$). Demographics, amount of graft material implanted, or new-onset thrombus had no association with PIS.

Conclusions

The composition of stent grafts may play a material role in the incidence of postimplantation syndrome in patients undergoing EVAR. Implantation of stent grafts based on woven polyester was independently associated with a stronger inflammatory response.

INTRODUCTION

In patients undergoing endovascular aneurysm repair (EVAR) for an abdominal aortic aneurysm (AAA), an acute phase inflammatory response may occur shortly after implantation.[1,2,3,4] This so-called postimplantation syndrome (PIS) is defined as fever coinciding with a rise in inflammatory markers.[5,6,7,8,9] PIS is thought to be transient and harmless, but its true significance is unknown and no clear guidelines exist for management.[10] Importantly, the cause of the inflammatory response remains unclear. Proposed mechanisms are related to the introduction of the different components of the stent graft[11,12] or the amount of mural thrombus within the aneurysm.[13]

Initial results of endovascular repair with the woven polyester Talent Abdominal Stent Graft (Medtronic, Minneapolis, Minn) showed a high incidence of fever and a systemic inflammatory response as the most common serious complication.[14] Based on clinical experience, PIS seems to be even more frequent since the recent introduction of the woven polyester Endurant Abdominal Stent Graft (Medtronic). It is not uncommon for patients to have fatigue and elevated body temperatures, sometimes for weeks after the procedure.

For optimal management of patients with postimplantation fever and rise in inflammatory markers, and to contribute to future stent graft design, a better understanding of the cause of PIS is necessary. This retrospective study investigates the role of graft material on the postimplantation syndrome by comparing two types of graft material, woven polyester and expanded polytetrafluoroethylene (ePTFE). Besides the type of material, the quantity of implanted graft and the association of new-onset thrombus with the inflammatory response are investigated.

METHODS

Study population

The study population was derived from a cohort of consecutive patients undergoing an EVAR procedure between 2004 and 2010 at the Erasmus University Medical Centre, Rotterdam, The Netherlands. Exclusion criteria were the concurrent use of different graft materials on the same patient, hybrid procedures combining endovascular with open surgical treatment, urgent EVAR, and recent surgery or major trauma within 30 days of the procedure. Patients with missing data on temperature or C-reactive protein (CRP) were also excluded, as were patients who had a postoperative complication that had an effect on inflammatory markers, including urinary tract infections, pneumonia, and hematomas (Figure 1).

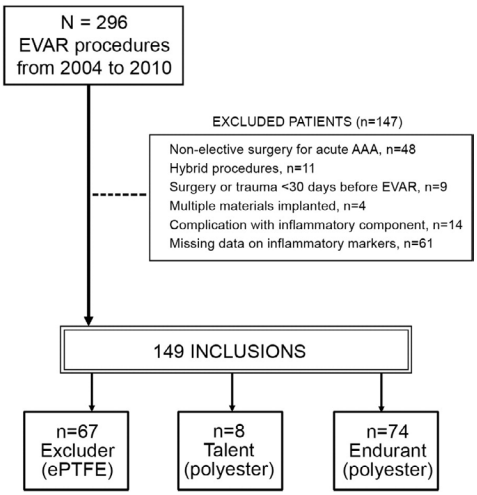

Figure 1. Flow chart of patient inclusion. *AAA,* Abdominal aortic aneurysm; *ePTFE,* expanded polytetrafluoroethylene; *EVAR,* endovascular aneurysm repair.

Baseline characteristics were comprised of gender, age, and all traditional cardiac risk factors from the Revised Cardiac Risk index,[15] as well as the incidence of chronic obstructive pulmonary disease, smoking, and hypercholesterolemia. Additionally, the use of medication with known anti-inflammatory or antipyretic effects such as aspirin, statins, and β-blockers, was recorded.

According to hospital protocol, all patients underwent an endovascular procedure with prophylactic antibiotics in the form of 1 gram of cefazolin 30 minutes before incision, and 5000 units of heparin before introduction of the stent graft deployment system. Additionally, low-molecular-weight heparin was administered in all surgical patients during hospital admission (2500 IU dalteparin daily in all patients, 5000 IU daily in those with a body weight over 80 kg). Type of anesthesia was selected at the discretion of the surgical team. The study was conducted according to the guidelines provided by the institutional review board.

Definition of endpoints

The primary endpoint of the study was the occurrence of PIS shortly after EVAR. PIS was defined as fever coinciding with an elevated serum CRP level. Fever was defined as a tympanic temperature of ≥38.0°C, and the upper level of normal for CRP was 10 mg/L in our institutional laboratory. Tympanic temperature and serum CRP levels were assessed each morning, starting 1 day before EVAR. Subsequent measurements were performed on the day of EVAR and then daily up to 4 days after implantation. As mentioned, patients with nongraft-related complications associated with inflammation

were excluded from the study, including patients with reported postoperative wound infections, pneumonia, and infections of the urinary tract.

Endograft composition

To evaluate the role of the graft component of endovascular aortic devices on the occurrence of PIS, enrolled patients were divided into two groups: in the first group, the graft composition was ePTFE; in the second group, both devices were composed of a woven polyester graft. The first group was comprised of patients exclusively treated with the low-permeability Excluder AAA Endoprosthesis (WL Gore and Associates, Flagstaff, Ariz). The second group was composed of patients treated with the Talent Abdominal Stent Graft or the Endurant Abdominal Stent Graft (both Medtronic). All used stent grafts were bifurcated, modular devices with a nitinol exoskeleton. An important difference between the two groups was that the low-permeability Excluder was available since late 2004, whereas the majority of woven polyester grafts were Endurant, which was first used in our hospital in 2008.

Other EVAR-related causes of PIS

In addition to the type of graft material used, the total quantity of implanted material may be of importance, as it may be possible that a certain type of graft is simply larger or more extensions are used. As a marker for size, the volume inside each graft was measured on contrast-enhanced computed tomographic angiography (CTA) using dedicated postanalysis software with central lumen line reconstructions (3mensio Vascular software; 3mensio Medical Imaging BV, Bilthoven, The Netherlands). Volume measurements were done semiautomatically, according to a standard protocol as described earlier.[16,17]

Finally, the amount of new-onset thrombus – filling the excluded aneurysm sac immediately after EVAR – was measured using the same dedicated software by calculating luminal volume before EVAR and comparing this with the postoperative volume measurements (Figure 2). The difference between the two measurements represents the excluded sac volume, discarding any chronic mural thrombus already present before the procedure. For both these measurements, CTA before and/or after EVAR is a necessity, thus excluding patients without available CTAs from these subanalyses.

Statistical analysis

All baseline characteristics and medication use were tabulated, as well as temperatures and CRP levels. Continuous variables were presented as means ± standard deviation or, in case of a non-Gaussian distribution, as medians and interquartile range (IQR) and compared with *t*-test or Mann-Whitney *U* statistics, respectively. Dichotomous variables were presented as counts and percentages and compared between groups

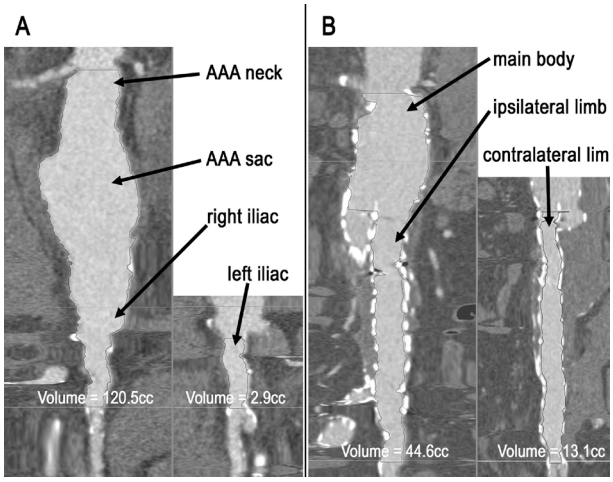

Figure 2. Luminal volume calculations before and after endovascular aneurysm repair (EVAR). An example of segmented aorto-iliac luminal volume measurements before **(A)** and after **(B)** endovascular repair using dedicated software. The difference in luminal volume is used as a quantitative measure for new-onset thrombus after EVAR.
Legend: *AAA,* Abdominal aortic aneurysm.

using Pearson χ^2 statistics. The maximum body temperature and CRP level from the first 4 days after the procedure was compared to the day before surgery. The changes in body temperature were compared for the two types of graft material using *t*-test, and changes in CRP were compared by Mann-Whitney *U* statistics. To test the association of graft size and new-onset thrombus with the postoperative rise in temperature and CRP, Pearson and Spearman correlation coefficients were calculated in the total population and within each group of graft material. Accounting for the historical difference between groups, we calculated the conditional probability of receiving a woven polyester graft based on baseline characteristics using propensity score analysis. Propensity scores were generated using logistic regression with graft material as the dependent variable. Variables included to generate the propensity scores were all those presented as group descriptive in Table 1, complemented by the type of anesthesia. To evaluate the association of graft material with PIS, a propensity-adjusted binary logistic regression analysis was performed, further correcting for statin use, type of anesthesia, new-onset thrombus, and graft size. Hazard ratios (HRs) and 95% confidence intervals (CIs) were presented. All statistical tests were two-sided and considered statistically significant when the *P* value was < .05. All analyses were performed using PASW statistics, version 17 for Windows (SPSS, Chicago, Ill).

Table 1. Baseline characteristics, medication use, and risk profile by graft material

	Woven polyester (n = 82)	ePTFE (n = 67)	*P* value
Baseline characteristics			
AAA diameter, mean (mm) ± SD	58.4 ± 11.0	61.1 ± 11.9	.22
Age, mean (years) ± SD	72.8 ± 7.2	72.4 ± 7.9	.75
Male gender, n (%)	71 (86.6)	60 (89.6)	.58
Ischemic heart disease, n (%)	32 (39.0)	34 (50.7)	.15
Diabetes mellitus, n (%)	14 (17.1)	10 (14.9)	.72
Renal dysfunction, n (%)	15 (18.3)	9 (13.4)	.42
Cerebrovascular disease, n (%)	7 (8.5)	10 (14.9)	.22
CHF, n (%)	5 (6.1)	8 (11.9)	.21
COPD, n (%)	5 (6.1)	19 (28.4)	<.001
Hypercholesterolemia, n (%)	23 (28.0)	21 (31.3)	.66
BMI, mean (kg/m^2) ± SD	26.6 ± 4.8	25.1 ± 3.2	.026
Creatinine, mean (µmol/L) ± SD	102.1 ± 38.4	97.3 ± 32.2	.42
Smoking, n (%)	20 (24.4)	26 (38.8)	.058
Medication use			
Aspirin, n (%)	49 (59.8)	34 (50.7)	.27
Statin, n (%)v	65 (79.3)	43 (64.2)	.040
Beta-blocker, n (%)	71 (86.6)	59 (88.1)	.79

Legend: *AAA,* Abdominal aortic aneurysm; *BMI,* body mass index; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *ePTFE,* expanded polytetrafluoroethylene; *SD,* standard deviation.

RESULTS

A total of eight Talent, 74 Endurant, and 67 Excluder stent grafts were included in the study. This amounts to a study population of 149 patients, divided in woven polyester (n = 82) and ePTFE (n = 67) grafts. Patients were predominantly male (87.9%) and had a mean age of 72.6 ± 7.5 years at the time of surgery. In terms of baseline characteristics, traditional cardiac risk factors were equally distributed among groups (Table 1). The preoperative AAA diameter was 59.8 ± 11.5 mm, without significant difference between the two groups. When compared to the ePTFE group, patients in the woven polyester group had a higher body mass index (26.6 ± 4.8 vs 25.1 ± 3.2; *P* = .026) and were more frequently medicated with statins (79.3% vs 64.2%; *P* = .040) Also, a higher proportion of patients in the woven polyester group received general anesthesia (73.2% vs 35.8%; *P* < .001). Besides general anesthesia (n = 84), other types of anesthesia used were spinal (n = 33), local (n = 24), or a combination (n = 8).

Graft type and PIS

The mean length of stay was 4.4 days (standard deviation, 4.7 days). The incidence of PIS was 46 (56.1%) for the woven polyester group, compared to 12 (17.9%) in the ePTFE group ($P < .001$). PIS occurred almost exclusively in the first 3 days after woven polyester implantation and the first 2 days after ePTFE implantation.

Broken down to individual inflammatory markers, a similar trend was observed. On the morning before surgery, temperatures were not significantly different between the woven polyester and ePTFE groups (36.6 ± 0.6°C vs 36.7 ± 0.5°C; $P = .15$), nor were CRP levels (5.0 [2.0-8.0] vs 3.2 [2.0-8.0]; $P = .30$) (Table 2). In the 4 days after EVAR, both body temperature and CRP levels rose significantly higher in the woven polyester group compared to the ePTFE group (Figure 3). When calculating the maximum rise in body temperature and CRP compared to baseline for both groups, patients that received a woven polyester graft had a higher rise in body temperature (+1.6 vs +0.9°C; $P < .001$) and CRP levels (+154.8 vs +38.0 mg/L; $P < .001$) compared with patients that received an ePTFE graft (Table 2).

Subanalyses of graft size and new-onset thrombus

A total of 72 patients from the woven polyester group (87.8%) and 64 from the ePTFE group (95.5%) had available imaging for in-graft volume measurements. The mean in-graft volume of the implanted grafts was 44.6 ± 13.7 mL. The woven polyester group had a larger in-graft volume than the ePTFE group (50.8 ± 13.3 mL vs 37.7 ± 10.6 mL; $P < .001$). In general, this marker for graft size showed a statistical correlation to the postoperative rise in temperature (Pearson rho 0.29; $P = .001$) and CRP (Spearman rho 0.26; $P = .003$). However, after stratifying for type of material, these correlations were no longer significant.

A total of 63 patients from the woven polyester group (76.8%) and 46 from the ePTFE group (68.7%) had available imaging for new-onset thrombus measurements. The mean

Table 2. Inflammatory markers before and after surgery by graft material

	Woven polyester (n = 82)	ePTFE (n = 67)	*P* value
Temperature (°C)			
Before surgery, mean ± SD	36.6 ± 0.4	36.7 ± 0.5	.15
Postoperative, mean ± SD	38.2 ± 0.7	37.6 ± 0.7	<.001
Difference, mean ± SD	1.6 ± 0.7	0.9 ± 0.8	<.001
CRP (mg/L)			
Before surgery, median [IQR]	5.0 [2.0-8.0]	3.2 [2.0-8.0]	.30
Postoperative, median [IQR]	164.0 [87.0-201.0]	49.0 [20.0-104.0]	<.001
Difference, median [IQR]	154.8 [82.6-198.5]	38.0 [13.7-94.0]	<.001

Legends: *CRP,* C-reactive protein; *IQR,* interquartile range; *ePTFE,* expanded polytetrafluoroethylene; *SD,* standard deviation. Postoperative values presented are the maximum for days 1 to 4 after the procedure.

volume of new-onset thrombus was 51.3 ± 45.8 mL, without significant differences between woven polyester and ePTFE groups (50.8 ± 45.1 mL vs 51.7 ± 46.6 mL; *P* = .91). Subsequent analyses showed no significant correlation between new-onset thrombus and the rise in temperature (*P* = .08) or CRP (*P* = .17).

Multivariable risk model for PIS

As mentioned, several possible confounders of the inflammatory status of the patients were found to be significantly different between groups. Therefore, differences in baseline characteristics were addressed in a propensity score analysis. The association of graft material with PIS was evaluated in a propensity-adjusted model, additionally corrected for differences in statin use, graft size, and new-onset thrombus. In this analysis, the use of woven polyester remained the only significant factor associated with an increased risk of developing postimplantation syndrome (HR, 5.58; 95% CI, 1.60-19.42; *P* = .007; Figure 4).

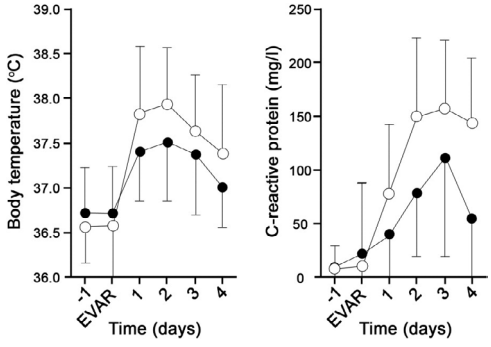

Figure 3. Day by day inflammatory response after stent graft implantation. Graphs display the mean ± standard deviation for body temperature and serum C-reactive protein (CRP) in relation to implantation of a stent graft made of woven polyester (*open circles*) or expanded polytetrafluoroethylene (ePTFE) (*closed circles*).
Legend: *EVAR,* Endovascular aneurysm repair.

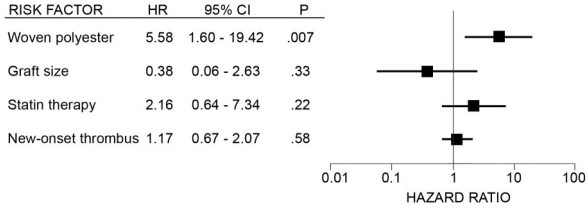

Figure 4. Multivariable associations with postimplantation syndrome (PIS). Hazard ratios (*HRs*) for individual variables in the propensity-adjusted multivariable analysis, illustrating that graft composition was independently associated with postimplantation syndrome. The natural logarithms of graft size and new-onset thrombus were used.
Legend: *CI,* Confidence interval.

DISCUSSION

With the growing application of EVAR and resolution of many significant issues related to this treatment option, particular details and previously overlooked problems are becoming more evident for physicians and warrant further analysis. PIS is a clear entity that affects a significant number of patients, but the mechanisms behind this phenomenon have been scarcely investigated. The current study shows that the graft type plays a primordial role in the development of an acute phase inflammatory response after EVAR. The implantation of stent grafts that include woven polyester in their composition is associated with significant changes in body temperature and serum CRP, compared to those that are made of ePTFE.

The current results suggest that ePTFE has less proinflammatory properties than woven polyester after endovascular implantation in humans. This is supported by an in vitro study by Swartbol et al[18] comparing the response of human white blood cells in vitro upon incubation with vascular grafts of ePTFE or woven polyester. The authors found that woven polyester triggered a significantly larger release of proinflammatory markers than ePTFE.

The differences in the incidence of fever between patients who receive stent grafts of woven polyester or ePTFE are previously described in small numbers.[12] Gerasimidis et al[12] described a total of 22 consecutive EVAR patients that received a woven polyester graft (n = 12) or ePTFE (n = 10) and compared the incidence of fever and the postprocedural changes in several biomarkers. Although the study lacked the power to observe a large difference in laboratory measurements, fever was observed more frequently in the woven polyester group (3 of 12 patients vs 1 of 10).[12]

Another suggested origin for PIS is the excluded aneurysm sac filling with new-onset thrombus, a process that may involve various proinflammatory cytokines.[13] The current study is the first to address this hypothesis in a quantitative manner, using dedicated software to calculate the excluded volume after EVAR. Data were not available for every patient in this study, and the amount of graft material was estimated using true, postimplantation graft volumes. Although both these limitations may have influenced the results, the measured volumes of excluded sac content in this study showed no correlation to PIS.

There are other differences between stent grafts, unrelated to graft material, which may also influence the proposed foreign body reaction. All stent grafts in this study have an exoskeleton made of nitinol, a nickel-titanium alloy. Unlike the others, the Excluder graft features an additional outer layer of ePTFE covering the alloy, whereas in the Endurant and Talent grafts, the metal and fabric are adjoined by stitches. In addition, these two latter features a bare top stent, further increasing the amount of nitinol directly exposed to the circulation. Apart from quantity, the precise balance between nickel and

titanium, or even the cutting and polishing, may differ between manufacturers, potentially affecting the antigenic properties of the nitinol.

Since the introduction of nitinol for medical application, it has been widely used in coronary and peripheral arterial "bare-metal" stents.[19] No inflammatory response is reported in these applications, despite frequent treatment of multiple and lengthy lesions, requiring large quantities of the material. Furthermore, the chemical production of nitinol prevents breakdown and special coating reduces nickel exposure.[20] It is, therefore, unlikely that differences in the application of nitinol between stent grafts may influence the postimplantation syndrome. We cannot, however, completely exclude this factor using our data. The stitching used in the Talent and Endurant devices can also not be ruled out as a possible confounder for the inflammatory response after implantation.

The hypothesis that endothelial damage, due to active fixation from the top stent, plays a role and may be dismissed by the current study. Evidently, if endothelial aggression due to penetration of foreign material such as hooks or barbs was key, the inflammatory response would be independent of graft type, since both the Excluder and the Endurant have active proximal fixation.

A final difference between stent grafts that could have played a confounding role in the incidence of PIS is the different delivery devices they come with. It is quite conceivable that a different method of graft delivery might affect either the rate of embolism or the duration of lower extremity ischemia, both of which stimulate an inflammatory response. Although we cannot provide data to refute these arguments, it seems unlikely that the delivery system, with its differences but also with many similarities, could explain the observed difference.

Certain limitations related to our study warrant consideration. First, a proportion of eligible patients had missing information on inflammatory markers, excluding them from this study. Although this is regrettable, such a limitation is inevitable in a retrospective study. To assess if a selection bias occurred, a comparison of baseline characteristics was performed between included patients and excluded patients. Demographics were not significantly different in any parameter, rejecting the possibility of selection bias in that regard. Coincidently, this study was not a randomized trial. The choice of graft was not random but based on individual parameters. This could have caused a selection bias, although factors that influence the choice of graft generally focus on anatomic suitability, and information on the inflammatory response was not available at the time. Additionally, due to chronologic differences between groups, baseline differences were observed in possible cofactors such as smoking but also the use of statins and general anesthesia. These differences mostly reflect the introduction of guidelines on perioperative treatment and subsequent improvement of risk reduction strategies, because most woven polyester grafts were implanted in recent years.[21] Statin therapy has been especially known to attenuate perioperative inflammation, if administered before sur-

gery.[22,23,24,25] However, as statin therapy was more frequent in the woven polyester group, it could, therefore, be expected to have attenuated rather than exaggerated the inflammatory response in this group compared to ePTFE. To address historical differences and the nonrandomized nature of the study, we performed a propensity-adjusted analysis with the addition of statin use as separate covariate, which identified the use of woven polyester as an independent predictor of PIS compared to ePTFE. Another limitation is that PIS was only measured during hospital stay. Theoretically, PIS could have occurred in patients that were discharged rapidly (ie, in the first 2-3 days), but patients are generally discharged when inflammation is decreasing and body temperatures are normal. Therefore, it is not expected that we missed many PIS cases. Last, for the CTA-based subanalyses, data were missing due to patient-dependent imaging protocols. However, the available data still represent the largest cohort ever published on the subject, and possible selection bias was not associated with the inflammatory endpoints of the study.

CONCLUSIONS

The type of fabric used in manufacturing endovascular stent grafts may play a material role in the development of postimplantation syndrome, measured by an increase in postprocedural body temperature and serum CRP. According to our findings, implantation of ePTFE-based endografts results in a less pronounced inflammatory response in comparison to those based on woven polyester.

DISCLOSURES

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Chapter 16

Spontaneous delayed sealing in selected patients with a primary type-Ia endoleak after endovascular aneurysm repair

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ABSTRACT

Objective

Direct additional therapy is advised for type-Ia endoleaks detected on completion angiography after endovascular aneurysm repair (EVAR). Additional intraoperative endovascular procedures are, however, often challenging or not possible, and direct open conversion is unattractive. The results of a selective, conservative strategy for patients with primary type-Ia endoleak has been analysed.

Methods

This was a retrospective, single-centre study (UMC, Utrecht, NL). From 2004 to 2008, all patients with a primary type-Ia endoleak and suitable anatomy for EVAR, stentgraft oversizing ≥15%, and optimal deployment were included. Complications during follow-up were studied and all sequential CTA scans were reviewed. These were compared with the remaining patients, treated during the same period.

Results

Fifteen patients were included (14 male, median age 77, range 67–85) with a median aneurysm diameter of 60 mm (48–80), an aneurysm neck diameter of 26 mm (21–32), a neck length of 29 mm (11–39), and infrarenal angulation of 49° (31–90). One patient suffered rupture 2 days after EVAR – leading to the only AAA-related death. Eight of the 15 type-Ia endoleaks disappeared spontaneously on the first postoperative CTA, obtained within 1 week of EVAR. On the second postoperative CTA, obtained a median of 5 months (1–12) after EVAR, all remaining endoleaks had sealed. One recurrence occurred at 4.85 years. During a median follow-up of 3.3 years, there were five secondary interventions. Compared with controls, there were more secondary (or recurrent) type-1a endoleaks (13% vs. 4%), endograft migrations (13% vs. 3%), sac growths (33% vs. 16%), and secondary interventions (33% vs. 23%). None of these differences however, were statistically significant.

Conclusions

All but one of the primary type-Ia endoleaks sealed spontaneously. Until sealing, the risk of rupture persisted, but subsequently only one recurrence of type-Ia endoleak was seen. In selected patients, a conservative approach for primary type-Ia endoleaks may be justified.

INTRODUCTION

The aim of endovascular aneurysm repair (EVAR) is to prevent aneurysm rupture by placement of a stentgraft, thereby eliminating pressure on the wall of the aneurysm.[1] The proximal fixation and sealing of the stentgraft is often considered the Achilles' heel of the EVAR procedure.[2] Incomplete proximal sealing results in a proximal type-1 endoleak in about 4% of all patients treated with EVAR.[3,4,5] A proximal type-1 endoleak can be dangerous as high-pressure blood flow persists in the aneurysm sac.[6] Primary type-1a endoleaks are proximal type-I endoleaks visible immediately after stentgraft deployment on the completion angiogram. Prompt treatment for these endoleaks is advocated, either by additional endovascular means (ballooning or placement of a cuff or balloon expandable stent) or by conversion to open surgery.[3,7,8] Endovascular correction of the endoleak is, however, often challenging and even impossible in many cases, either because there is no possibility to extend the stentgraft proximally without compromise of renal or mesenteric vessels or because the diameter of the neck is too large for additional (balloon expandable) stent placement. Immediate conversion to open surgery, on the other hand, is associated with a high mortality rate of up to 20–40%, although this rate has declined over the years.[9,10] Spontaneous sealing of primary type-Ia endoleaks is also anecdotally reported, but many believe that even spontaneously sealed type-I endoleaks require therapy, as the chance of recurrence is unacceptably high.[11]

We hypothesised that if a patient's anatomy (specifically neck length, diameter, tortuosity angles, and shape) is considered suitable for EVAR, preoperative measurements have been performed precisely (with the use of a centre lumen line), the stentgraft is ≥15% oversized (using outer-to-outer diameter measurements as reference) and the stentgraft is deployed at the optimal position below the lowermost renal artery, primary type-Ia endoleaks may resolve spontaneously in most cases. Furthermore, these type-Ia endoleaks may not recur, making additional treatment unnecessary. The objective of this study was to analyse the results of a selective conservative approach for primary type-Ia endoleaks in patients with EVAR-suitable anatomy and adequate stentgraft sizing and deployment.

METHODS

From August 2004 to December 2008, 285 patients underwent planned endovascular aortic procedures at the University Medical Center, Utrecht, The Netherlands. Patients treated for isolated iliac aneurysms, anastomotic or mycotic aneurysms, non-aneurysmal disease, and those with prior abdominal aortic surgery were excluded. This resulted in a cohort of 216 patients. Criteria for treatment were maximum aortic diameter greater

than 55 mm, fast growth (>5 mm in 6 months or 10 mm in 1 year), or presence of symptoms. According to the local EVAR protocol, all AAA patients underwent preoperative imaging by computed tomographic angiography (CTA). Preoperative stentgraft sizing was performed, using dedicated software with centre lumen line reconstructions (CLL) for optimal diameter and length measurements during the entire study period, and stentgraft oversizing of 15–20% was considered ideal. Postoperatively, CTAs were performed within 1 week after EVAR (typically at 48–72 hours, before discharge), and yearly thereafter. Additional scans were performed as indicated by the treating physician. All patient data were entered prospectively into a dedicated database of EVAR patients.

Patient selection

A retrospective analysis of the prospective database was performed. All patients with an intraoperative clear proximal type-I endoleak after stentgraft placement and ballooning of the sealing and overlap zones were identified and included in the study group. The remaining patients were included in a control group for comparison of complications and secondary interventions.

Patients with a type-Ia endoleak were only left untreated (and consequently included in this study) if the anatomy of the neck was considered suitable for EVAR, if preoperative stentgraft sizing was performed with the use of a CLL, if the stentgraft was correctly oversized, and if the stentgraft was deployed at the intended, optimal position. The anatomy of an aneurysm neck was considered suitable for EVAR if the length was ≥10 mm, the diameter was ≤32 mm, the infrarenal angulation was ≤60°, and ≤50% of the circumference consisted of thrombus or calcification. Moreover, patients with infrarenal angulation of 60–90° were also considered suitable if the aneurysm neck length was ≥15 mm.

Evaluation

Age, gender, symptoms at presentation, and intraoperative values were noted. Intraoperative values analysed were stentgraft size and type, operation time, volume of contrast agent used, total minutes of fluoroscopy, estimated total blood loss, administration of anticoagulants, activated clotting time, and procedure-related problems. Furthermore, the postoperative course and possible complications or re-interventions were investigated. All pre- and postoperative CTA scans of included patients were transferred to a workstation (3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) for re-evaluation.

CTA scans were performed on a 64-slice helical CT scanner (Philips Medical Systems, Best, The Netherlands) with a standardised acquisition protocol. Slice thickness was 0.9 mm and radiation exposure parameters were 120 kVp and 300 mAs, resulting in a CT dose index (CTDIvol) of 17.6 mGy. Early and late arterial phase scans were obtained.

Measurement

Preoperative CTAs were reviewed for maximum AAA diameter, total aneurysm volume, neck length, neck diameter, supra- (α) and infrarenal (β) neck angulation, and calcification and thrombus lining the neck. All available postoperative CTAs were investigated for maximum AAA diameter, total aneurysm volume, the presence of endoleaks, and stentgraft migration.

All measurements were performed using CLL reconstructions. Volume and angle measurements were performed according to earlier published protocols.[12,13] The neck diameter was measured 1 cm caudal to the lowermost renal artery. The presence of calcification and thrombus in the aneurysm neck were also visually quantified at this level. Stentgraft migration was defined as a migration of the most proximal stentgraft ring of ≥10 mm according to the reporting standards for EVAR.[1]

Endpoints

The primary endpoint was persistent sealing of the type-Ia endoleak. Secondary endpoints were freedom from; secondary intervention, secondary type-Ia endoleak, migration, post-implantation sac growth, AAA-related death, and all-cause death.

Statistical methods

Baseline characteristics were described as counts and percentages (dichotomous variables), or medians and range (continuous variables). Differences were assessed using Fisher's exact test or Mann–Whitney *U* test, as indicated. Differences in endograft model were tested with Person's chi-square test. All tests were two-sided and significance was considered when $p < 0.05$. Statistical analysis was performed using the IBM SPSS Statistics 20 (IBM Inc., Chicago, IL, USA).

RESULTS

Fifteen patients with a primary type-Ia endoleak met the inclusion criteria (14 male, median age 77, range 67–85, 6.9% of all EVAR patients, Table 1). Fourteen patients were asymptomatic at presentation, and one patient presented with a symptomatic intact AAA (case 10). The preoperative median aneurysm diameter was 60 mm (48–80) and the aneurysm sac volume was 217 mL (116–552) (Table 2). The median neck diameter was 26 mm (21–32) and neck length 29 mm (11–39). The suprarenal angle (α) was 31° (13–82) and the infrarenal angle (β) was 49° (31–90). During the study period, there were no direct conversions to open repair and one patient received an aortic cuff to treat a type-Ia endoleak caused by low-deployment. No primary type-Ia endoleaks were left untreated in the control group.

Table 1. Baseline characteristics.

Variable	Study group (*N* = 15)	Control group (*N* = 201)	*p*
Age – median (range)	76 (67–85)	74 (47–89)	.086
Male gender – *N* (%)	14 (93)	180 (90)	1.0
ASA III/IV – *N* (%)	9 (60)	116 (58)	1.0
Endograft model			.01
Talent bif, *N* (%)	13 (86)	115 (57)	
Talent AUI, *N* (%)	1 (7)	7 (3)	
Zenith, *N* (%)	1 (7)	2 (1)	
Excluder, *N* (%)	–	43 (21)	
Endurant, *N* (%)	–	34 (17)	

Legend: Bif = bifurcated; AUI = aorto-uni-iliac.

Table 2. Preoperative aneurysm neck morphology (study group).

Pt	AAA ∅ (mm)	*α* angle (°)	*β* angle (°)	Neck length (mm)	Neck calcif (%)	Neck thromb (%)	Neck ∅ (mm)	MB ∅ (mm)
1	64	44	67	17	0	<25	25	28
2	48	43	90	31	0	<25	21	26
3	80	20	59	12	0	0	28	34
4	60	36	35	29	0	0	26	32
5	64	16	50	11	25–50	0	21	26
6	65	16	31	30	<25	25–50	28	34
7	69	82	81	16	<25	0	28	32
8	60	34	31	16	0	0	21	26
9	58	13	39	32	0	<25	29	34
10	74	27	49	34	0	0	25	30
11	55	23	31	39	<25	25–50	32	36
12	60	31	39	18	<25	<25	27	32
13	52	32	65	30	0	<25	26	30
14	54	13	34	32	<25	25–50	28	32
15	69	65	70	15	<25	25–50	26	30

Legend: Pt = patient; ∅ = diameter; *α* = suprarenal; *β* = infrarenal; calcif = calcification; thromb = thrombus; MB = main body.

Thirteen patients were treated with a Talent bifurcated stentgraft (Medtronic, Minneapolis, MN, USA), one with both a Talent bifurcated and a Talent aorto-uni-iliac device and one patient with a Zenith bifurcated stentgraft (Cook, Bloomington, IN, USA). Significant differences were observed in the type of grafts used in the study and control groups, where the distribution of types of graft was greater (Table 1). The median stentgraft oversizing was 21% (10–31) and eight patients (53%) were treated with an

endograft sized ≥32 mm proximally. Patient 11 had an hourglass neck 39 mm in length, and oversizing was 15–20% in the mid-section, despite a 10% oversizing only in the proximal 10 mm.

All patients received 5000 units of heparin just before catheterisation. The activated clotting time (ACT) was maintained ≥2 times normal during all procedures. Stentgraft deployment was successful and uncomplicated in 14 patients. In one patient a bifurcated stentgraft was inadvertently deployed 2 cm below the intended position (case number 7). An aorto-uni-iliac stentgraft was subsequently placed through the bifurcated stentgraft at the intended proximal position, followed by a contralateral iliac occluder and a femoro-femoral crossover bypass. As the second stentgraft was placed at the optimal position, this patient was still included in the study group. Blood loss was <150 cc during all EVAR procedures and the median operation time was 120 minutes (80–173). Median contrast volume used was 110 mL (70–170), and median fluoroscopy time (in half-dose setting) was 20 minutes (8–43). All 15 patients had a clear, unmistakable, proximal type-I endoleak at the completion angiogram, which was verified by two of three vascular surgeons with extensive experience in EVAR (HV, FM or JvH) (Figure 1).

In all patients a CTA was obtained within 1 week of EVAR, and all had a minimum of 1 yearly CTA during postoperative surveillance. The type-Ia endoleak had disappeared spontaneously on the first postoperative CTA in 8 of the 15 patients (Table 3). In the other seven patients, a clear type-Ia endoleak was still seen. In one of these patients the aneurysm ruptured 2 days after EVAR, causing death before treatment was possible (case 7). This patient had lumbar pain and hypotension, which led to a CTA investigation 48 hours postoperatively, where a large type-Ia endoleak and a posterior retroperitoneal rupture were evident. On the second postoperative CTA, obtained a median of 5 months (1–12) after EVAR, no more type-Ia endoleaks were seen.

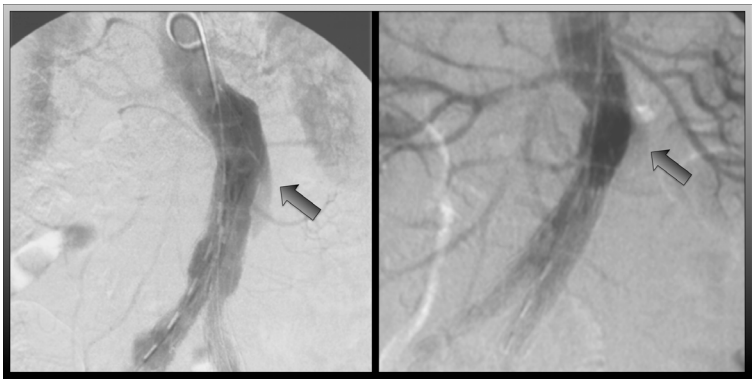

Figure 1. Examples of intraoperative type-Ia endoleaks managed conservatively. Arrow indicates the type-Ia endoleak.

Table 3. Outcome of patients after conservative management of primary type-Ia endoleaks.

Pt	Sp. seal (d)	Rec 1aEL (y)	Migration (y)	Sac growth (y)	AAA rupt (y)	Total FU (y)	Death (y)	Death cause
1	Y (51)	N	N	Y (1.96)	N	5.52	N	–
2	Y (2)	N	N	N	N	5.51	Y (5.51)	Cancer
3	Y (112)	N	N	N	N	4.71	Y (4.71)	Cancer
4	Y (2)	N	N	N	N	4.05	N	–
5	Y (370)	N	N	Y (1.99)	N	3.56	N	–
6	Y (134)	N	N	N	N	2.02	N	–
7	N	N	N	N	Y (0.01)	0.01	Y (0.01)	Early rupture
8	Y (3)	N	N	N	N	0.58	Y (0.58)	Undetermined
9	Y (147)	Y (4.85)	N	Y (4.85)	N	5.31	N	N
10	Y (4)	N	Y (1.25)	N	N	2.29	N	N
11	Y (2)	N	N	N	N	2.07	Y (2.07)	Infection
12	Y (2)	N	Y (1.85)	N	N	4.07	N	N
13	Y (2)	? (2.05)	N	Y (2.05)	N	2.97	N	N
14	Y (2)	N	N	N	N	2.17	Y (2.17)	Cancer
15	Y (238)	N	N	Y (1.65)	N	1.67	N	N

Legend: d = days; FU = follow-up; Pt = patient; Rec 1aEL = recurrent type-Ia endoleak; rupt = rupture; Sp. = spontaneous; y = years; ? = unconfirmed.

An unmistakable recurrence of a type-Ia endoleak was observed in one patient (case 9), 4.85 years after EVAR (Table 4). This was associated with dilatation of the proximal neck beyond the diameter of the implanted endograft. At this time, the previously stable aneurysm sac exhibited growth, and the patient was successfully converted to open repair. In a second patient, sac growth was noted 1.85 years after EVAR (case 13). As a result of neck dilatation and proximal migration (<10 mm) in a previously angulated neck (65° preoperatively), a proximal endoleak was not imaged, but was suspected because of the short proximal seal. This patient underwent successful implantation of a proximal extension cuff. No other recurrences were observed.

After discharge, the median follow-up was 3.27 years (range 0.58–5.52). During this period, five patients had secondary interventions (Table 4). Cases 9 and 13 were for recurrent type-Ia endoleak (case 9) and insufficient proximal fixation and sealing without endoleak (case 13) and have been described above. One patient underwent secondary intervention after 2 years for an aneurysm diameter growth of 16 mm (volume increase of 136 mL in combination with an aortic neck dilation of 8 mm) in the absence of an endoleak (case 1). Conversion to open repair was performed without further complications. During the conversion procedure, there was no visible endoleak when opening the aneurysm sac. One other patient underwent implantation of a proximal extension cuff 1.25 years after EVAR for stentgraft migration of 10 mm. This was probably caused

by a neck dilation of 5 mm (case 10). Stentgraft migration occurred in one other patient after 1.85 years (case12). This was successfully treated by implantation of an aorto-uni-iliac device.

Six patients died during follow-up: one as a result of a ruptured aneurysm 2 days after EVAR; three from cancer; one from infection; and one the cause for which could not be determined (Table 3). No other AAA-related deaths occurred in the study group.

In comparison with the control group, patients included in the study group had shorter follow-up time, and shorter time to first intervention, although these differences were not statistically significant (Table 5). There was a greater proportion of patients suffering from secondary (or recurrent) type-Ia endoleak (13% vs. 4%), endograft migration (13% vs. 3%), and sac growth (33% vs. 16%). Similarly, a greater proportion required secondary intervention (33% vs. 23%) and particularly conversion to open repair (13% vs. 5%). None of these differences however, was statistically significant.

Table 4. Secondary interventions after conservative management of primary type-Ia endoleaks.

Pt	Sec. interv. (y)	Cause for sec. interv.	Type of sec. interv
1	Y (1.96)	Sac growth without visible EL	Conversion to open
7	Y (0.01)	Rupture	Conversion to open
9	Y (4.85)	Proximal type-Ia EL	Conversion to open
10	Y (1.25)	Migration without visible EL	Proximal extension
12	Y (1.85)	Migration without visible EL	Conversion to AUI
13	Y (2.05)	Sac growth without visible EL	Proximal extension

Legend: Sec. interv = secondary intervention; y = years.

Table 5. Comparison between patients after conservative management of primary type-Ia endoleaks and the remaining EVAR-treated population.

Variable	Study group (*N* = 14) [a]	Control group (*N* = 201)	*p*
Total FU (y), median (range)	3.27 (0.58–5.52)	3.93 (0.09–8.88)	.652
Time to first complic., median (range)	2.03 (0.58–5.51)	2.92 (0.00–8.88)	.824
Type-Ia endoleak during FU, *N* (%)	1 (7)	8 (4)	.843
Migration, *N* (%)	2 (13)	5 (3)	.078
Conversion to open repair, *N* (%)	2 (13)	9 (5)	.172
Post-implant rupture, *N* (%)	1 (7)	1 (0.5)	.134
Sac growth, *N* (%)	5 (33)	32 (16)	.145
Secondary intervention, *N* (%)	5 (33)	46 (23)	.354

Legend: y = years. a - Only considering discharged patients.

DISCUSSION

In this study, the conservative management of primary type-1a endoleaks in patients with adequate anatomy, planning, and implantation led to spontaneous resolution in most cases. A watchful attitude towards primary type-1a endoleaks in selected patients may be preferable to immediate conversion or complex endovascular techniques. However, our data suggest an increased risk of late complications and secondary interventions that must be factored into the decision of whether to observe or intervene.

The natural history of an untreated type-1a endoleak remains undetermined. Although common sense suggests that rupture risk is the same as the risk of an untreated AAA of similar diameter, Venermo et al. suggest that EVAR offers protection from rupture despite the presence of sac pressurisation.[14] These authors suggest that growth, rather than the presence of endoleak, is a better predictor of rupture after EVAR. In their series of 21 patients with untreated type-Ia endoleak, only one rupture occurred (2.5 years after EVAR) after a 2 cm enlargement. In this study, one rupture occurred 2 days after EVAR. The cause for this cannot be fully explained. An iatrogenic lesion of the aneurysm wall cannot be ruled out, as the procedure was complex and the temporal relationship between implant and rupture is unusual.

The cause of primary type-1a endoleaks in well planned and executed cases is most likely to be multifactorial. Coagulation abnormalities (antiplatelet + intraoperative anticoagulation with ACT >2), morphological aspects of the neck (shape, angulation, irregularities caused by thrombus or plaques), and structural characteristics of the endograft may contribute to varying degrees. The spontaneous disappearance of type-1a endoleaks after appropriate stentgraft sizing and deployment in this specific patient group is not surprising, once the coagulation abnormalities are (at least partially) corrected and the self-expanding nature of the stentgrafts leads to gradual neck remodelling and improved graft-wall apposition. Late-resolution endoleaks (beyond 1 week) occurred in patients who were either chronically anticoagulated (cases 5 and 15), had angulated and relatively short necks (cases 1 and 3), or had an irregular wall due to thrombus (case 6) (Table 2).

Anecdotal reports have suggested a high chance of recurrence after sealing of primary type-1a endoleaks has occurred.[5,15,16] Only one recurrence was detected after 5 years, probably caused by progression of disease. It is believed that this low recurrence rate is directly associated with the criteria for watchful waiting. Data suggest, however, that patients with spontaneously sealed proximal endoleaks are at high risk of complications and more likely to require secondary interventions. Therefore, particular attention to image surveillance and a low threshold for intervention is advisable, especially for endoleaks persisting beyond 1 week. The subgroup of patients with angulation 60–90° appeared to be at higher risk of complications (Tables 2 and 3), but the contribution of

the previously existing type-Ia endoleak is not dissociable from the higher risk resulting from less favourable anatomy alone.

When a device is placed at the intended position just below the lowermost renal artery and a type-1a endoleak persists despite re-ballooning, alternatives to immediate conversion or vigilance are scarce. Placement of a proximal extension cuff is redundant, and (balloon expandable) stent placement (such as "giant" Palmaz stent [Cordis Corp, Miami Flakes, FL, USA]) is limited by maximum diameter and complexity.[15] The Chimney technique potentially allows the resolution of type-1a endoleaks with reasonable results in the mid-term[17,18] and endostaples (Aptus Endosystems, Sunnyvale, CA, USA) are also available, and may be used to enhance proximal fixation and seal. Early experience with this technology suggests high technical success rates and promising results, but the durability of this adjunct remains unknown.[19] Off-the-shelf fenestrated or branched devices have recently been marketed or are under development by most major manufacturers, and may provide a better solution in patients with appropriate anatomy.

Limitations

Firstly, the study sample is small and consequently the number of events for individual endpoint analysis is restricted. The absence of statistical significance between the study and control groups should be interpreted as a likely type-1 statistical error, and not as proof of equivalence. Also, the majority of patients were treated with the Talent endograft, which is stiffer and has less efficient fixation than most modern alternatives. In these patients, AAA neck configuration was not evaluated, and could help explain the occurrence of primary type-Ia endoleaks in otherwise favourable conditions. Lastly, the exact proportion of patients treated successfully with re-ballooning of the proximal attachment site could not be determined.

CONCLUSION

All but one of the primary type-1a endoleaks after EVAR in this specific 15 patient group sealed spontaneously and only one clear recurrence was observed, after 5 years. Although the data suggest that these patients may be at higher risk of complications and may require more secondary interventions, a conservative approach may be justified under strict circumstances, especially when endovascular options are not feasible and direct conversion to open repair is considered high-risk. Future off-the-shelf devices allowing for extension of the proximal sealing zone may present a more durable and elegant solution.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the late Jasper van Keulen for his contribution for this study.

CONFLICT OF INTEREST

Prof. Hence J. M. Verhagen, Prof. Frans L. Moll and Dr. Joost A. van Herwaarden have received consulting fees from Medtronic AVE.

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Chapter 17

Commentary on "Type II endoleak after endovascular aneurysm repair"

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British Journal of Surgery 2013;100:1262-1270

Sir,

Intervention for isolated type II endoleaks is controversial. The potential hazard of current techniques should be clearly outbalanced by the expected benefit, and this is not so. In the compiled data presented by Sidloff and colleagues, only 14 (0·06 per cent) of 21 744 patients suffered from rupture in the presence of an isolated type II endoleak. When reviewing the original publications thoroughly, a causal nexus is generally speculative. We disagree with interpretation of these data as being supportive of intervention.

Evidence suggests that a direct association between type II endoleaks and rupture is dubious: sac expansion also occurs in the absence of type II endoleaks,[1] and their 'successful' occlusion frequently fails to arrest growth (the only reasonable endpoint).[2] Furthermore, systolic perigraft flow upon mobilization (suggesting position-dependent endoleaks)[3] and unexpected device integrity failure[4,5] have been identified during conversion – both valid and possibly overlooked causes of rupture.

Type II endoleaks may represent outflow of direct endoleaks, or simply be 'innocent bystanders'. The absence of ruptures after these secondary procedures (even when failed) is probably due to poor indication (reflecting unnecessary treatment) or insufficient follow-up, and must not be interpreted as proof of efficacy as suggested. When expansion is present, priority should go to exclusion of direct endoleaks, correction of insufficient seal and possibly graft relining. Treating type II endoleaks may actually divert attention from the underlying problem, aside from generating permanent imaging artefacts, and result in a false notion of safety. We find it unreasonable to subject patients to potentially harmful therapies for which the benefit is so doubtful.

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Chapter 18

Conservative management of persistent aortocaval fistula after endovascular aortic repair

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ABSTRACT

Endovascular repair is a valid alternative for patients with abdominal aortic aneurysms. However, in patients with concomitant aortocaval fistulas, type II endoleaks may result in a persistent communication between the aneurysm sac and the inferior vena cava. In these patients, prompt closure of the persistent fistula has been advocated. We present a patient with an abdominal aortic aneurysm, with aortocaval fistula, who was managed endovascularly. Aneurysm sac shrinkage was observed despite persistent aortocaval communication due to type II endoleak. This case demonstrates that conservative management of type II endoleaks associated with persistent aortocaval fistulas is possible and may result in favorable aneurysm sac remodelling.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is a valid alternative over open reconstruction in patients with (ruptured) abdominal aortic aneurysms (AAAs).[1] However, in patients with concomitant arteriovenous (AV) fistulas, type II endoleaks may result in a persistent communication between the aneurysm sac and the venous system. In the current literature, early closure of the fistula has been advocated due to concerns about future aneurysm-related complications.[2,3] We present an AAA patient with an aortocaval fistula who was managed conservatively and in whom favorable aneurysm sac remodelling was observed, despite a persistent aortocaval communication due to a large type II endoleak.

CASE REPORT

A 61-year-old man presented at the emergency department with acute low back and abdominal pain. The patient had a history of hypertension and chronic obstructive pulmonary disease. Prescription medications included a β-blocker, an angiotensin II inhibitor, and a short-acting β2-adrenergic receptor agonist. On admission, his heart rate and blood pressure were within normal reference ranges (72 beats/min and 123/87 mm Hg, respectively). Physical examination revealed a tender, pulsatile abdominal mass, without abdominal bruit or thrill. No clinical signs of venous hypertension or heart failure were observed. Laboratory results showed no hepatic or kidney dysfunction. A computed tomography angiography (CTA) demonstrated a large AAA (10 cm in transverse diameter) with an associated aortocaval fistula (Figure 1).

The patient's anatomy was suitable for EVAR, and a bifurcated Endurant endovascular device (Medtronic Inc, Minneapolis, Minn) was used for exclusion. The perioperative final angiography showed an evident type II endoleak from the inferior mesenteric artery, but no further action was taken.

The patient had an uneventful postoperative recovery and was discharged after 5 days. In addition, postoperative renal and hepatic function remained normal.

A postoperative CTA showed persistent communication with the inferior vena cava (IVC) as a result of the type II endoleak (Figure 1). To evaluate the systemic repercussion of the persistent aortocaval fistula, the patient was referred for a formal cardiac evaluation after 3 months. He was asymptomatic, and results of electrocardiography were normal. Echocardiography showed a normal systolic left ventricular ejection fraction, with no signs of increased right atrial filling pressure and a physiologic collapse of the IVC. Consequently, no further action was taken. After 1 year of follow-up, CTA showed shrinkage of the aneurysm sac diameter by 10 mm and an 8% reduction in volume compared with the postoperative CTA,[4] despite the persistent type II endoleak (Figure 2).

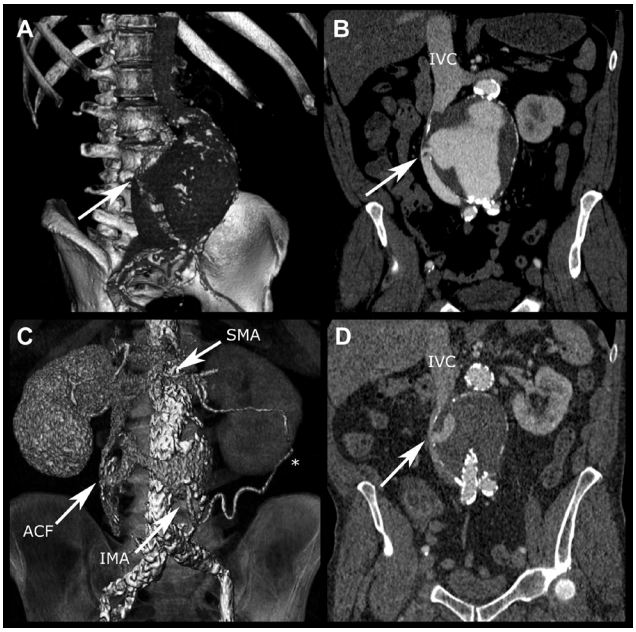

Figure 1. A preoperative (A) luminal three-dimensional reconstruction and a (B) coronal view of the computed tomography angiography (CTA) show a 10-cm large abdominal aortic aneurysm (AAA) with associated aortocaval fistula (ACF, white arrowheads). A postoperative (C) reconstruction and a (D) coronal view show the persistent aortocaval fistula at the 1-year follow-up.
Legend: *Artery of Drummond; IMA, inferior mesenteric artery; IVC, inferior vena cava; SMA, superior mesenteric artery.

DISCUSSION

Persistent AV fistulas after EVAR have been reported, but the natural history of this complication remains unknown; moreover, there is no clear evidence in the current literature supporting treatment over observation. Our case demonstrates that persistent aortocaval communication due to type II endoleak is possible and that a conservative approach may be preferable in the absence of systemic manifestations and in the face of favorable aneurysm sac remodelling.

Aortocaval fistulas are, by definition, high-flow fistulas that may result in complications due to increased cardiac output and venous hypertension.[5,6,7] Treatment is therefore advised. Patients with aortocaval fistulas have traditionally been treated with open repair, with mortality rates ranging from 16% to 66%.[5] Because EVAR has been adopted as valid treatment for (ruptured) AAAs,1 also in the presence of aortocaval fistulas, persistent communication between the aneurysm sac and the IVC may occur due to a type II endoleak. The question remains if—and how—we should manage these persistent fistulas.

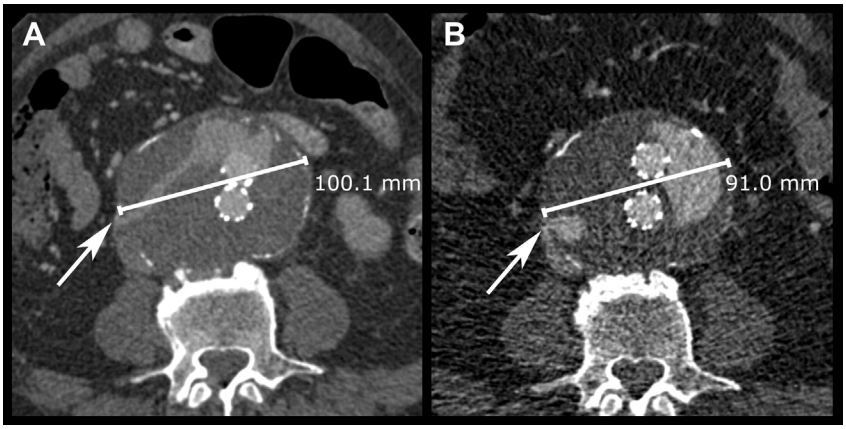

Figure 2. Postoperative computed tomography angiography (CTA) at (A) 6 weeks and at the (B) 1-year follow-up shows a 10-mm decrease in diameter.
Legend: Notice the large type II endoleak associated with a persistent aortocaval fistula (white arrowheads).

Type II endoleak is defined as persistent retrograde flow into the aneurysm sac from the inferior mesenteric, lumbar, or other arteries, without attachment-site leak.[8] They are classified as (a) simple, with one patent branch or (b) complex, with two or more patent branches.[9] These endoleaks are considered important because they may result in repressurization of the excluded aneurysm sac, with consequent growth and, ultimately, rupture. However, in the presence of persistent caval communication, type II endoleaks are subject to different flow and pressure dynamics caused by the connection with the low-pressure venous system (2-8 mm Hg).[10] The connection causes a pressure gradient, resulting in a decrease of in-sac pressure (Figure 3), mimicking the concept of aneurysm sac fenestration.[11] Owing to the low-pressure nature, this special type of type II endoleak has a very low probability of aneurysm sac growth. This was confirmed in our patient, in whom we observed significant aneurysm sac shrinkage at 1 year (Figure 2).

Several cases of endovascular treatment for AAA patients with aortocaval fistulas have been described.[12,13,14,15] However, only four case reports of persistent aortocaval fistulas have been published to date. Burke et al[2] reported a patient with a type II endoleak 4 days postoperatively, which was immediately treated with a cuff in the IVC and glue in the aneurysm sac. Kopp et al[3] reported a similar patient who underwent secondary coiling of a persistent type II endoleak. Lastly, Vetrhus et al[15] suggested that persistent fistulas in this context tend to resolve spontaneously, which did not occur in our patient. The fistulas in their two patients resolved on-table in one patient and after 4 weeks in the other, without further intervention.[15] Taken together, the chance of a persistent aortocaval fistula after EVAR is rather small but is considerable due to the high frequency of type II endoleaks after EVAR.

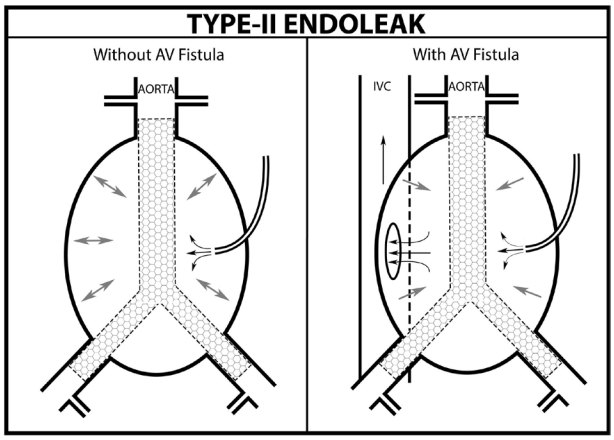

Figure 3. Different dynamics are shown in the aneurysm sac between a type II endoleak (left) without and (right) with an arteriovenous (AV) fistula. IVC, Inferior vena cava.

We treated our patient conservatively because no systemic repercussions of the AV fistula were present and secondary interventions for type II endoleaks are generally reserved for persistent endoleaks (≥6 months) associated with aneurysm sac enlargement.[16] However, we acknowledge that conservative management in our patient might result in complications. Increased cardiac output and, ultimately, heart failure may develop from AV fistulas. Nevertheless, we considered this risk was relatively small because the arterial component of the fistula in our patient resulted from retrograde flow from the inferior mesenteric artery. Moreover, a physiologic collapse of the IVC was observed, emphasizing the low-pressure nature of the fistula. Nonetheless, careful and continued cardiac evaluation is required to ensure early identification of this possible complication.

In addition, embolization may occur as a result of dislodgment of aneurysm sac debris; however, we believe that the risk for clinically significant embolization is minute. First, the chance of embolization from untreated AAAs is very small.[17] Second, closing an AV fistula with an implant may also induce thromboembolism. Lastly, the chance of embolization due to manipulation during secondary intervention to close the AV fistula is probably higher than the embolization risk itself.

Because compression of the IVC was observed, thrombosis could occur. Therefore, implantation of an endograft in the IVC could be considered to exclude the AV fistula and treat IVC compression. However, this compression is frequently observed in EVAR patients, and caval thrombosis is anecdotic. Also, stent graft placement in a significantly compressed IVC may yield a suboptimal result, with a risk of endograft collapse or acute stent thrombosis, or both.

CONCLUSIONS

Our case shows that in the absence of systemic repercussions, persistent aortocaval fistulas due to type II endoleak after EVAR may be managed conservatively and that favorable remodeling of the aneurysm sac is possible. Nevertheless, close observation, including periodic cardiac evaluation, is mandatory. Secondary intervention may be reserved for patients with persistent aortocaval fistulas combined with aneurysm sac enlargement or systemic manifestations.

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Chapter 19

Treatment of post-implantation aneurysm growth by laparoscopic sac fenestration: long-term results

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ABSTRACT

Objectives

Sac growth after endovascular aneurysm repair (EVAR) is an important finding, which may influence prognosis. In case of a type II endoleak or endotension, clipping of side branches and subsequent sac fenestration has been presented as a therapeutic alternative. The long-term clinical efficacy of this procedure is unknown.

Methods

The study included eight patients who underwent laparoscopic aortic collateral clipping and sac fenestration for enlarging aneurysms following EVAR. Secondary interventions and clinical outcome were retrieved from hospital records. Sac behaviour was evaluated measuring volumes on periodical computed tomography angiography (CTA) imaging using dedicated software.

Results

Follow-up had a median length of 6.6 (range 0.6–8.6) years. During this time, only three patients successfully achieved durable aneurysm shrinkage (n = 2) or stability (n = 1). The remaining patients suffered persistent (n = 2) or recurrent sac growth (n = 3), all regarded as failure of fenestration. A total of six additional interventions were performed, comprising open conversion (n = 2), relining (n = 1) and implantation of iliac extensions (n = 3). All additional interventions were successful at arresting further sac growth during the remainder of follow-up.

Conclusions

Despite being a less invasive alternative to conversion and open repair, the long-term outcome of sac fenestration is unpredictable and additional major procedures were often necessary to arrest sac growth.

INTRODUCTION

Sac growth after endovascular aneurysm repair, reportedly occurring in 40% of patients, is an important finding that may influence prognosis. In case of sac growth and the presence of type II endoleaks or endotension, clipping of side branches and subsequent sac fenestration was suggested in the past as a therapeutic alternative. Long-term efficacy of this procedure is unknown. The current study provides the single largest case series and longest follow-up after this procedure. Based on our results, sac fenestration is not advisable as primary treatment in patients suffering from sac growth in the presence of type II endoleaks or endotension.

Endovascular aneurysm repair (EVAR) of abdominal aortic aneurysm (AAA) has developed since 1991[1] and is now frequently the preferred method of treatment. The ultimate goal of EVAR is to prevent death from aneurysm rupture by excluding the aneurysm sac from the circulation, thereby relieving it from pressure. After EVAR, most aneurysms will stabilise or shrink in diameter. Some aneurysms, however, will continue to expand.[2,3,4]

Continued sac expansion after EVAR can have several explanations, but endoleaks and graft porosity (endotension) are frequently cited as culprits. In the case of sac growth, most physicians propose additional treatment to prevent the aneurysm from rupturing or to prevent aortic dilatation near the proximal or distal sealing zones, giving rise to possible migration and/or type I endoleaks. When an endoleak is associated with growth, a secondary endovascular procedure or conversion to open repair is usually performed. When no endoleak is found, the solution is more challenging, as the cause of continued aneurysm expansion is frequently unclear.

Previously, laparoscopic fenestration of the aneurysm sac was suggested as treatment for patients with an enlarging aneurysm sac after EVAR, with clipping of aortic sac collaterals.[5] Although the early results were promising, long-term durability of this treatment remains unknown. The aim of the current study was to evaluate the long-term effects of this treatment on sac behaviour, to provide guidance in future decision making.

METHODS

Patient selection

From June 1999 to October 2005, a total of 143 AAA patients underwent an EVAR procedure in our hospital. During follow-up, sac growth was observed in 34 patients (23.8%). Type II endoleaks were detected in 21 cases (14.7%). These were either observed or treated with percutaneous interventions, such as coil-embolisation, glue injections and endoscopic clipping of lumbar arteries, depending on sac behaviour. In case of a growing aneurysm sac where no endoleak was detected or when an endovascular approach

of type II endoleak was technically unsuccessful or failed to arrest growth, an alternative approach was proposed. Laparoscopic fenestration of the aneurysm sac was then performed, which was preceded by clipping of patent inferior mesenteric artery (AMI) and lumbar arteries. To evaluate the effect of fenestration on sac behaviour, all patients who underwent this procedure were included. The sole exclusion criterion for this study was the lack of a minimum two post-fenestration imaging studies, as that would make observations on sac behaviour impossible. The study was conducted in agreement with the Institutional Medical Ethics Committee guidelines.

Fenestration procedure

The technical details of this intervention were described previously.[5] In summary, all visible lumbar arteries were clipped endoscopically through a retroperitoneal approach, and a patent inferior mesenteric artery (AMI) was clipped laparoscopically. Cleared from all patent side branches, the aneurysm was then fenestrated. During this phase of the operation, the operators could check for residual back-bleeding and suture any remaining type II endoleaks. Also, the sac contents were removed at this time and an omentum slip was inserted whenever technically possible in the sac to prevent immediate closure of the fenestration, reduce exposure of the bare endograft to the small intestines and possibly facilitate resorption of hygroma in the early stages after fenestration.

In one case, the procedure was converted to open suturing of all patent side branches and fenestration of the sac. The primary operator during all procedures was the same, experienced vascular surgeon (J.H.), who was assisted by an experienced laparoscopic surgeon.

Efficacy of fenestration

At the time of these procedures, sac growth was a phenomenon that was aggressively treated. Therefore, the preferential outcome of this treatment at the time was to achieve sac stability or shrinkage. Primary end point of the current study is therefore persistent or recurrent sac growth, which is considered failure of treatment. Aneurysm-related death and additional vascular interventions were recorded as secondary end points. Information on survival and the cause of death was retrieved from hospital records.

Analysis of sac behaviour

Measurement of the aneurysm sac was performed on computed tomography angiography (CTA) images. The first CTA, within 48 h after the fenestration, was considered the baseline for future follow-up. CTAs were then performed approximately every 6–12 months, according to institutional protocol. All hospital records were reviewed for additional interventions and rationale behind treatment decisions. Sac behaviour was scored by two complementary methods.[6,7] First, the single largest diameter of the

aneurysm sac was measured. Second, the total sac volume was quantified on each CTA and plotted in time-related curves, regarding the first measurement after fenestration as baseline. All measurements were performed on a workstation with dedicated software (3Mensio Vascular v4.2; 3Mensio Medical Imaging B.V., Bilthoven, The Netherlands) and using centre-lumen line (CCL) reconstruction. Volume measurements were obtained according to a standardised and previously validated protocol.[8] Sac growth was defined as >5% increase in volume compared to baseline or in a 12-month interval. All data was subsequently analysed using the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population

In the presented time window, a total of nine patients with a growing aneurysm after EVAR underwent aneurysm sac fenestration. One patient died of non-Hodgkin lymphoma 3 months after the procedure, having received only one CTA after the procedure, and was therefore excluded from the current study. From the remaining eight patients (seven men), one patient suffered from a common iliac artery aneurysm rather than an AAA, but was similarly treated by EVAR and later fenestration for continued growth. In one patient, the endoscopic procedure was converted to an open fenestration procedure, as described.5 At the time of fenestration, the eight patients had a median age of 65.2 (range 55.1–74.3) years. Patient baseline characteristics are detailed in Table 1. There was no perioperative mortality.

Table 1. Descriptive statistics for the study population.

Baseline characteristics	All patients (*n* = 8)
Age in years, median (range)	65.2 (55.1–74.3)
Female gender, *n* (%)	1 (12.5)
Ischaemic heart disease, *n* (%)	2 (25)
Diabetes mellitus, *n* (%)	1 (12.5)
History of stroke, *n* (%)	0
Congestive heart failure, *n* (%)	1 (12.5)
Renal dysfunction, *n* (%)	1 (12.5)
Cardiac arrhythmias, *n* (%)	1 (12.5)
Hypertension, *n* (%)	4 (50)
History of smoking, *n* (%)	3 (37.5)
COPD, *n* (%)	0

Legend: COPD = chronic obstructive pulmonary disease.

Procedural details

Four patients were treated with an Excluder AAA Endoprosthesis (W.L. Gore and associates, Flagstaff, AZ, USA), one of which was the low-permeability design introduced in 2004 (Table 2). The remaining implanted grafts were three Zenith AAA Endovascular Grafts (Cook Medical, Bloomington, IN, USA) and one Ancure Graft (Guidant, Menlo Park, CA, USA). Fenestration took place at a median of 1.7 (range 0.5–5.8) years after EVAR. Pre-fenestration sac diameters measured on CTA had a median of 73.2 mm (range 56.5–91.0 mm). The indication for fenestration was persistent or recurrent sac growth for all cases. In 50%, a type II EL could be detected as the possible culprit (Table 2). Attempts to treat these first with glue injections and coil embolisations had been unsuccessful. Upon reviewing the imaging studies in preparation of the procedures, no intense inflammatory component was observed nor was this noticed during the operation. During the procedures, the operators concurred in having achieved proper exposure and the ability to clip all side branches. As confirmation, in only one case residual back-bleeding was observed upon opening the aneurysm sac, which was sutured from within. An omentum slip to leave in the fenestration was available in five out of eight patients.

Follow-up had a median length of 6.6 (range 0.6–8.6) years. During this time, only three patients experienced durable aneurysm sac shrinkage (n = 2) or stability (n = 1) and were considered a success. In these three cases where sac growth was successfully arrested, two cases suffered progression of disease leading to dilatation of a common iliac artery (Case #2 and #5). Although this prompted the endovascular extension of one of the distal sealing zones (Table 3), this was not regarded as failure of fenestration.

The remaining five cases suffered persistent sac growth (n = 2) or recurrent growth after initial shrinkage (n = 3), all regarded as failure of fenestration. The two cases with persistent sac growth comprised one patient with a persistent type II endoleak despite clipping and fenestration, who was converted after 6 months (Case #4), and another patient without detectable endoleaks but an original design Excluder in situ (Case #7).

Table 2. Details on EVAR follow-up prior to fenestration.

Case	Implanted graft type	Time since EVAR (years)	Sac diameter (mm)	Detected endoleak
1	Excluder OD	1.6	74.7	None
2	Excluder OD	0.7	68.0	Type II
3	Zenith	1.7	83.5	None
4	Zenith	2.6	69.9	Type II
5	Ancure	5.8	71.6	Type II
6	Zenith	2.4	56.5	None
7	Excluder OD	1.6	84.3	None
8	Excluder LP	0.5	91.0	Type II

Legend: EVAR = endovascular aneurysm repair, OD = original design, LP = low-permeability design.

This patient was presumed to suffer from endotension, but refused additional treatment until over 5 years after fenestration, when relining of the endograft finally arrested sac growth.

The three cases with recurrent sac growth included one patient that showed shrinkage during the first 7 years, but on the latest CTA suddenly had growth of the aneurysm sac (Case #3) suggesting re-pressurisation, and one patient with a persistent type II endoleak who showed shrinkage at first but recurrent growth within 15 months, spurring conversion (Case #8). In the final case, primary indication for EVAR was a combination of a large iliac aneurysm and a small AAA (Case #6). Sac shrinkage was observed in the first two years after fenestration, but eventually volume and diameter increased again until, finally, contrast was observed in the iliac aneurysm sac, resulting in an extension of the distal dealing zone.

No technical aspects of the procedures or observation made during surgery could be identified as playing a part in the success rate of fenestrations. As mentioned earlier, no (untreated) back-bleeding was observed during the fenestration that could eventually predispose a patient to a residual or recurrent type II endoleak. Furthermore, the impossibility to mobilise an omentum slip for insertion in the fenestration was no predictor for outcome (arresting growth in two, conversion in one).

In summary, six patients underwent additional interventions after fenestration. Two patients were converted to open repair, both suffering from persisting type II endoleaks and early sac (re-)growth. One patient was relined for persistent sac growth, in the presence of an original design Excluder endoprosthesis. In addition, three patients underwent implantation of iliac extensions, one of which suffered from recurrent iliac sac growth and the other two from common iliac artery dilatation due to progression of disease. All secondary interventions after fenestration were successful at arresting further sac growth during the remaining duration of follow-up.

Table 3. Details on fenestration follow-up and outcomes.

Case	Baseline volume	Mid-term volume	Latest volume	Follow-up (years)	Sac growth	Status endoleak	Additional intervention
1	152	81	81	8.6	No	n/a	None
2	97	97	96	8.6	No	Treated	Iliac extension
3	263	244	289	8.0	Yes	n/a	None
4	239	239	263	0.6	Yes	Persistent	Conversion
5	239	164	151	6.3	No	Persistent	Iliac extension
6	47	37	43	7.0	Yes	n/a	Iliac extension
7	188	387	254	6.0	Yes	n/a	Relining
8	432	381	431	1.3	Yes	Persistent	Conversion

Legend: Volumes are abdominal aneurysm sac volumes in ml. Sac growth was defined as >5% volume change compared to baseline or in a 12-month interval.

DISCUSSION

EVAR has become the preferred method of treatment in many AAA patients, especially when the aortic anatomy is favourable. Despite the early survival advantage, EVAR is associated with greater aneurysm-related complications and therefore most agree on the need for life-long follow-up with imaging studies to evaluate migration, stent integrity, endoleaks and aneurysm size.[9,10,11] Post-implantation growth has received particular attention because it is observed with relative frequency and suggests continued pressurisation of the aneurysm sac, and therefore failure of treatment (despite relative rarity in clinical consequences).[12] After EVAR, the majority of patients have either a gradual decline or stabilisation of their aneurysm dimensions over the years.[13] When growth occurs, however, a plausible explanation should be sought and treatment promptly offered. While it may be the accepted standard of care that patients with type I or III endoleaks require rapid intervention, opinions vary over the implications of type II endoleaks, especially in cases where the diameter of the aneurysm stabilises or only grows slowly.[14,15] Within the last decade, studies reported that selective surveillance of a type II endoleak is a safe course.[16] Controversially, Jones et al. reported that persistent type II endoleak increases the risk for rupture and the need for conversion,[17] while data from the EUROSTAR registry suggested that it actually seems to protect the patient against rupture.[14] When the current patients were diagnosed with a growing aneurysm after EVAR, endotension and type II endoleaks were aggressively treated. In 2002, Veith et al. reported on a summit with 27 interested leaders who reached a consensus that growing aneurysms without detection of endoleaks should be treated surgically or by repeated EVAR procedure.[17] Concerning type II endoleaks, Steinmetz et al. reported that if no sac growth is seen, no additional intervention is necessary.[15] However, general opinion among the leaders previously mentioned was that persistent type II endoleaks required treatment, either with coil/glue embolisation18 or laparoscopic clipping.[19]

With that historical backdrop, a series of nine patients with growing aneurysms without detectable endoleaks or with persistent type II endoleaks were treated by laparoscopic clipping of side branches and aneurysm sac fenestration. Although the short-term results were promising,[5] the current study is the first to show that long-term results are sub-optimal in a large proportion of patients, raising doubt over the applicability of this previously described technique. The ultimate goal of the clipping and fenestration procedure was to halt sac growth. Durable aneurysm, sac stability was only achieved in three patients, two of who underwent additional procedures for progression of the disease in the common iliac arteries. Out of the other five cases, two were converted to open repair, one was relined, one was extended at the distal sealing zone and one was diagnosed with recurrent sac growth on the latest scan. In general, the two-step procedure was not particularly successful in achieving its goal of durable sac stability.

The first step in the procedure was to clip all lumbars and other possible side branches to treat or prevent type II endoleaks. Noticeably, out of four cases presenting with a type II endoleak prior to fenestration in our study, the endoleak persisted in three, despite the subjectively good view on lumbar arteries during this procedure. The only successful elimination of a type II endoleak was achieved in the one patient that was converted, and therefore clipping of collaterals and sac fenestration was performed as an open procedure, reducing the endoscopic success rate of clipping to nil. Interestingly, an open aneurysm sac with a subsequently demonstrable endoleak had no clinical consequences in our series. Although minimally invasive clipping of lumbar side branches has been frequently performed, right-sided lumbar arteries are technically difficult to expose and clip.[20] In some cases, endoscopic clipping may be unsuccessful, resulting in residual type II endoleaks.[21] This could have contributed to the failure of arresting type II endoleaks durably, in the current study. An alternative approach is primary fenestration and subsequent sewing of back-bleeding lumbars from within the sac.[22,23]

In the current study, fenestration was performed after clipping of the side branches, allowing for visual control by scanning for residual back-bleeding, as previously described by Dion et al. in 2001.[24] Only in one case, back-bleeding was still observed, and this was sutured from within the sac. Although sac contents were thoroughly evacuated after fenestration, the residual type II endoleaks could have been masked by mural thrombus or other debris, missed at the time of surgery. This illustrates that laparoscopic fenestration is a demanding procedure and, even in the hands of experienced vascular and laparoscopic surgeons, can lead to underexposure of the inside of the sac, and thus incomplete removal of thrombus and assessment of back-bleeding side branches.

The most logical indication for fenestration would therefore be endotension as a result of increased graft porosity. Transudate of fluid through the graft fabric is well described, particularly after implantation of the original Excluder endograft (W.L. Gore and associates, Flagstaff, AZ, USA).[18] Releasing the hygroma would theoretically result in arrested growth and prolonged success. This idea has also been defended by others, both with open[19] or with percutaneous sac fenestration. In our series, two patients implanted with the Original Design Excluder continued to exhibit growth without detectable endoleaks prior to fenestration. After fenestration, sac stability was observed in one, but sac growth persisted in the other, who later underwent successful relining with a low-permeability graft. This sac growth could be explained by healing of the fenestration, resulting in the recurrence of hygroma, allowing re-pressurisation. Goodney et al. and Kougias et al. have published on their experience with relining, with similar good results at short term.[20,21] This alternative solution, although promising, still lacks long-term data, but is generally accepted as first-line treatment in case of a growing sac with an original Excluder endograft in situ, or when graft integrity is thought compromised at a specific location.[22,23] Importantly, standard CTA is not the most sensitive technique for type II

endoleak visualisation, and definite diagnosis of endotension is often only possible after opening the aneurysm sac and visualising no bleeding aortic collaterals.[25] Therefore, it is theoretical to reserve this technique for endotension cases.

The current report is limited by its observational design and by the small number of patients. Also, the indication for treatment was individualised and no strict criteria were observed, with potential selection bias. For the purpose of demonstrating the safety and efficacy of the technique, however, these limitations – albeit important – can be accepted to prevent others to subject their patients to this ineffective treatment as well.

In conclusion, the results after fenestration are quite variable and, more importantly, largely unpredictable. Sac growth was observed after fenestration in five out of eight cases, spurring additional interventions in the majority. Therefore, we cannot recommend fenestration as primary treatment for sac growth. Other techniques may hold more promise when minimally invasive interventions fail, risk of rupture is considered high and the patient is too frail for aortic cross-clamping and endograft explantation.

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Chapter 20

Clinical outcome and morphological determinants of mural thrombus in abdominal aortic endografts

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ABSTRACT

Objective

Endograft mural thrombus has been associated with stentgraft or limb thrombosis following EVAR. This study aims to identify clinical and morphological determinants of endograft mural thrombus accumulation and its influence on thromboembolic events after EVAR.

Methods

A prospectively maintained database of patients treated by EVAR at a tertiary institution from 2000 to 2012 was analyzed. Patients treated for degenerative infra-renal AAA and with available imaging for thrombus analysis were considered. All measurements were performed on 3D center-lumen line CTA reconstructions. Patients with thrombus accumulation within the endografts' main-body with a thickness > 2mm and an extension > 25% of the main-body's circumference were included in the study group and compared to a control group which included all remaining patients. Clinical and morphological variables were assessed for association with significant thrombus accumulation within the endografts' main-body using multivariate regression analysis. Estimates for freedom thromboembolic events were obtained from Kaplan-Meier plots.

Results

Sixty-eight patients (16.4%) presented endograft mural thrombus. Median follow-up time was 3.54 years (interquartile range 1.99–5.47 years). Ingraft mural thrombus was identified on the 30-day CTA in 22 patients (32.4% of the study group), 6-month CTA in 8 (11.8%) and in the 1-year CTA in 17 (25%). Intraprosthetic thrombus progressively accumulated over the study period in 40 patients of the study group (55.8%). Overall, 17 patients (4.1%) presented endograft or limb occlusions, 3 (4.4%) in the thrombus group and 14 (4.1%) in the control group (P=.89). Thirty-one patients (7.5%) received an AUI endograft. Two endograft occlusions were identified among AUI devices (6.5%, overall 0.5%). None of these patients showed thrombotic deposits in the main-body nor any outflow abnormalities were identified on the immediately preceding CTA. Estimated freedom from thromboembolic events at 5-years was 95% in both groups (P=.97). Endograft thrombus accumulation was associated with >25% proximal aneurysm neck thrombus coverage at baseline (OR1.9 95%CI 1.1-3.3), neck length ≤15mm (OR2.4 95%CI 1.3-4.2), proximal neck diameter ≥30mm (OR 2.4 95%CI 1.3-4.6), AUI (OR 2.2 95%CI 1.8 – 5.5) or polyester-covered stentgrafts (OR 4.0, 95%CI 2.2 – 7.3) and with main-component "barrel-like" configuration (OR 6.9, 95%CI 1.7-28.3).

Conclusion

Mural thrombus formation within the main-body of the endograft is related to different endograft configurations, main-body geometry and device fabric but appears to have no association with the occurrence of thromboembolic events over time.

INTRODUCTION

The surgical management of abdominal aortic aneurysms (AAA) has progressively shifted towards endovascular repair (EVAR) as the primary treatment[1] for moderate and high risk patients. Limb thrombosis and endograft occlusion are infrequent but potentially devastating complications which have limited the clinical success following EVAR[2,3] and have been associated to preceding endograft mural thrombus accumulation.[4,5] However, the evidence for this is scarce and potentially biased.

Endograft mural thrombus formation has been detected as early as 1 week after endograft deployment and its course is still not completely understood.[4] Optimal management of asymptomatic thrombotic formation within abdominal aortic stentgrafts has not been determined; although most experts defend conservative surveillance,[6] oral anticoagulation therapy has also been reported.[7] There is a clear need for further evidence to support either conduct.

Our hypothesis is that thrombus accumulation within the main body of the endograft is not associated to the occurrence of thromboembolic events.

METHODS

We designed a retrospective case-control study based on a prospectively maintained observational database of all patients undergoing EVAR in a high-volume center in the Netherlands. The study complies with the Helsinki statement on research ethics and no informed consent was required according to institutional guidelines on research ethics.

Patients

From 2000 to 2012, EVAR was performed in 473 patients with AAA at the Erasmus University Medical Center, Rotterdam, The Netherlands. The type of repair offered was individualized according to anatomical features, health status and history of previous abdominal surgery (hostile abdomen). Patient preference was accounted for before obtaining informed consent. Patients with previous aortic surgery or without degenerative abdominal aortic aneurysm (*i.e.* with isolated iliac aneurysms, mycotic aneurysms, anastomotic or traumatic pseudoaneurysms) were not included as well as patients from

whom a postoperative computerized tomography angiography (CTA) could not be obtained.

Patients presenting ingraft thrombus with a thickness > 2mm and an extension of > 25% of the main-body's circumference in at least 3 consecutive 1-mm slices in any postoperative CTA were included in the thrombus group (Figure 1). For case selection, all postoperative CTA's were analyzed with center-lumen line (CLL) reconstruction. The remaining patients formed the control group. Patients who received a stentgraft other than the ones deployed in the thrombus group were also excluded from the study for homogeneity (2 patients with Powerlink [Endologix] stentgrafts).

Postoperative Surveillance

Institutional follow-up protocols have changed significantly over the time period of the study. From the initial practice which contemplated a contrast-enhanced computerized tomography angiography (CTA) at 1, 6, 12 months and yearly thereafter, the 6 month CTA has been reserved only for patients with high risk of complications. Additionally, and according to the treating physician's expectation, selected patients with expected lower risk of complications or with renal function impairment have been alternatively followed with colored-duplex ultrasound (DUS) or by non-contrasted CT.

Data management

Baseline clinical, anatomical and intraoperative data were acquired at the time of surgery. All subsequent long-term follow-up data was prospectively obtained upon outpatient visits and/or regular patient record consult.

Image analysis and measurements

All measurements (diameters, lengths, angles, cross-sectional area and volumes) were performed using semiautomatically generated center lumen line (CLL) reconstructions on a workstation with dedicated reconstruction software (3Mensio Vascular 4.2, Medical Imaging B.V., Bilthoven, The Netherlands), and according to previous validated methodology.[8] All long-term imaging data was obtained by a single observer with experience in image analysis (N.O).

A centered ellipse was assumed as the most approximate form to represent the cross-sectional area of the main-body. For cross-sectional area calculation, the largest and lesser diameters were measured and the respective radius was determined. Cross-sectional area was calculated as: Area= $rA*rB*\pi$ (in which rA is the largest radius and rB the lesser radius and π value was rounded to 6 decimal digits). For lumen reduction determination, the difference between the cross-sectional areas of the main-body and the patent lumen was calculated at the point of maximum thrombus accumulation.

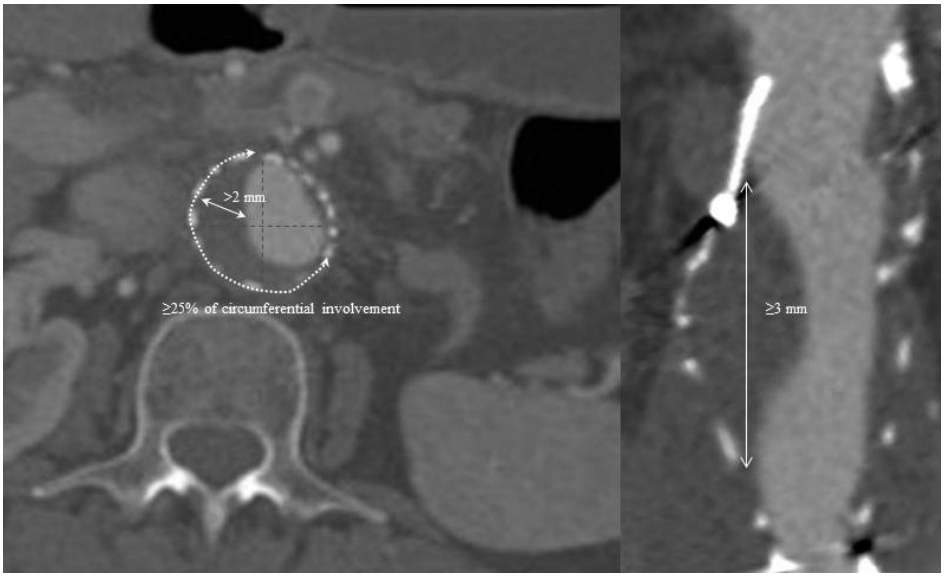


Figure 1. Method for determining inclusion in the thrombus group

Definitions

Reporting was done in accordance to the guidelines from the Society for Vascular Surgery (SVS) / American Association for Vascular Surgery (AAVS) *ad hoc* Committee for Standardized Reporting Practices in Vascular Surgery.[9] Cardiac status was defined and scored according to the SVS / AAVS medical comorbidity grading system.[10]

Thromboembolic events were defined as the composite of endograft occlusion, iliac limb occlusion, thromboembolic acute limb ischemia and blue toe syndrome. Oversizing was determined from the ratio between the implanted main body diameter and the reference neck diameter in the first 15mm of the infrarenal aneurysm neck. Neck length was defined as the distance between the distal point of the lowermost renal artery ostium and the beginning of the aneurysm.

Variation of the main-body cross-sectional area was defined in percentage from the ratio between the maximum cross-sectional area assumed by the endoprosthesis' main body and the minimum main-body cross-sectional area identified in the first 10mm of the stentgraft.

Endpoints

The primary endpoint of this study was freedom from thromboembolic events. Additionally, clinical and morphological variables were explored for association with significant thrombus accumulation within the endograft.

Table 1. Univariate analysis for ingraft thrombus accumulation.

Demographic variables[§]	Thrombus (N= 68)	No thrombus (N=346)	P value	OR (95% CI)
Age ≥70 years	34 (50.0)	231 (66.8)	.008	0.50 (0.29-0.84)
Male gender	59 (86.8)	312 (90.2)	.400	-
Previous history or continuous smoking at time of implantation[a]	49 (77.8)	221 (69.1)	.166	-
Cardiac status ≥2[b]	14 (20.6)	62 (17.9)	.563	-
Hypertension	48 (70.6)	217 (62.7)	.338	-
Cancer[c]	11 (20.0)	56 (18.7)	.816	-
ASA class III/IV	34 (50.0)	165 (47.7)	.738	-
Single antiplatelet therapy at time of implantation	61 (88.7)	289 (83.5)	.215	
Dual antiplatelet therapy at time of implantation	1 (1.5)	6(1.7)		
Oral anticoagulation at time of implantation[d]	7 (10.3)	50 (15.4)	.278	0.63 (0.27 – 1-46)
Elective EVAR	56 (82.4)	270 (78)	.426	-
AAA Ø, mm	61 (54.0 – 74.3)	60 (55.0-72.3)	.497	-
AAA volume, cc	190.0 (150.8-369.0)	188.0 (143.0-281.0)	.595	-
Aneurysm growth ≥5 mm	10 (14.7)	50 (14.6)	.978	
Neck thrombus > 25%	26 (38.2)	94 (27.2)	.016	1.98 (1.21-3.24)
Neck calcification >25%	19 (27.9)	65 (18.9)	.089	1.67 (0.93-3.04)
Proximal neck length ≤15 mm	21 (30.9)	55 (15.9)	.004	2.36 (1.31-4.26)
Proximal neck Ø ≥30 mm	15 (22.1)	42 (12.1)	.030	2.05 (1.06-3.96)
α Angle, degrees	20.0 (10.25-36.8)	21.0 (12.0-34.8)	.782	-
β Angle, degrees	34.0 (19.3-53.3)	35.0 (23.0-53.8)	.141	-
AUI graft configuration	10 (14.7)	21 (6.1)	.014	2.66 (1.19-5.94)
Main-body diameter ≥ 31 mm	32 (54.2)	104 (33.1)	.002	2.39 (1.36-4.20)
Endograft fabric - Polyester	49 (72.1)	186(53.8)	.005	2.22 (1.25-3.92)
Ratio between cross-sectional areas of mainbody and limbs ≥ 2.3	42 (61.8)	136 (39.4)	.001	1.93(1.14-3.29)
Main-body cross-sectional area variation ≥50%	9 (13.2)	23 (6.6)	.063	2.14 (0.94-4.86)
Distal landing zone in the EIA	26 (38.2)	92 (26.6)	.052	1.71 (0.99-2.95)

Legend: [§]Continuous data are presented as mean ± standard deviation of median (IQR) and categorical data as count (percentage). [a] Unavailable data for 31 patients (7.5%) [b] According to the SVS / AAVS medical comorbidity grading system. [c] Unavailable data for 59 patients (14.9%) [d] Unavailable data for 21 patients (5.1%). [e]Measured between cross-sectional area at the start of the first covered stent and maximum cross-sectional area of the endograft main body. ASA – American Society of Anesthesiologists classification system. AUI – aorto-uni-iliac. EIA – External iliac artery. OR – odds ratio. 95%CI – 95% Confidence interval.

Statistical analysis

Categorical variables are presented as count and percentage and were compared using the Pearson's $\chi 2$ test. Continuous variables are presented as mean and standard deviation, or median and interquartile range (IQR). Differences between groups were analyzed using Mann-Whitney U Test for independent non-parametric data, and the Student t-test and significance with the independent samples test for variables with normal distributions. Survival curves for freedom from thromboembolic events were estimated by Kaplan-Meier methods and equality was tested with the Mantel-Cox log rank test. Multivariate logistic regression was performed to assess independent association between endograft mural thrombus accumulation and significant variables determined by univariate analysis. Confidence intervals (CI) of 95% were used and statistical significance was considered if $P < .05$. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 21.0 (IBM Inc, Chicago, Ill, USA).

RESULTS

Among the 473 AAA patients submitted to EVAR at our Institution from 2000 to 2012, 414 full-filled the inclusion criteria. Mean age was 71.8 (± 9.0), 371 (89.6%) were males. Sixty-eight patients presenting intraprosthetic mural thrombus were included in the study group and the remaining 346 were considered as controls. Baseline characteristics are depicted in Table 1.

Median follow-up was 3.54 years (1.99 – 5.47) and did not differ among groups (thrombus group - 3.99 years [2.26-3.41], no-thrombus group - 3.44 years [1.80 – 5.37], P=.107).

Median time at diagnosis of mural thrombotic deposition was 12.0 months (1.2 – 23.0 months) in the thrombus group (N=68). Substantial mural thrombus was identified on the 30-day CTA in 22 patients (32.4%), 6-month CTA in 8 (11.8%), 1-year CTA in 17 (25%), 2-year CTA in 9 (13.2%), and 3-year CTA or after in 12 (17.6%).

Thromboembolic events

Seventeen patients (4.1%) presented with thromboembolic events after a median time of 15.0 months (6.0 – 23.8). Main-body occlusions were reported in 2 patients in the control group (0.5% overall), both aortouniiliac devices (AUI). None of these patients showed thrombotic deposits in the main-body, nor any runoff abnormalities were noted on the immediately preceding CTA, performed 2 months earlier in both cases. In one patient, the endograft occlusion had been preceded 1 year before by a stentgraft migration which had been treated with an AUI conversion. This patient ultimately underwent an axillar-bifemoral bypass. The second patient was treated primarily for a ruptured AAA

with an AUI stentgraft which occluded after 12 months of follow-up and was treated with thrombolysis followed by surgical thrombectomy.

Thromboembolic events including device occlusion, iliac limb occlusions, acute limb ischemia or blue toe syndrome occurred in 3 patients (4.4%) with significant mural thrombus and in 12 (3.5%) of the patients of the no-thrombus group (P=.70). Thirteen patients were treated with catheter-directed thrombolysis followed by iliac percutaneous transluminal angioplasty in 6 patients, limb extensions in 3 patients, surgical thrombectomy in 2 patients, a femoral-femoral crossover in one. The remaining 2 patients had no significant symptoms and remained untreated. None of the reported patients underwent major amputations. The estimated freedom from thromboembolic events at 2 and 5-years were 95% in the thrombus group while in the no-thrombus group they were 96% and 95% (P= 0.97) (Figure 2).

Clinical variables

Overall, 62 patients (91.2%) in the study group and 296 patients (85.5%) were on antiplatelet therapy at time of implantation (Table 1, P=.215). Regarding oral anticoagulation therapy, there were 7 patients (10.3%) in the study group and 50 (15.4%) in the control group were receiving this therapy at time of implantation (P=.24). Oral anticoagulation

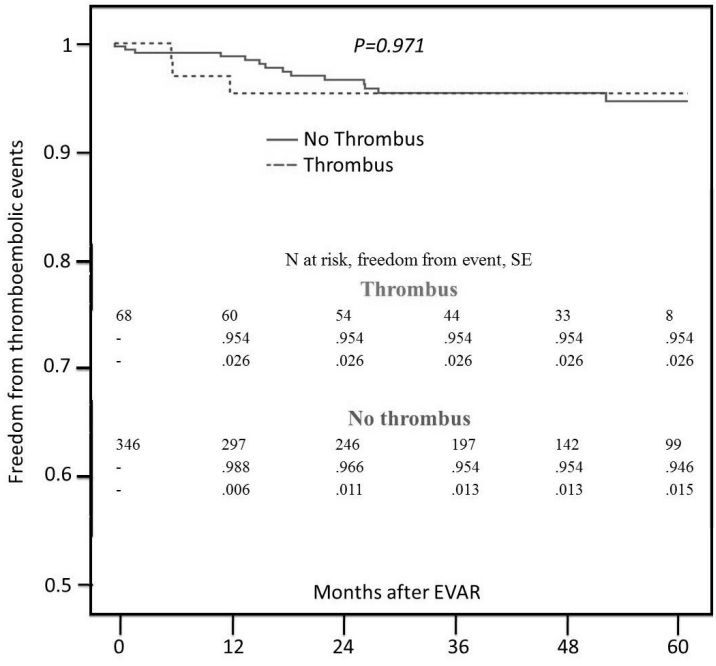


Figure 2. Kaplan-Meier survival estimates for freedom from composite endpoint endograft/limb occlusion/ acute limb ischemia.

at time of implant was found not to be a significant protection factor against ingraft thrombus accumulation on univariate regression analysis (HR 0.63, 95% CI 0.27-1.46).

In regard to previous or concurrent tobacco abuse at time of implantation, the study group did not differ significantly from the controls (P=.166, Table 1).

Morphological characteristics

Median AAA diameter at baseline was 60.0 millimeters (mm) (55.0 – 72.0 mm) and did not differ significantly among groups (P=.5, Table 1). Aneurysm growth ≥5mm was identified in 10 patients in the study group (14.7%) and in 50 in the control group (14.6%) (P=.978).

Patients with shorter proximal aortic necks (≤15mm) at baseline presented higher odds of thrombus formation (Odds ratio [OR] 2.4, 95%CI 1.3-4.2, Table 2). Overall median native aortic neck diameter at baseline was significantly larger in the study group (P=.03). Patients with preoperative neck diameters ≥ 30 mm presented higher odds of endograft mural thrombus build-up (OR 2.4, 95% CI1.3-4.6).

Greater than 25% proximal native neck thrombus coverage at baseline occurred in 26 patients (38.2%) in the study group and in 94 patients (27.2%) of the control group (P=.016). On multivariate analysis, baseline proximal aneurysm neck thrombus was an independent predictor of ingraft thrombus development (OR 1.9, 95%CI 1.1-3.3).

In the study group, thrombus extended into the iliac limbs in 15 patients (22.1%) while in the control group, focal thrombus deposits were identified in 24 cases (6.9%) within the iliac limbs (P<.001). In regard to the iliac arteries, iliac stenosis was identified in 1 pa-

Table 2. Multivariate analysis for ingraft thrombus accumulation.

	Multivariate analysis		
Clinical variables	**OR**	**95% CI**	**P value**
Age ≥ 70	0.81	0.49-1.37	.429
Morphological variables			
Neck thrombus ≥ 25%	1.90	1.10-3.31	.020
Neck calcification ≥ 25%	1.66	0.90-3.07	.105
Neck length ≤ 15mm	2.35	1.31-4.23	.004
Neck diameter ≥30 mm	2.39	1.25-4.58	.008
Device-related variables			
AUI graft configuration	2.20	1.88-5.49	.050
Polyester fabric	3.98	2.17-7-29	<.001
Ratio between cross-sectional areas of mainbody and limbs ≥ 2.3	1.17	0.68-2.02	.576
Variation of main-body cross-sectional area ≥ 50 %	6.92	1.69-28.31	.007
Distal landing zone EIA	1.24	0.67-2.30	.495

Legend: OR – Odds ratio. 95%CI – 95% Confidence interval. AUI – aorto-uni-iliac. EIA – External iliac artery. mm – milimeters.

tient (1.5%) in the thrombus group and in 10 (2.9%, P=.51) in the control group (patent lumen > 7mm, extension <3cm). The external iliac artery was one of the distal landing zones in 26 (22%) patients in the study group and in 42 (14.2%) in the control group (P=.052) but was not found to be an independent predictor of main-body thrombus formation in multivariate analysis (Table 2). Bilateral external iliac landing in bifurcated devices or external iliac landing of AUI devices was separately assessed for association to ingraft thrombus accumulation but was also statistically not significant in univariable analysis (P=.816).

Thrombus dynamics

First thrombotic deposits were identified among the study group on the 30-day CTA in 22 patients (32.4%), the 6-month CTA in 8 (11.8%), the 1-year CTA in 17 (25%), the 2-year CTA in 9 (13.2%), and the 3-year CTA or after in 12 (17.6%).

Forty-four of these patients (64.7%) had undergone more than 1 CTA during follow-up. Mean variation of the maximum thickness was 3.3mm (± 5.01) and ranged from -3.20 to +29.5mm. Partial thrombus regression was identified in 4 patients (9.1%), ranging from -0.40mm to -3.20mm in maximum thickness. Complete resolution was not identified and of these 4 patients, only 2 were on anticoagulants. The remaining 40 patients from this subgroup (58.8% of the study group) all demonstrated progressive thrombus accumulation from the first positive postoperative CTA for mural thrombus until the last CTA available (Figure 3). At the last CTA available, median lumen-reduction by mural thrombosis in the study group was 33.2% and ranged from 12.7% to 78.5%.

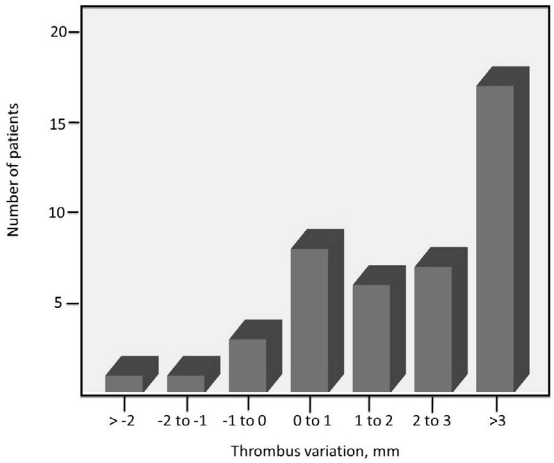
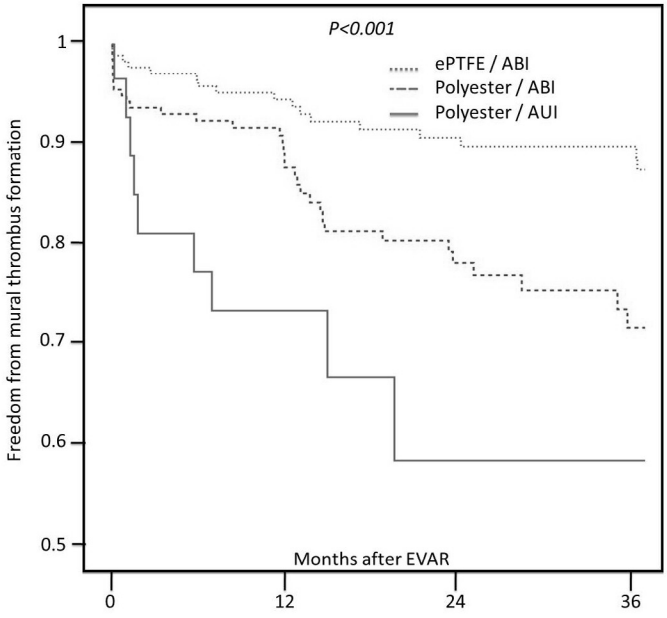


Figure 3. Thrombus thickness variation.
Subgroup analysis of patients in the study group with more than 1 postoperative CTA (N=44) during a median follow-up of 3.54 years (1.99 – 5.47).
Legend: Measurements were performed using the last available and first postoperative CTA.

Device-related features

Deployed devices differed significantly among groups (P=.007). Overall, Endurant (Medtronic, Santa Rosa, Calif) stentgrafts were implanted in 190 patients (45.9%), Excluder Low-Permeability devices (W.L.Gore and Associates, Flagstaff, Ariz) in 124 (30.0%), Excluder stentgrafts (original device) in 55 (13.3%), Zenith endografts (Cook, Bloomington, Ind) in 25 (6%), Talent devices (Medtronic) in 16 (3.0%), and Lifepath System balloon-expandable endografts in 4 (1.0%).

AUI endografts were implanted in 10 patients in the study group (14.7%) and in 21 (6.1%) controls. AUI configuration was found to account for a 2.2-fold odds increase of ingraft thrombotic deposition (95% CI 1.9-5.5, Table 2). As referred previously, both de-



N at risk, freedom from event, SE

ePTFE / ABI			
179	135	107	80
-	.945	.907	.898
-	.018	.024	.025
Polyester / ABI			
204	110	69	37
-	.893	.781	.716
-	.024	.037	.047
Polyester / AUI			
30	16	5	3
-	.734	.584	.584

Figure 4. Kaplan-Meier survival estimates for freedom from mural thrombus comparing different combinations of endograft configuration and fabric.

vice occlusions occurred in AUI devices but none had been preceded by intraprosthetic thrombotic deposits.

In our population polyester-coated devices (Endurant, Zenith, Talent and Lifepath devices) were more prone to building-up significant thrombus (OR 4.0, 95% CI 2.2-7.3). Six-month estimates for freedom from ingraft thrombus was 77% for polyester-based AUI endografts, 92% for polyester-covered aortic bi-iliac (ABI) endografts and 96% for ePTFE-covered ABI endografts. At 18 months, the estimated freedom from thrombus formation was 67%, 81% and 92% respectively (P <.001) (Figure 4). Increased endograft thrombus accumulation was found in cases of "barrel-like" configuration of the main component (Figure 5) with a cross-sectional area increase ≥ 50% throughout the main-body (OR 6.9, 95% CI 1.7-28.3, Table 2).

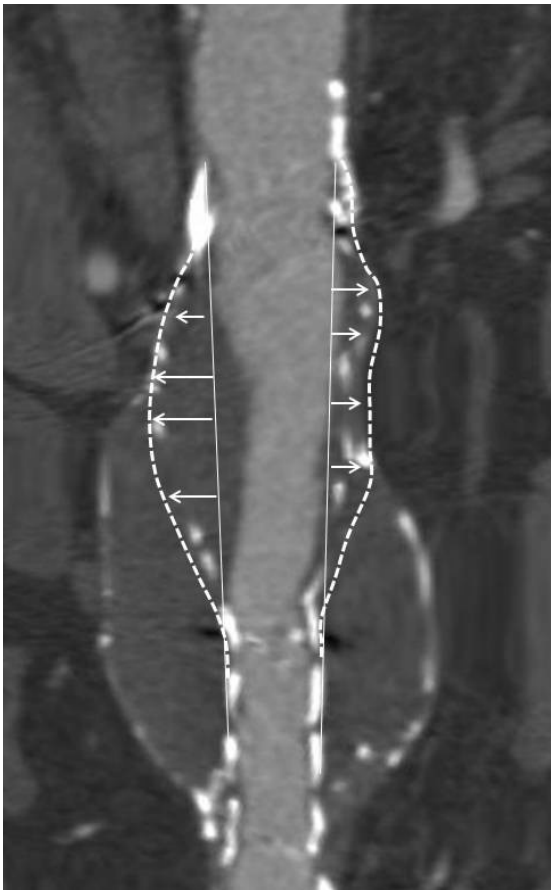


Figure 5. Midsection dilatation of the main-body component with thrombus formation.
Legend: Dashed lines and arrows demonstrate the barrel-like configuration of the main-component within the aneurysm sac.

Thrombus formation within the iliac limbs was identified in 10 (19.6%) of the patients with bell-bottom (≥ 24mm) iliac extensions and in 29 (8%) of those without (P=.008). Deposition of thrombus within the main body was not significantly different among patients with large (≥20mm) (P=.35) or bell-bottom (≥24mm) iliac limbs (P=.34).

DISCUSSION

Development of significant mural thrombus has cast uncertainty upon long-term outcomes following EVAR and several mechanisms have been proposed to explain its formation. We provide the largest study assessing the clinical impact of mural thrombus formation within the main-body of abdominal aortic endografts and identify clinical, morphological and device-related risk factors for its development. This information was obtained in a large population of EVAR patients with long-term follow-up and adds new insights into the mechanisms of mural thrombus accumulation within the main component of abdominal aortic endografts. Although a frequent event, in our population, endograft mural thrombus formation was not associated to thromboembolic events over follow-up. Endograft characteristics such as configuration, fabric and main-body geometry were found to be distinctly associated to appearance of ingraft thrombus.

Endograft mural thrombosis is a common event in abdominal aortic endografts, with reported rates ranging from 19 to 33%[6,11,12] but has also been reported in thoracic aortic stentgrafts.[13,14] Whether ingraft mural thrombus predicts future limb or endoprosthesis occlusion on the long-term has remained unresolved.[4] Moreover, different strategies have been suggested following diagnosis including intensification of surveillance or even oral anticoagulation.[7] Mestres *et al* reported an association between endograft mural thrombotic deposits and device occlusion over a follow-up period of 24 months (P=.003).[5] In contrast, in our population an increased propensity of graft or limb occlusions among the study group was not identified. Additionally, limb occlusions did not occur preferentially among patients with thrombus accumulation within the endografts' main body nor were those events preceded by thrombus deposition on the immediately preceding CTA. Indeed, limb occlusion may be related to kinking or the presence of iliac lesions with hemodynamic impact as pointed out by van Zeggeren *et al.*[15] Therefore, our results suggest that neither an interventional attitude nor an intensification of postoperative imaging are warranted in patients presenting ingraft mural thrombus.

Thrombus accumulation within the endograft seems to be a dynamic phenomenon. Cases of partial regression were identified among our study group but we did not identify complete resolution as reported elsewhere.[4] This discrepancy may be explained by our inclusion criteria which selected patients with significant thrombus load within the endograft and the follow-up time. Although only a small proportion of our population

was receiving oral anticoagulation, it was not found to be protective against endograft thrombus accumulation as reported also by Wu *et al*[16] or to induce thrombus regression among the study group.

Ingraft thrombus accumulation is a multifactorial process, resulting from the complex interaction of systemic and local hemodynamic factors, hemorrheological properties and endograft characteristics. Smoking is associated to a sustained low-grade systemic inflammatory response and produces an imbalance of rheological, coagulation and endothelial functions.[17] The consequent increase in blood viscosity[18] has been demonstrated to modify wall shear stress.[19] However, in our sample, we could not relate thrombus accumulation to smoking habits.

Mestres *et al* proposed that mural thrombus of the aneurysmatic native aorta might lead to incomplete expansion of the endografts' main-body and subsequent generation of turbulent flow which might predict endograft thrombus formation.[5] However, as demonstrated by Bastos Gonçalves *et al,* [20] after stentgraft implantation, aneurysm neck thrombus progressively reduces over time and ultimately disappears. Moreover, in a significant proportion of our study group, thrombus reappeared intraluminally within the device over follow-up similarly to Houdini´s famous "Walking through a brick wall" illusion. We hypothesize that in addition to device-related factors, hemorrheological and hemodynamic factors may also play a role in this "Houdini-effect".

Abdominal aortic blood flow patterns are complex, differing significantly according to the physiological state.[21,22,23] Local morphological features such as angulation[24] and aortic arch-generated vortical flow patterns may also influence wall shear stress and blood stasis.[25,26] Endograft implantation may further modify these flow patterns,[27,28] which may in part contribute to the consistently reported reduced time elapsed until detection of the first ingraft thrombotic deposits.[4,5,11,16] Our study group also demonstrated such findings. Chong *et al* demonstrated *in vitro* that proximal aneurysm neck angulation may produce complex turbulent flow and recirculation patterns within abdominal aortic endografts.[29] However, in our population, we were not able to demonstrate this association.

Endograft features seem to play a role in the development of ingraft thrombus. Wu *et al*[16] correlated intraprosthetic thrombus development with a specific device (the Zenith endograft). However, more importantly, stentgraft configuration[30] and main-body geometrical configuration may be the responsible factors for ingraft thrombus formation, leading to modified flow conditions within the device and to thrombus accumulation.[6,31] Wu et also correlated thrombus development to flow deceleration ("plug-flow") within the device. Accordingly, this hemodynamic condition seems is produced by sharp cross-sectional area decreases such as in AUI devices or in stentgraft extension to the external iliac arteries. In our population, both AUI configuration as well as an increased ratio between main-body and cumulative limb cross-sectional areas were associated to an increased risk of endograft mural thrombosis in univariable analysis, which is in accor-

dance with other reports.[5] However, we hypothesized that the higher prevalence of AUI stentgrafts among the study group might contribute greatly to this finding and when correcting for this factor, unlike Wu *et al,*[16] a higher ratio between the cross-sectional areas of main-body and limbs and distal landing in the external iliac artery were not found to be independent predictors of thrombus accumulation.

Our results suggest that along with device configuration, a geometrical "barrel-like" conformation of the main component following endograft deployment may also play a role. This event may be more pronounced in devices with larger diameters and in patients with shorter neck lengths, thus restraining less the endograft's full expansion to its diameter. Consequently, decreased flow velocities and recirculating fluxes in the peripheral endograft lumen can lead to subsequent thrombus accumulation.[16] In our study, patients receiving larger devices and with shorter proximal neck presented more frequently endograft thrombus. Additionally, mid-section dilatation of the main-component ("barrel-like configuration") was also found to be an independent predictor of significant endograft thrombus lining. The same mechanism can also explain the similar phenomenon among patients with bell-bottom iliac extensions in our study which was statistically significant.

Device fabric may also play a role in mural thrombus accumulation. Polyester has been reported to be more thrombogenic than others fabrics.[32,33] In line with the findings of other authors[5,6] we also identified an increased risk of intraprosthetic thrombus accumulation in patients receiving polyester-covered devices.

The method of thrombus assessment chosen may be pointed out as a drawback in our study. Thrombus-covered circumference has been preferentially used in studies reporting on mural thrombus within the native aorta.[10,34,35,36,37] However, this method does not inform on the thickness neither on degree of lumen reduction caused by the thrombotic accumulation. Quantitative methods as reported by Wyss *et al*[38] although providing overall quantification, fail to inform also on circumferential involvement or degree of lumen restriction, as the latter also depends on the distribution of thrombus within the endoprosthesis and its' dimensions. Our selection criteria conciliated both the circumferential coverage of the endografts' main-body surface by thrombus along with its maximum thickness to in part overcome these limitations. Furthermore, unlike other reports which resorted to non-dedicated imaging software[5] or did not also provide circumferential or quantitative assessments,[4,6,16] we provide maximum lumen reduction by thrombus formation calculated from reproducible measurements performed on dedicated imaging software. Other limitations that can be noted are the retrospective design of our study thus conferring data regarding patient compliance to antiplatelet therapy following EVAR and duration of oral anticoagulation irretrievable. Also histopathological confirmation of the thrombus was not performed. However, we chose significant thrombus thickness and circumferential coverage thresholds for the selection of the thrombus group to exclude patients with focal thrombus or fibrin ac-

cumulation. Importantly, our results must be interpreted with caution in light of the limited follow-up period of our studied population and therefore subsequent investigation is warranted to further assess the clinical significant of intraprosthetic thrombus following EVAR. Finally, our conclusions may not apply to endografts deployed in other anatomical locations but further investigation is warranted.

CONCLUSIONS

The present study suggests that development of thrombotic deposits within the main-body of abdominal aortic endoprosthesis is not associated to endograft or limb thrombosis. Consequently, a conservative approach may be followed in patients with asymptomatic intraprosthetic thrombus accumulation over mid-term. Long-term results are still necessary to determine the safety of watchful waiting in these cases. In regard to surveillance, our findings do not support an intensification of the imaging protocol in patients with uneventful mural thrombus formation within abdominal stentgrafts. Additionally, oral anticoagulation did not decrease the odds of developing significant thrombus within abdominal aortic endografts. In our study, significant endograft thrombus deposition was independently associated to baseline thrombus load in the proximal aneurysm neck, proximal neck diameter, AUI endograft configuration and to polyester fabric.

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Chapter 21

Incidence and treatment results of Endurant endograft occlusion

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ABSTRACT

Objective

The Endurant endograft (Medtronic Inc, Minneapolis, Minn) is a new-generation device specifically developed to perform well in complex abdominal aortic aneurysm anatomy. Previous reports on the 1- and 2-year results of endovascular aneurysm repair (EVAR) with the Endurant endograft showed excellent outcome, including prevention of migration and type I endoleaks, but occurrence and outcome of post-EVAR occlusion have not been determined in a large multicenter patient cohort with midterm follow-up, which is the objective of this study.

Methods

Data of consecutive patients treated with the Endurant from December 2007 to April 2012 in three Dutch tertiary vascular referral hospitals were prospectively gathered and retrospectively analyzed. Follow-up consisted of regular office visits, computed tomography angiography at 1 and 12 months after EVAR, and subsequently, duplex ultrasound imaging or computed tomography angiography at regular intervals. Patients with ruptured aneurysms or with earlier abdominal aortic surgery were excluded. The incidence and clinical outcome of endograft occlusions were analyzed. An expert review board assessed all cases in the search for possible causes of occlusion.

Results

Included were 496 patients (87.7% male), who were a median age of 74 years (range, 68-78 years). Median follow-up was 1.7 years (range, 0-4.6 years). Twenty graft occlusions (4.0%) occurred during follow-up. Median time between primary EVAR and detection of the occlusion was 1 month, with 55% occurring ≤60 postoperative days and 90% ≤1 year. No association was found between occlusion and sex ($P = .28$), age ($P = .96$), or use of an aortouniiliac device ($P = .66$). Technical error was the considered cause of the occlusion in 12 patients (60%). The estimated freedom from occlusion was 98.4% at 30 days, 95.7% at 1 year, and 95.3% at 3 years. Presenting symptoms of occlusion were acute limb ischemia in 50%. Treatment was surgical (75%) or percutaneous (25%). Successful revascularization was achieved in 17 of 20 patients, but reocclusions occurred in five, resulting in a transfemoral amputation in one patient. Occlusion-related mortality was 0.6% (3 of 496).

Conclusions

At a median follow-up of 1.7 years, Endurant endograft occlusion occurred in 4.0% of 496 patients. Most occlusions occurred ≤2 months after EVAR, and rarely after 1 year. A technical justification for occlusion could be found for 60% of patients. A more liberal

intraoperative and early postoperative (re)intervention strategy may reduce the occlusion rates and improve outcome.

INTRODUCTION

Aortic endograft occlusion is a known complication after endovascular aneurysm repair (EVAR),[1,2,3,4,5,6] with a reported incidence of 0% to 7.2%, with significant variability (Table 1).[2,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25] Although most of the newer-generation endografts have been associated with lower incidences of graft occlusion compared with first-generation endografts,[5,10] occlusion remains one of the major causes of secondary interventions and rehospitalization after EVAR.[13,26,27]

The Endurant stent graft (Medtronic Inc, Minneapolis, Minn), one of the newest-generation endovascular devices, was specifically developed to perform well in complex abdominal aortic aneurysm (AAA) anatomy. However, treatment of more complex AAA anatomies may result in higher rates of complications, including stent graft occlusion. Previous reports on the 1-year and 2-year results of the Endurant endograft showed excellent outcome, including prevention of migration and type IA endoleaks.[21,22,23,24] However, the occurrence and outcome of occlusions after EVAR have not yet been determined in a large multicenter patient cohort with midterm follow-up, which is the objective of this study.

METHODS

Data of all consecutive patients treated with an Endurant endograft between December 2007 and April 2012 in three Dutch tertiary vascular referral hospitals (University Medical Center, Utrecht; Erasmus University Medical Center, Rotterdam; and St. Antonius Hospital, Nieuwegein) were prospectively gathered and retrospectively reviewed. Included were all patients treated electively for an infrarenal AAA or aneurysm of the common iliac artery, or both. The study excluded patients with ruptured AAAs or patients who had previously undergone abdominal surgery.

EVAR at the three institutions is performed by board-certified vascular surgeons and interventional radiologists, who perform at least 50 EVAR procedures yearly.

Follow-up assessment

Follow-up consists of regular office visits at 1 and 12 months and yearly thereafter. Computed tomography angiography (CTA) is routinely performed ≤30 days after the index procedure and at 1 year, and subsequently, the choice of imaging modality is

individualized (eg, duplex ultrasound [DUS] imaging or CTA). Follow-up duration was calculated until the day of the last imaging examination performed to ensure that the study also included asymptomatic occlusions.

The study group included all patients with endograft occlusion on imaging examinations. Early occlusion was defined as occurring ≤60 days of the index procedure, and delayed occlusion was defined as occurring at a later stage. CTAs or DUS images of asymptomatic patients were not evaluated for the presence of nonhemodynamically

Table I. Reported rates of limb thrombosis in literature

Study (first author)	Year	No.	Endovascular devices used	Follow-up duration	Incidence of occlusion (%)	Occlusion-related mortality (%)
Carroccio[2]	2002	351	Mixed	20 months	3.7	0
Erzurum[4]	2004	823	Mixed	24.2 months	2.7	0.12
Cochennec[5]	2007	460	Mixed	23 months	7.2	3
Maleux[6]	2008	288	Mixed	39 months	3.1	0
EVAR 1[7]	2010	624	Mixed	6 years	3.2	Not stated
EVAR 2[8]	2010	229	Mixed	3.1 years	2.2	Not stated
DREAM[9]	2010	178	Mixed	6.4 years	6.7[a]	Not stated
Van Marrewijk (EUROSTAR)[10]	2005	6787	Mixed	21 months	5	Not stated
Mehta, et al [11]	2010	1768	Mixed	34 months	1.4	0.05
Karthikesalingam[12]	2010	553	Mixed	31 months	1.1	Not stated
Conrad[13]	2009	832	Mixed	35 months	2.9	0
Abbruzzese[14]	2008	565	Mixed	30 months	6[b]	0.35
Bos[15]	2009	92	Excluder[c]	36 months	0	0
Maleux[16]	2012	121	Excluder	4.05 years	1.6	Not stated
Bastos Gonçalves[17]	2012	144	Excluder	5 years	1.4	0
Mertens[18]	2011	143	Zenith[d]	66 months	5.6	Not stated
Sivamurthy[19]	2006	248	Zenith	24 months	5.2	0
Jean-Baptiste[20]	2009	447	Zenith	24 months	1.8	0
Torsello[21]	2010	45	Endurant[e]	30 days	2.2	0
Troisi[22]	2010	156	Endurant	9 months	1.9	0
Van Keulen[23]	2011	100	Endurant	1 year	3.0	1
Rouwet[24]	2011	80	Endurant	1 year	1.3	0
Stokmans[25]	2012	1151	Endurant	30 days	2.0	Not stated
Current study	2012	496	Endurant	1.7 years	4.0	0.6

Legend: *DREAM,* Dutch Randomised Endovascular Aneurysm Management; *EUROSTAR,* European Collaborators on Stent-Graft Techniques for Aortic Aneurysm Repair; *EVAR 1,* Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm; *EVAR 2,* United Kingdom Endovascular Aneurysm Repair 2. a)Includes all thrombo-occlusive complications. b) Intervention for thrombosis or stenosis. c) W. L. Gore and Assoc, Flagstaff, Ariz. d) Cook, Bloomington, Ind. e) Medtronic, Minneapolis, Minn.

significant stenosis, but we did identify all patients who were treated for an asymptomatic preocclusive limb lesion.

Stent graft occlusions were identified during the postoperative hospital stay after the primary EVAR procedure, at office visits during follow-up, or at emergency department visits when the onset of symptoms was acute. All patients included in the study group presented with symptoms, which were classified according to Rutherford et al.[28] Presence of graft occlusion was confirmed by CTA, angiography, or magnetic resonance angiography (MRA; Figure 1). The decision whether to treat an occlusion and the type of intervention were at the discretion of the treating vascular team. Presenting symptoms, treatment, and outcome after treatment of patients with a graft occlusion were recorded according to the Reporting Standards for Endovascular Aortic Aneurysm Repair.[29]

A review board evaluated all imaging studies and interventional details of the patients included in the study group during a consensus meeting. The review board included vascular surgeons and interventional radiologists from the study hospitals and three interventionists from unrelated hospitals, not involved in any aspects of the study. All review board members were very experienced in endovascular aortic procedures. The probable causes of occlusion in each individual case were discussed, and a conclusion was reached by consensus.

Statistical analysis

Categoric variables are reported as counts and percentages and continuous variables as means ± standard deviation or medians (interquartile range), according to the normality in distribution. Association between early and delayed occlusion and sex, type of endo-

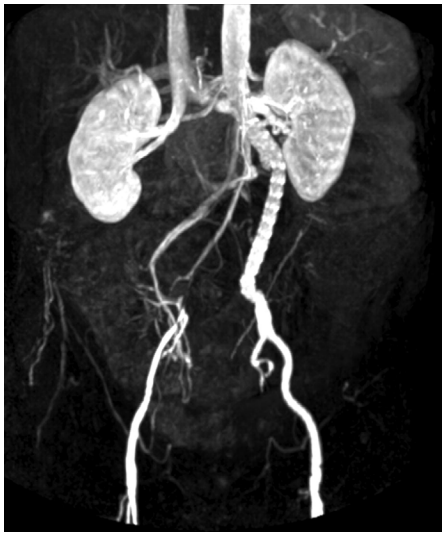

Figure 1. Endograft occlusion is confirmed by magnetic resonance angiography (MRA).

graft (aortouniiliac [AUI] or bifurcated), and treating hospital was tested using logistic regression and Cox regression χ^2 tests, respectively. Association with age was tested using the nonparametric Mann-Whitney *U* test. Kaplan-Meier estimates for freedom from occlusion were obtained for the overall population. Differences were considered significant at $P < .05$. Statistical analysis was performed with SPSS 20.0 software (SPSS Inc, Chicago, Ill).

Results

From December 2007 to April 2012, 631 patients with an aneurysm of the infrarenal abdominal aorta or common iliac artery, or both, were treated with an Endurant stent graft. The study excluded 95 patients who were treated for a ruptured aneurysm and 40 patients with earlier abdominal aortic surgery, resulting in 496 patients (435 men [87.7%]) included in this study. Median age at time of primary EVAR was 74 years (range, 68-78 years; Table 2).

Details of the primary EVAR procedure

An AUI stent graft was implanted in 38 patients (7.7%), and a bifurcated device was used in 458 (92.3%), yielding 954 graft limbs at risk for occlusion. No patients had signs of (imminent) endograft occlusion at the end of the initial procedure, which was checked with a completion angiogram.

Outcome at 30 days

All-cause 30-day mortality was 0.8% (n = 4; Table 3). Thirty-day occlusion-related mortality was 0.2% (n = 1). This patient died of ischemic complications after unsuccessful embolectomy of an occluded graft limb that developed 1 day postoperatively in the presence of pre-existent severe atherosclerosis and a previous bilateral above-knee amputation. All other patients died of nonsurgical complications.

Table 2. Patient and operative characteristics

Variable	No. (%) or median (IQR)
Patients	496
Male	435 (87.7)
Age, years	74 (68-78)
Aortouniiliac stent raft	38 (7.7)
Graft limbs at risk	954

Legend: *IQR,* Interquartile range.

Midterm results

Median follow-up was 1.7 years (range, 0-4.6 years). Five patients were lost to follow-up. All-cause mortality during follow-up was 13.1% (n = 65), with aneurysm-related mortality in six (1.2%). No patients died of AAA rupture. Three patients (0.6%) died of complications resulting from stent graft infection.

Endograft occlusions

During follow-up, there were 20 endograft occlusions (4.0%). Mortality was occlusion-related in three patients (0.6%). These patients died of ischemic complications after unsuccessful revascularization (n = 1), reperfusion syndrome (n = 1), and during open conversion of an inflammatory aneurysm with significant retroperitoneal fibrosis, due to uncontrollable bleeding from aortic laceration at the site of cross-clamping (n = 1). No association could be found between occlusion and sex (P = .28), age (P = .96), or use of an AUI device (P = .66). Overall, the treating hospital had no significant association with the chance of occlusion (P = .08), but looking specifically at early occlusions, a difference in hospitals could be found (odds ratio, 3.08; 95% confidence interval, 1.13-8.39; P = .028). The estimated freedom from occlusion was 98.4% at 30 days, 95.7% at 1 year, and 95.3% at 3 years (Figure 2).

Two patients were treated for an asymptomatic preocclusive limb lesion (an asymptomatic and documented progressive thrombus of a graft limb) that was found on routine postoperative imaging. They were successfully treated with oral anticoagulation (acenocoumarol, n = 1) or surgically with relining of the former endograft limb with a new Endurant endograft limb (n = 1). These patients were not included in the occlusion

Table 3. Early and midterm outcome

Variable	No. (%) or median (IQR)
Patients	496
30-day outcome	
Overall 30-day mortality	4 (0.8)
30-day EVAR-related mortality	1 (0.2)
Patients with occlusion	7 (1.4)
30-day occlusion-related mortality	1 (0.2)
Midterm outcome	
Follow-up, years	1.7 (0-4.6)
All-cause mortality	65 (13.1)
Overall EVAR-related mortality	6 (1.2)
Patients with occlusion	20 (4.0)
Occlusion-related mortality	3 (0.6)

Legend: *EVAR,* Endovascular aneurysm repair; *IQR,* interquartile range.

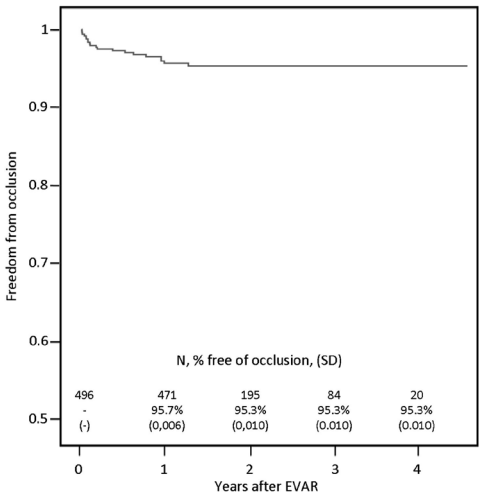

Figure 3. Left, Tortuous right external iliac artery in a patient with both infrarenal aortic aneurysm and right common iliac artery aneurysm. **Right,** The right limb of the Endurant endograft has been positioned in the kink of the right external iliac artery, which limits the flow considerably. This patient later developed a right limb graft occlusion.

group but are mentioned here as part of a possible spectrum of thrombotic complications that could eventually lead to occlusion if left untreated. In addition, one patient developed a symptomatic stenosis after an occlusion of the contralateral endograft limb, also prompting intervention.

Clinical presentation of occlusion

Presenting symptoms in 10 of the 20 patients with occlusion were acute ischemia with numbness, sensory loss, but no rest pain in three (15%), with an occlusion (Rutherford IIa) or acute ischemia with rest pain or loss of motor function, or both, in seven (35%; Rutherford IIb). The remaining 10 (50%) presented with claudication without rest pain (Rutherford stage I-III) and were diagnosed during regular follow-up (Table 4).

Detailed analysis of patients with occlusion

Occlusion occurred in two AUIs (5.2% of all AUIs) and in 18 bifurcated stent grafts (3.9% of all bifurcated endografts). Total occlusion of the endograft occurred in three patients. In patients with only one affected limb, no significant difference could be found regarding the side of occlusion, with 10 of 17 (58%) noted as contralateral limb occlusions.

Median time between primary EVAR and detection of the occlusion was 1 month (range, 0-15 months), with 55% (11 of 20) occurring within the first 60 postoperative days (early occlusions), 35% (7 of 20) between 2 and 12 months, and 10% at >12 months after EVAR.

Table 4. Symptoms

Variable	No. (%)
Occlusions	20 (4.0)
Asymptomatic occlusions	0 (0)
Acute symptoms	
Rutherford class[a]	
IIa	3 (15)
IIb	7 (35)
Nonacute symptoms	
Rutherford class I-III[b]	10 (50)

Legend: a) Acute ischemia. b) Chronic limb ischemia.

All patients were prescribed a platelet aggregation inhibitor (n = 16) or a vitamin K antagonist (n = 4) at the time of occlusion.

In 12 patients (60%), a technical error was considered to be the cause of the occlusion, including extreme oversizing, positioning of the graft in a kink of the iliac vessel limiting outflow considerably (Figure 3), performance of the completion angiogram without removing the stiff guidewire, or an overlooked indication for percutaneous transluminal angioplasty/stenting, both within the endograft limb or resulting from the presence of a hemodynamically significant stenosis of flow-limiting dissection in the external iliac artery during the initial procedure. No technical cause for the obstruction was found in the other eight (40%). An outflow problem was identified in two of these patients, and two presented with very challenging anatomy, with severe tortuosity of the iliac arteries or a narrow aortic bifurcation, which might have been the cause for the occlusion. For the other six patients, the occlusion remained unexplained.

Overall, there was a violation of the instructions for use in six of 20 (30%) patients. Oversizing was considered excessive (20% to 35%) in three patients, and extreme (>35%) in four patients. Nine patients had one or more risk factors for occlusion, including three with a known malignancy at time of occlusion and seven with a medical history of stroke or cardiac arrhythmia. Details on the individual patients with endograft occlusion are presented in Table 5 and Figure 4.

In four of 20 patients (20%), an in-graft stenosis was reported on follow-up imaging before the occlusion, which might have been a risk factor for the future occlusion. No treatment was started at the time of these investigations because of absence of clinical symptoms and absence of >50% luminal stenosis. The occlusion in another four patients was already present on the first follow-up imaging.

Table 5. Anatomic and operative details of patients with occlusion

Pt	Days to occlusion	Occluded side	History of PAD	Severe iliac tortuosity	Within IFU	Extension to IEA	Open IIA	Iliac component diameter	Iliac oversizing, %	Stiff wire removed
1	1	Left (I)	Yes	No	No	Yes	No	24	14	Yes
2	2	Left (C)	No	No	Yes	No	Yes	13	44	Yes
3	3	Right (C)	No	Yes	Yes	No	Yes	13	8	Yes
4	12	Right (I)	Yes	No	Yes	No	No	16	60	Yes
5	20	Right (C)	Yes	No	Yes	No	Yes	10	11	Yes
6	21	Right (I)	No	No	Yes	Yes	No	13	30	Yes
7	28	Right (C)	No	Yes	No	Yes	No	10	43	No
8	32	Right (I)	Yes	No	No	Yes	Yes	24	5	No
9	34	AUI	Yes	Yes	Yes	No	Yes	13	18	Yes
10	40	Left (I)	No	No	Yes	Yes	No	16	14	Yes
11	42	Right (C)	No	No	Yes	No	No	13	30	Yes
12	62	Left (C)	No	Yes	No	Yes	No	13	30	Yes
13	121	Left (C)	No	No	Yes	Yes	No	13	44	Yes
14	183	Body	No	No	Yes	No	Yes	R:13, L:10	18/10	Yes
15	186	Left (I)	No	No	Yes	No	Yes	24	33	Yes
16	275	Right (C)	No	No	Yes	No	Yes	10	10	Yes
17	341	Right (I)	No	No	Yes	No	Yes	16	33	Yes
18	241	Right (C)	No	Yes	No	Yes	No	16	33	Yes
19	457	Right (C)	No	Yes	Yes	No	Yes	24	9	Yes
20	458	AUI	No	No	No	No	Yes	20	20	Yes

Legend: *AUI,* Aortouniiliac; *C,* contralateral; *I,* ipsilateral; *IEA,* external iliac artery; *IFU,* instructions for use; *IIA,* internal iliac artery; *L,* left; *PAD,* peripheral arterial disease; *R,* right.

Treatment

Different treatment modalities were used depending on the clinical presentation, the patient's physical status, and the underlying cause of occlusion. Open surgical treatment was performed in 15 patients (75%) with occlusion, comprising embolectomy (n = 4), graft extension (n = 1), femorofemoral crossover bypass (n = 5), axillofemoral bypass (n = 2), and embolectomy with stent placement (n = 3). In four of these patients, an initial attempt was made to perform catheter-based thrombolysis but this was unsuccessful.

Percutaneous treatment was successfully performed in five (25%), including thrombolysis with (n = 4) or without (n = 1) additional percutaneous transluminal angioplasty/stent placement (Table 6).

Table 6. Treatment

Variable	No. (%)
Open surgery	15 (75)
Embolectomy	4 (20)
Graft extension	1 (5)
Femorofemoral crossover bypass	5 (25)
Axillofemoral bypass	2 (10)
Embolectomy with stent	3 (15)
Initial thrombolysis attempt	4
Percutaneous intervention	5 (25)
Thrombolysis/PTA with stent	4 (13.6)
Thrombolysis/PTA without stent	1 (4.5)

Legend: *PTA,* Percutaneous transluminal angioplasty.

Treatment results

Successful revascularization was achieved in 17 of 20 occlusions (85%). The remaining three patients died as a result of ischemia-related (n = 2) or intraoperative bleeding (n = 1) complications, as described previously.

After successful revascularization reocclusion occurred in five of 17 patients (29.4%), including occlusion of a femorofemoral crossover bypass (n = 2) and reocclusion after thrombolysis in combination with stent placement (n = 2) or after surgical embolectomy (n = 1). Time to reocclusion varied from 2 weeks to 7 months after the initial revascularization. Reocclusion presented as acute ischemia in these five patients, and invasive treatment was performed to restore vascularization with a femorofemoral crossover bypass (n = 2), thrombolysis (n = 1), or thrombectomy and extension of the graft limb (n = 1). Revascularization failed in one patient, resulting in above-knee amputation.

DISCUSSION

In this cohort of 496 patients treated with an Endurant endograft and monitored for a median of 1.7 years, 20 occlusions occurred (4.0%). Occlusion-related mortality was 0.6% overall (3 of 496) and 15% (3 of 20) in the occlusion group.

EVAR has been increasingly used to treat AAAs. Early advantages of EVAR over open surgical repair are well known,[30,31,32,33] and new-generation endografts have been developed in recent years to broaden the treatment range. The Endurant endograft, with a hydrophilic coating, smaller delivery system, and increased flexibility, was specially designed to overcome complex aortoiliac anatomy. With these expanding indications, it is important to assess the occurrence of subsequent complications, such as stent graft

or access artery occlusion, and the need for secondary interventions to obtain patency during follow-up.

Previous evaluations of the Endurant stent graft found the incidence of graft-related occlusion varied from 1.3% to 3%.[21,22,23,24] These occlusion rates are comparable to those in the present study, but we acknowledge that there is some overlap of patients in these studies and ours.

Makaroun et al[34] recently published the results from the United States regulatory trial of the Endurant Stent Graft System.[34] They found an occlusion rate of 2.7% at 1 year, with all four cases occurring within the first 60 days.

In a European multicenter study by Torsello et al[21] of 45 patients treated with the Endurant stent graft, one graft limb thrombosis (2.2%) was diagnosed at 30 days of follow-up, which was successfully treated.[21] No other occlusions occurred during 1 year of follow-up. Troisi et al[22] performed a single-center study to evaluate results of the Endurant stent graft in 156 patients with a mean follow-up of 9 months. The endograft occlusion rate was 1.9% (n = 3), and all three patients were treated successfully. The rates of occlusion of these reports are, therefore, comparable to the results of this study.

A wide range (0%-7.2%) of graft occlusions has been reported in follow-up studies of other EVAR devices.[2,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25] The publication dates, institutional characteristics, follow-up duration, and patient cohorts in these studies are very heterogenic, which may explain the variability in occlusion rates even within single-graft studies. In our own study, where institutional protocols are very similar, a significant difference was still found in the occlusion rates of the participating hospitals.

More than half of all occlusions in this study occurred ≤2 months after EVAR, and 90% occurred within the first year. This observation is in agreement with previous publications[2,5] and alerts to the importance of careful observation and patient information, especially during the first year after EVAR. In this study we used a review board to come to a consensus on possible causes for limb occlusion. This review board concluded that a technical error was responsible for occlusion in 60% of all patients and in 73% of those with early occlusions. A more liberal intraoperative and early postoperative (re)intervention strategy may reduce the occlusion rates and improve outcome. Importantly, completion angiography should be performed after removal of the stiff guidewire and the imaging thoroughly checked to assess for irregularities or stenosis. This should also include rotational views in which the angled and tortuous iliac arteries are perpendicularly visualized. Direct pressure measurements at the sheaths after all endovascular material is removed may also aid in the identification of any hemodynamic obstruction to flow.

We observed a significant proportion of patients with a history of peripheral arterial disease, with poor outflow vessels, and very challenging iliac anatomy, possibly increasing the risk of occlusion. Facilitating iliac access with improved delivery systems may

have the perverse effect of increasing the risk of occlusive complications. Although we cannot objectively demonstrate that these factors increase risk significantly, treatment of patients with major obstructive disease and very unfavorable anatomy undoubtedly increases the chance of endograft occlusion.

Occlusion in five patients occurred without any suggestive cause. Aneurysm remodeling might play an important role in patients with delayed occlusion, but this remains unproven. Circumferential thrombus deposition, occurring in >20% of patients, also may increase risk.

Mestres et al[35] found that the presence of intragraft mural thrombus significantly increased the risk of endograft occlusion. However, the study by Wegener et al[36] found no association with graft occlusion, and the thrombotic deposits in 15% disappeared completely during follow-up, without specific therapy. It is known from clinical practice that some patients are prone to thrombosis of vascular conduits, a problem seldom investigated. This may be a result of a genetically determined variability to foreign body response or antiplatelet resistance, or as a result of sheer stress, and may correspond to patients without obvious underlying causes for thrombosis and with recurrent events. Nine patients in the occlusion group presented with one or more possible risk factors for thrombosis in their medical history, including malignancy, cardiac arrhythmias, or cerebrovascular accident or transient ischemic attack, that might have contributed to the development of the occlusion.

Clinical presentation of occlusion was acute in only 50% of patients, with the remaining presenting with claudication. Other studies report higher percentages of acute presentation.[5,37] The risk was naturally higher in patients with acute limb ischemia, where all of the deaths occurred, and the clinical consequences of this complication should not be underestimated.

All patients in our study required an intervention to re-establish flow to the ischemic extremity, and open surgery was preferred for most patients. Although initial revascularization was successful in >80%, we observed a reocclusion rate of 29.4%, all of which required secondary intervention. We do not have a clear explanation for this high reocclusion rate, although an outflow obstruction may have been a contributing factor in at least three patients.

Numerous causes and predictive factors for graft obstruction have been suggested in the literature, such as extension of the graft limb to the external iliac artery,[2,4] smaller limb diameter,[2] AUI endograft,[35] younger age,[5] the presence of thrombus in the native aorta,[26] or type of device.[1,4,10,37,38] In the present study, we evaluated sex and older age (>65 years) and found no significant association with occurrence of occlusion. Also, the type of device (bifurcated vs AUI endograft) did not influence the outcome.

One of the limitations of this study is its retrospective design. Also, we could not obtain detailed anatomic information for patients without occlusions, and analysis of risk

factors for occlusion is limited. Our data suggest, however, that additional factors other than the stent graft material may play an important part in the occlusion rates, particularly on the patient selection criteria or institutional policies on additional intraoperative or postoperative preventive intervention.

CONCLUSIONS

Endograft occlusion after EVAR is an important complication that persists with newer-generation devices. In this study, occlusion occurred in 4.0% of patients treated with the Endurant stent graft during a median follow-up of 1.7 years. The risk of occlusion is higher within the first 2 months after EVAR, rarely occurring after 1 year. The estimated freedom from occlusion at 30 days, 1 year, and 3 years was 98.4%, 95.7%, and 95.3%, respectively. A technical justification for occlusion could be found for 60% of patients. These correspond to most early events and could potentially be prevented by adopting a more aggressive strategy for identification and treatment of intraoperative and early postoperative signs of kinking, stenosis, or irregularities. Still, the reason for occlusion in a number of patients is unexplained. Institutional practice and case-mix may influence occlusion rates significantly.

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LZ and FBG contributed equally to this article and share first authorship.

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AUTHOR CONFLICT OF INTEREST

Drs Verhagen, van Herwaarden, Moll, and de Vries have a proctor agreement with Medtronic and are paid consultants.

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Chapter 22

Iliac seal zone dynamics and clinical consequences after endovascular aneurysm repair

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ABSTRACT

Objectives

To evaluate the dynamics of the iliac attachment zone after EVAR, and its association with clinical events.

Methods

A tertiary institution's prospective EVAR database was inquired to identify common iliac arteries at risk. Internally validated measurements were made, using centre-lumen line reconstructions. Iliac dilatation and endograft limb retraction were the main endpoints. Associations between dilatation, retraction, oversizing and distal seal length were investigated. Association with clinical events (sealing or occlusion) were also explored.

Results

Of 452 primary EVAR patients treated from 2004 to 2012, 341 were included (mean age 72y, 12% female, 597 common iliac arteries). Median follow-up was 23.4 months. At 30 days mean iliac diameter increased from 14mm to 15mm, P<0.001. Over follow-up, this difference increased to 17mm, P<0.001. Dilatation beyond the implanted graft diameter was present in 73 (12%). Retraction ^{3} 3mm was observed in 149 (25%). Iliac dilatation was weakly correlated to oversizing (R=0.11, P=0.008) and to endograft retraction (R=0.22, P<0.001).

There were 25 (4%) iliac seal complications, and 8 (1%) occlusion-related complications. Seal length (OR: 0.92 per mm), dilatation (OR: 1.12 per mm) and retraction (OR: 1.08 per mm) were independent risk factors for seal-related complications. Iliac dilatation was the only risk factor for occlusion (OR: 1.28 per mm).

Conclusions

The iliac seal zone remains dynamic after EVAR. Iliac dilatation and endograft limb retraction are common findings over follow-up, and both are risk factors for clinically relevant loss of iliac seal. Optimizing the iliac seal length is recommended to minimize the risk of complications.

INTRODUCTION

The importance of the iliac seal zones after endovascular aneurysm repair (EVAR) is not completely understood. The true incidence of iliac dilatation and retraction is largely unknown, and the potential consequences – loss of seal or occlusion – are undetermined.

While much attention has focused on the hostile proximal neck over the years, there is a lack of evidence regarding the risk of iliac complications that in turn may account for a growing proportion of EVAR-related complications. Clarification of the significance and particularities of distal sealing zone dynamics after implantation may help reduce iliac-related complications and consequently improve clinical success of EVAR.

There have been publications suggesting that adverse iliac anatomy increases the risk of complications.[1,2,3,4,5,6] However, difficulties in serial morphological assessment of iliac arteries have resulted in a gap in perception of post-implant iliac changes and possible complications.

This study aims to identify the progression of the distal sealing zone over time and its association with clinical events.

METHODS

Population

We conducted a retrospective study based on a prospectively kept database of AAA patients treated by EVAR in a single tertiary institution from 2004 to 2012. Inclusion criteria were: treatment with an endovascular device with landing zone in the common iliac arteries and surveillance using computed tomography angiography (CTA). Patients with infectious or anastomotic aneurysms were excluded from the analysis.

Measurements

All measurements were performed by two observers trained in image analysis (FBG, NO), after manual centre-lumen line reconstruction using dedicated post-processing software (3Mensio, Bilthoven, The Netherlands). All measurements are performed outer-to-outer wall. According to local practice, preoperative CTA had to be performed no more than 3 months before operation, and the first postoperative CTA was performed within 30-days (typically at day 2 or 3, before hospital discharge). Local surveillance protocol during the study period included annual CTA.

To assess iliac dilatation in a standardized fashion, the iliac bifurcation was used as landmark and the iliac diameter measured at a fixed distance from this landmark. The first postoperative CTA was used as reference and the iliac diameter was measured 10mm proximal to the distal edge of the implanted stentgraft. The distance to the iliac

bifurcation was registered and the pre-implantation iliac diameter was measured at the same level. Using the same technique, the last available post-operative iliac diameter was obtained (Figure 1).

To assess endograft limb retraction over time, the distance from most distal portion of the stentgraft and the iliac bifurcation and the diameter of the iliac arteries at the level of the last stent were measured at the first and last available exams.

Validation of this technique was performed on a random sample of 30 patients. Inter-observer agreement was high (Spearman's Rho 0.969 for iliac diameter and .0.989 for distance from graft to iliac bifurcation).

Measurement of iliac seal length was performed by measurement of the length of full circumferential graft-wall apposition in a CLL reconstruction, as described elsewhere (Figure 2).[7]

Definitions

Iliac dilatation was defined as an increase greater than 2mm or 10% of the outer-to-outer iliac diameter 1cm proximal to the distal edge of the last stent. Dilatation beyond implanted graft diameter was considered if the outer-to-outer iliac diameter exceeded the implanted graft diameter by 2mm (estimated wall thickness). Endograft retraction was considered present if the distance between the iliac bifurcation and the distal edge of the last stent increased by more than 2mm. Oversizing was calculated by using the following formula: (implanted limb diameter – native iliac diameter)/native iliac diameter. Adverse clinical events were considered if one of the following occurred: type-Ib endoleak or need for iliac limb extension (pre-emptive) – iliac seal complications; or endograft limb occlusion beyond 30-days (iliac occlusion complications).

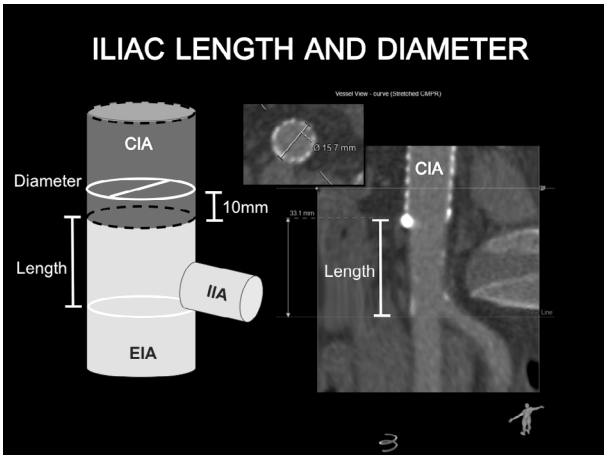

Figure 1. Method for serial length and diameter measurements at the iliac sealing zone
Legend: CIA – Common Iliac Artery; EIA – External Iliac Artery, IIA – Internal Iliac Artery.

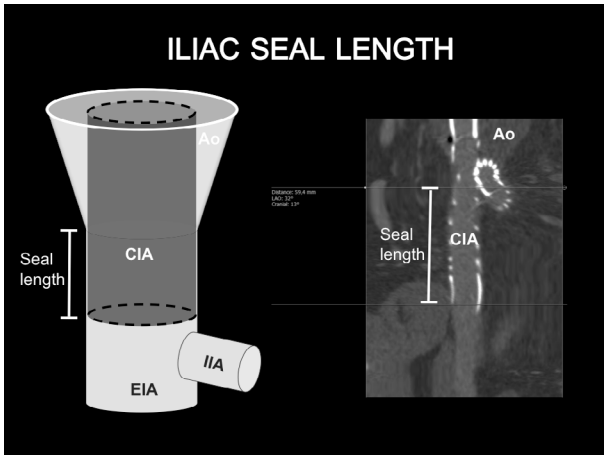

Figure 2. Method for serial measurement of iliac sealing length
Legend: CIA – Common Iliac Artery; EIA – External Iliac Artery, IIA – Internal Iliac Artery.

Endpoints

The primary endpoints for this study were dilatation of the common iliac arteries and endograft limb retraction. Furthermore, we investigated the potential clinical consequences of lilac dilatation and limb retraction on seal and occlusion complications.

Statistical analysis

Discrete variables are presented as counts and percentages, and continuous variables are presented as mean ± standard deviation if normally distributed, or median (interquartile range) if the distribution is non-parametric. Individual differences in length and diameter over time were tested using related samples Wilcoxon signed rank test. The correlation between postoperative iliac seal length, iliac dilatation and endograft limb retraction was tested using Spearman's correlation coefficients. Associations between endograft limb retraction and aneurysm sac growth and distal seal complications (type-Ib endoleaks, limb occlusion or need for iliac extension) were tested using Mann-Whitney U statistics. A multivariable logistic regression model was created to determine the risk of seal and occlusion complications associated with iliac diameter at implant, iliac seal at implant, AAA maximum diameter, iliac dilatation and iliac retraction. All statistical analysis were performed using SPSS software v20.

RESULTS

Four hundred and fifty two patients were treated with EVAR from 2004 to 2012 at the Erasmus Medical Centre. Of these, eight had infectious aneurysms, 38 had anastomotic

Table 1. Baseline characteristics

Age – mean yrs (SD)	72.3 (7.5)
Female Gender – N (%)	42 (11)
Pre-operative AAA maximum diameter (mm) – median (IQR)	61 (56-71)
Common iliac diameter (mm) (590/597) – median (IQR)	14 (12-16)
Used endografts	
Medtronic Endurant	322 (53.9)
Gore Excluder	238 (39.9)
Medtronic Talent	22 (3.7)
Cook Zenith	5 (0.8)
Others	12 (2.0)
AUI configuration –N (%)	26 (4.3)
Implanted diameter (mm) (593/597) – median (IQR)	16 (14-20)
Percentage iliac oversizing (590/597) – median (IQR)	20 (9-33)
Common iliac seal length @30d (597/597) – median (IQR)	28 (19-38)

Legend: SD – Standard Deviation, AAA – Abdominal Aortic Aneurysm, IQR – Inter Quartile Range, AUI – Aorto-Uni Iliac.

aneurysms and one was a traumatic aneurysm. From the remaining 405 patients, another 64 patients were excluded because they did not have two postoperative CTAs of which one within 30-days of operation for comparison of iliac morphology. Three hundred and forty one patients (597 common iliac arteries) were available for analysis, and followed for a median of 23.4 months (9.3-42.8).

Baseline characteristics

Mean age of the study population was 72.3±7.5, and there were 41 (12.0%) females. The median pre-operative AAA diameter was 61mm (56-71), and the median iliac diameter was 14mm (12-16). The median iliac oversizing chosen for device implantation was 20% (9-33). A variety of devices were used in this patient cohort, with predominance of the Endurant (189/341, (55.4%) and Excluder (130/341, 38.1%) devices. AUI devices were used in 26/341 (7.6%) patients. Baseline characteristics are summarized in Table 1.

Iliac dilatation and limb retraction

At the 30-day CTA, the median distance from the distal edge of the endograft to the iliac bifurcation was 21mm (14-31), and the median iliac seal length was 28mm (19-38). The median iliac diameter, measured 10mm proximal to the distal edge of the implant, increased from 14mm to 15mm, P<0.001, Table 2. Over follow-up, this difference increased to 17mm, P<0.001, and the majority iliac arteries exhibited dilatation ^{3} 2mm (340/597, 56.9%). Iliac dilatation beyond the implanted graft diameter was present in 73 iliac arteries (12.2%).

Table 2. Iliac seal dynamics over follow-up

		P value
Pre-operative iliac diameter (mm) – median (IQR)	14 (12-16)	
Iliac diameter at 30-days (mm) – median (IQR)	15 (13-17)	<0.001
Iliac diameter at last CTA (mm) – median (IQR)	17 (14-20)	<0.001
Iliac dilatation		
Median (IQR)	3 (1-4)	
2mm or greater – N (%)	340 (57)	<0.001
Iliac limb retraction		
Median (IQR)	0 (0-2)	
3mm or greater – N (%)	149 (25)	<0.001

Legend: IQR – Inter Quartile Range, AUI – Aorto-Uni Iliac.

Retraction [3] 3mm was observed in 149 (25.0%) iliac arteries. In cases with iliac seal complications (N=25), the median iliac dilatation was 3mm (1-6.5) and median retraction was 4mm (0-8.5). Dilatation beyond the graft diameter was present in 7/25 (28%), and retraction >5mm in 11/25 (44%).

Iliac dilatation was weakly but significantly correlated to the degree of oversizing (R=0.11, P=0.008) and to endograft retraction (R=0.22, P<0,001). No association was found between endograft retraction and AAA baseline diameter or the degree of oversizing.

Predictors of iliac complications

After the initial post-operative period, there were 25 (4.2%) iliac seal complications, and 8 (1.3%) occlusion-related complications. Univariable analysis of possible risk factors for iliac seal complications revealed baseline AAA diameter (P=0.018), baseline iliac diameter (P=0.020), iliac seal length at 30 days (P<0.001) iliac dilatation (P=0.024) and iliac limb retraction (P<0.001) as significant (Table 3). The degree of oversizing was not associated with seal complications in this cohort. Multivariable analysis confirmed iliac seal length (OR: 0.923 per mm increase, 95%CI: 0.886-0.961), iliac dilatation (OR: 1.120 per mm increase, 95%CI: 1.009-1.243) and iliac limb retraction (OR: 1.085 per mm increase, 95%CI: 1.010-1.165) as independent risk factors. Regarding limb occlusion, only iliac dilatation was found as a risk factor (OR: 1.276 per mm increase, 95%CI: 1.122-1.450), Table 4. No multivariable analysis was possible due to the low number of occlusion events.

Table 3. Uni- and multivariable associations for sealing complications

Risk factor	Univariable			Multivariable	
	With complication Median (IQR)	*Without complication Median (IQR)*	*P value*	*Odds Ratio*	*95% Confidence Interval*
Preop AAA diam	70 (58.5-83-5)	61 (55-71)	0.018	1.022	0.995 – 1.050
Preop liac diameter	18 (16-24)	14 (12-16)	0.020	1.079	0.970 – 1.201
Iliac seal @ 30d	11 (4-23)	28 (20-38)	<0.001	0.923	0.886 – 0.961
Iliac dilatation (mm)	3 (1-6.5)	2 (0-3)	0.024	1.120	1.009 – 1.243
Iliac retraction (mm)	4 (0-8.5)	0 (0-2)	<0.001	1.085	1.010 – 1.165
% Oversizing	20 (8-41)	20 (9-33)	0.924		

Legend: AAA – Abdominal Aortic Aneurysm

Table 4. Univariable associations for occlusion complications

Risk factor	Univariable		
	With complication Median (IQR)	*Without complication Median (IQR)*	*P value*
Preop AAA diam	*60 (59-81)*	*61 (55-71)*	*0.552*
Preop Iliac diameter	13.5 (12-15)	14 (12-16)	0.512
Iliac seal @ 30d	38.5 (14-49)	28 (19-38)	0.450
Iliac dilatation (mm)	5.5 (3-7)	2 (0-3)	<0.001
Iliac retraction (mm)	2 (0-3)	0 (0-2)	0.155
% Oversizing	38 (3-48)	20 (9-33)	0.136

Legend: AAA – Abdominal Aortic Aneurysm

DISCUSSION

After EVAR, the iliac sealing zone remains dynamic and is a possible source of morbidity and, ultimately, treatment failure. Although attention has focused on the proximal seal, the present study suggests that iliac dilatation and endograft limb retraction are common occurrences and are associated with clinical consequences.

Much of the difficulty in reporting iliac-related complications resides on the capacity to accurately assess and reproduce measurements. Reporting measurements on the proximal attachment site can be done using well-standardized methods. In contrast, the complexity of the iliac sealing zones likely explains the lack of standardization for reporting and consequently the paucity and conflicting nature of published data.[8] For

this publication, we propose a technique based on centre-lumen line measurements and anatomical landmarks, which allows for consecutive measurements of the distal iliac seal zone at the same exact location, as well as quantification of the retraction of iliac components of endografts. Using this tool, we were able to demonstrate that both iliac dilatation and endograft limb retraction are frequent events, and that these two occurrences are correlated. However, this correlation is weak, suggesting other factors also play an important role.

Iliac dilatation over time has been demonstrated before. Kaladji et al. studied the evolution of 179 patients over a mean of 24 months, and found iliac dilatation to be very frequent (mean increase 2-3mm, depending on level). Although they could not find a correlation to clinical events, the authors sent a word of caution.[2] Previously, Falkensammer et al. had shown that dilatation was more pronounced in patients with previously existing iliac ectasy.[9] and both Albertini et al. and Hobo et al. reported a higher risk of complications in patients with larger iliac arteries, a finding our study also corroborates.[6,10]

According to the present results, iliac dilatation follows two stages, one acute immediately post-implant and another gradually occurring over time. This reproduces the phenomenon already well characterized at the proximal aneurysm neck, following implantation of oversized self-expanding nitinol-based devices.[11] Although uncommon at the proximal neck, iliac expansion beyond the diameter of the implanted endograft is a not rare event even at long-term, has shown by Adiseshiah et al. and confirmed in this study.[12]

Iliac limb retraction is an interesting and relevant finding of this study. Sideways displacement of endograft limbs within the aneurysm sac has been associated to adverse events after EVAR.[13] This observation may be a surrogate finding of limb retraction (in the absence of proximal migration and adequate component overlap). In fact, Waasdorp et al. found that patients with limb displacement had larger aneurysms and shorter iliac fixation zones, findings consistent with the results of this study. We demonstrate that iliac retraction is a common event, associated to both iliac seal length (ie, contact area with the iliac artery wall) and iliac dilatation (reducing the resistance to displacement resulting from radial force). This effect had been suggested before by Arko et al, in an in-vitro study evaluating the importance of iliac fixation in preventing longitudinal displacement of a stentgraft.[14] Importantly, rigid endograft limbs were used in patients included in both these publications. Contrary to prior interpretation, the use of more flexible iliac limbs has not diminished the incidence of retraction, as the results of this study demonstrate.

Benharash et al later found, in a study analyzing 92 patients treated between 2000 and 2004, that shorter iliac fixation length was associated with the risk of proximal device migration, and suggested coverage of the entire distance of the common iliac artery as a

protective factor.[15] Others have also linked the chance of distal migration to insufficient distal seal.[16,17] Although we did not test for the association between proximal migration and distal seal, our results strongly corroborate that longer seal zones protect from device displacement at the distal end.

There are important limitations to this study that must be considered. Firstly, there is a bias in patient and graft selection that limits the extrapolation of these results to all EVAR populations. In particular, there is a paucity of patients treated with devices with stiffer iliac components. These may yield different results in terms of the chance of retraction and/or occlusion, and change the results significantly. Also, the retrospective design of the study has the potential risk of selection bias. Finally, the method used to determine iliac morphology and dynamics, although reproducible, is relatively complex and may not be practical to use in a clinical setting.

Despite the limitations, two recommendations can be made based on these results. Firstly, the authors suggest maximization of the iliac seal zone by extending the iliac components as close as possible to the iliac bifurcation. In patients where an adequate iliac seal (>15mm) cannot be achieved, extension to the external iliac artery may be considered, possibly with preservation of the internal iliac artery with the use of an iliac bifurcated device when technically feasible and clinically justified. Secondly, extra attention should be given to surveillance of patients with distal seal in ectatic iliac arteries, especially in the long-term. Since CT is necessary to determine progressive loss of seal and/or retraction, we suggest these patients should not be followed using DUS-only protocols. Depending on baseline, annual or bienal CTA is advised, replaced by non-contrast CTA in patients with renal impairment.

In conclusion, the results of this study demonstrate that the iliac seal zone remains dynamic after EVAR implantation. Iliac dilatation and endograft limb retraction are common findings over follow-up, and both are risk factors for clinically relevant loss of iliac seal. Optimization of the iliac seal zone and added attention to sealing in ectatic iliac arteries are recommended.

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PART VI

RISK-ADAPTED POSTOPERATIVE SURVEILLANCE AFTER EVAR

Chapter 23

Adequate seal and no endoleak on the first postoperative computed tomography angiography as criteria for no additional imaging up to 5 years after endovascular aneurysm repair

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ABSTRACT

Objective

Intensive image surveillance after endovascular aneurysm repair is generally recommended due to continued risk of complications. However, patients at lower risk may not benefit from this strategy. We evaluated the predictive value of the first postoperative computed tomography angiography (CTA) characteristics for aneurysm-related adverse events as a means of patient selection for risk-adapted surveillance.

Methods

All patients treated with the Low-Permeability Excluder Endograft (W. L. Gore & Assoc, Flagstaff, Ariz) at a tertiary institution from 2004 to 2011 were included. First postoperative CTAs were analyzed for the presence of endoleaks, endograft kinking, distance from the lowermost renal artery to the start of the endograft, and for proximal and distal sealing length using center lumen line reconstructions. The primary end point was freedom from aneurysm-related adverse events. Multivariable Cox regression was used to test postoperative CTA characteristics as independent risk factors, which were subsequently used as selection criteria for low-risk and high-risk groups. Estimates for freedom from adverse events were obtained using Kaplan-Meier survival curves.

Results

Included were 131 patients. The median follow-up was 4.1 years (interquartile range, 2.1-6.1). During this period, 30 patients (23%) sustained aneurysm-related adverse events. Seal length <10 mm and presence of endoleak were significant risk factors for this end point. Patients were subsequently categorized as low-risk (proximal and distal seal length ≥10 mm and no endoleak, n = 62) or high-risk (seal length <10 mm or presence of endoleak, or both; n = 69). During follow-up, four low-risk patients (3%) and 26 high-risk patients (19%) sustained events ($P < .001$). Four secondary interventions were required in three low-risk patients, and 31 secondary interventions in 23 high-risk patients. Sac growth was observed in two low-risk patients and in 15 high-risk patients. The 5-year estimates for freedom from aneurysm-related adverse events were 98% for the low-risk group and 52% for the high-risk group. For each diagnosis, 81.7 image examinations were necessary in the low-risk group and 8.2 in the high-risk group.

Conclusions

Our results suggest that the first postoperative CTA provides important information for risk stratification after endovascular aneurysm repair when the Excluder endograft is used. In patients with adequate seal and no endoleaks, the risk of aneurysm-related adverse events was significantly reduced, resulting in a large number of unnecessary

image examinations. Adjusting the imaging protocol beyond 30 days and up to 5 years, based on individual patients' risk, may result in a more efficient and rational postoperative surveillance.

INTRODUCTION

The early survival benefit of endovascular aneurysm repair (EVAR) over open surgery has resulted in a gradual paradigm shift, with the former progressively becoming the preferred strategy for treatment of patients with aortic abdominal aneurysms (AAAs).[1,2,3] The main drawback of EVAR remains the durability of the procedure, with frequent need of secondary intervention for continued success.[2,4,5,6,7] To assess treatment failure and ultimately prevent death from rupture, intensive life-long postoperative surveillance strategies are recommended, which include at least annual computed tomography angiography (CTA), duplex ultrasound (DUS) imaging, abdominal radiography, or a combination of these.[8]

Intensive image follow-up strategies are not innocuous, however. Contrast-induced nephropathy and radiation exposure are worrisome factors when CTA is used as the preferred strategy.[9,10] Alternatively, DUS imaging is laborious, window and operator dependent, and requires intravenous contrast to obtain comparable results.[11] With both imaging techniques, examinations and subsequent follow-up visits are costly and involve significant resource allocation, which is only justifiable if patients are at risk of complications.

Preoperative risk factors for EVAR-related complications, especially anatomic risk factors, have been studied extensively, with fairly consistent results.[12, 13, 14 and 15] However, complications may ensue even in patients with anatomic suitability. This additional risk may result from intraoperative variables or vessel-graft interactions that cannot be evaluated beforehand. The first postoperative CTA may provide valuable additional information and sharpen the predictive capacity for adverse events during follow-up. This, in turn, can help in patient selection, reserving the intensive image follow-up protocols to patients at higher risk.

The purpose of this study was to evaluate the prognostic capacity of the first postoperative scan and identify a subgroup of patients at very low risk of AAA-related adverse events after EVAR.

METHODS

This study complies with the Declaration of Helsinki on research ethics.

Study design: This single-institution retrospective study was based on a prospectively kept database of AAA patients treated by EVAR since 2000 at Erasmus University Medical Center, Rotterdam, The Netherlands.

Patient population

From January 2000 until December 2011, 449 patients with aortoiliac aneurysms were treated at our institution. For this study, only AAA patients treated with the Low-Permeability (LP) Excluder Endograft (W. L. Gore and Assoc, Flagstaff, Ariz) were included. Exclusion criteria were previous abdominal aortic surgery or infectious aortic pathology. Patients treated until December 2007 were also included in a recently published study aimed at long-term results and morphologic analysis.[16] All patients were assessed preoperatively using CTA and entered the institutional follow-up protocol that included an early postoperative CTA (typically before hospital discharge), a CTA at 6 months and 1 year, and then CTAs yearly thereafter.

Since 2007, the 6-month examination has been waived and CTA surveillance replaced by DUS imaging in selected patients considered at lower risk according to the treating physician's expectations in concurrence with the Clinical Practice Guidelines of the European Society for Vascular Surgery.[8] Also, DUS imaging or noncontrast CTs were performed as an alternative to CTA in patients with impaired renal function.

Preoperative baseline characteristics included age, sex, American Society of Anesthesiologists classification, and anatomic details. Intraoperative details were obtained from operative records and included all intraoperative complementary procedures. Subsequent information was obtained from patient records, and all AAA-related complications and secondary interventions were noted. Cause of death was obtained for patients who died during follow-up.

Image acquisition and analysis

CTA image acquisition was performed according to institutional protocols for EVAR using a 16-slice or 64-slice Brilliance CT scanner (Philips Medical Systems, Best, The Netherlands). Per protocol, collimation is 16 mm $\times$ 1.5 mm or 64 mm $\times$ 0.6 mm, and pitch is 1.15 or 1.2, for 16-slice and 64-slice, respectively. Field of view is the entire abdomen, and the window is set at 350/150 with an increment of 1.0 mm. Radiation parameters are 120 kVp and 150 mA. Intravenous nonionic iodixanol contrast (Visipaque 320; GE Healthcare, Buchler GmbH & Co KG, Braunschweig, Germany) is administered at a dose of 120 mL, using bolus triggering in the juxtadiaphragmatic descending aorta at a threshold of 100 Hounsfield units over the baseline. Detailed preoperative and postoperative measurements were available in our institutional database.

In addition, all first postoperative CTA were reanalyzed using manually generated center lumen line reconstructions of the proximal and distal sealing zones using post-

processing 3Mensio Vascular 4.2 software (3Mensio Medical Imaging BV, Bilthoven, The Netherlands). For the proximal seal, markers were placed in the center of the lumen using axial slices starting at the superior mesenteric artery and at every 2 mm progressing downward until the flow divider. For the distal seal, markers were placed starting distal to the end of the endograft limb and progressing upward until the aortic bifurcation. The sealing length was considered to be the distance where the entire circumference of the aortic and iliac vessel walls and the endograft are completely adjacent. This can be easily verified using the reconstructed axial slices and the distance measured in the stretched-view window (Figure 1). One vascular surgeon with experience in image analysis (F.B.G.) performed all of the measurements.

The duration of each CTA analysis was typically <5 minutes. Intraobserver variability was tested for a sample of 30 patients, with very good agreement (Pearson correlation coefficient, 0.940; $P < .001$). A second observer (K.v.L.) repeated these measurements, without significant variability (Pearson correlation coefficient. 0.938; $P < .001$). Bland-Altman plots were created for intraobserver and interobserver variability (Figure 2).

Definitions

Anatomic suitability was defined according to the instructions for use for the Excluder Endograft.[17] A patient was considered to have suitable anatomy if all of the following criteria were met: neck diameter, 19 to 28 mm; neck length, >15 mm; thrombus or calcification in <50% of the aortic circumference, and neck angulation <60°.

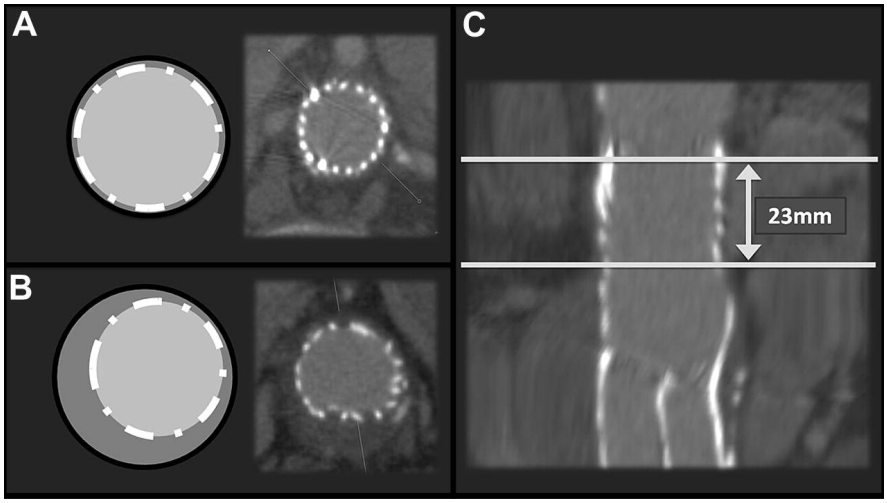

Figure 1. Method for determining seal length using center lumen line reconstruction. **A,** Reconstructed axial slice shows adequate seal, 2 mm below the renal arteries, with good wall-graft apposition in the entire vessel circumference. **B,** Same patient, 30 mm below the renal arteries, shows inadequate seal. **C,** Length of adequate proximal seal, measured in stretched view.

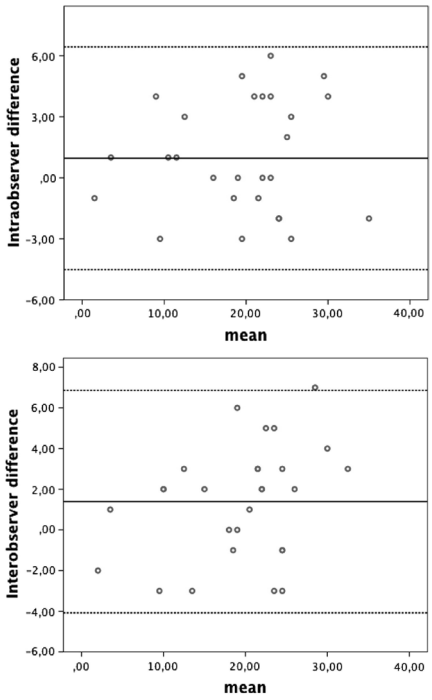

Figure 2. Bland-Altman plots show (*top*) intraobserver and (*bottom*) interobserver variability on neck length measurements.

Table 1. Univariable and multivariable analysis of first postoperative CTA variables associated with AAA-related adverse events during follow-up (Cox regression).

Variable	No. (%)	Univariable HR (95% CI)	Multivariable HR (95% CI)
Seal length <10 mm	38 (29)	4.32 (2.08-8.98)	3.89 (1.86-8.15)
Endoleak on first postoperative CTA	48 (37)	2.61 (1.27-5.39)	2.19 (1.06-4.54)
Endograft kinking	3 (2)	0.05 (0-5981.2)	…
Suboptimal deployment	38 (29)	1.23 (0.58-2.64)	…
Oversizing <10%	35 (27)	0.53 (0.21-1.30)	…

Legend: *AAA,* Abdominal aortic aneurysm; *CI,* confidence interval; *CTA,* computed tomography angiography; *HR,* hazard ratio.

Oversizing was determined retrospectively according to the following formula: (implanted main-body diameter – reference neck diameter in first 15 mm of intrarenal neck)/reference neck diameter in first 15 mm of infrarenal neck. Insufficient oversizing was considered if <10%.

Additional intraoperative procedures were classified as any additional act performed intraoperatively, not part of the standard endograft implantation, such as proximal cuff or giant Palmaz stent placement, or iliac balloon angioplasty or stenting.

Sufficient postoperative seal was considered if a minimum seal length of 10 mm was present proximally and distally. This 10-mm threshold was based on the manufacturer's instructions for use (minimum proximal neck of 15 mm and iliac landing zone of 10 mm) accounting for a margin of error in the proximal deployment of 5 mm.[16]

Early postoperative endoleak was considered as type I, II, III, or undetermined endoleaks observed on the first postoperative CTA.

Deployment accuracy was measured as the distance from the lower edge of the lowermost renal artery and the point where the entire circumference of the aortic wall is covered by the endograft. Suboptimal deployment was defined as positioning of the proximal segment markers of the endograft >5 mm below the optimal position, immediately below the lowermost renal artery. Because distance measurements on intraoperative angiography were unreliable, the distance from the lowermost renal to the endograft on the first CTA was used as a surrogate.

Endograft kinking was considered present if some part of the device displayed a sharp angular image >90°, which was retrospectively identified and consensual after examination by two vascular surgeons experienced in EVAR.

Sac growth was defined as an increase in diameter >5 mm compared with the first postoperative examination, according to the reporting standards for EVAR.[18] Inversely, sac shrinkage was considered as a reduction in diameter >5 mm.

Table 2. Baseline characteristics

Variable[a]	Low risk (n = 62)	High risk (n = 69)	*P*
Age, years	70.9 ± 7.7	73.4 ± 7.3	.058
Female	4 (6)	9 (13)	.25
AAA diameter, mm	63.3 ± 13.8	64.0 ± 15.5	.8
Neck diameter, mm	24.1 ± 2.5	24.4 ± 3.0	.63
Neck length, mm	32.9 ± 14.2	32.4 ± 15.3	.85
ASA class III or IV	34 (55)	30 (43)	.22
Symptomatic/ruptured	11 (18)	10 (14)	.64
Angulation			
Suprarenal	21 ± 17	24 ± 17	.41
Infrarenal	34 ± 17	37 ± 21	.32
Neck thrombus	25 (40)	20 (29)	.2
Neck calcification	0	0	…
Iliac stenosis	4 (6)	8 (12)	.37
Iliac tortuosity	14 (23)	18 (26)	.69
Iliac aneurysms	18 (29)	20 (29)	>.99
Anatomic suitability	50 (81)	45 (65)	.053

Legend: *AAA,* Abdominal aortic aneurysm; *ASA,* American Society of Anesthesiologists. a) Continuous data are presented as the mean ± standard deviation and categoric data as number (%).

Table 3. Details of the inclusion criteria of the high-risk group

Inclusion criteria	No. (%) (n = 69)
Seal length <10 mm	38 (55)
Short proximal seal	18 (26)
Short distal seal	22 (32)
Endoleak	48 (70)
Type Ia	4 (6)
Type Ib	2 (3)
Type II	37 (54)
Type III	0 (0)
Type undetermined	5 (7)
Seal length <10 mm and endoleak	17 (25)

AAA-related adverse events were defined as a composite of the following: occurrence of type Ia, type Ib, type III, or undetermined type endoleaks on postoperative examinations, AAA growth >5 mm in diameter during follow-up, migration >10 mm, device failure, AAA-related death, postimplantation AAA rupture, or any AAA-related secondary intervention.[18]

End points

The primary study end point was freedom from AAA-related adverse events. Individually, elements of this composite end point were analyzed separately as secondary end points.

Statistical analysis

To assess the importance of different variables obtained from the first postoperative CTA (seal length, presence of endoleak, endograft kinking, and deployment accuracy), univariable Cox regression analysis was performed. The degree of oversizing was also tested as a possible confounder. Significant variables were then entered in a multivariable model to test for interaction and used as selection criteria for inclusion in a high-risk or low-risk group. Baseline and intraoperative characteristics, as well as distribution of events during follow-up, were compared between groups using count and percentages. Categoric variables are presented as count and percentage and were compared with Pearson χ^2 tests. Continuous variables are presented as mean and standard deviation and were compared using Student *t*-tests or are presented as median and interquartile range (IQR) and were compared with Mann-Whitney *U* tests for nonparametric distributions. A Kaplan-Meier survival estimate was calculated for freedom from AAA-related adverse events. Estimates for low-risk and high-risk groups were compared using the log-rank (Mantel-Cox) test of equality. Differences were considered significant if $P < .05$. Statistical analysis was performed using IBM SPSS Statistics 20 software (IBM Inc, Chicago, Ill).

Table 4. Events during follow-up

Variable	Low risk (n = 62), No. (%)	High risk (n = 69), No. (%)	*P*
AAA-related adverse events, patients	4 (6)	26 (38)	<.001
Secondary intervention, events	4	31	<.001
Proximal stent/cuff	0	9	
Limb extension	2	11	
Coil/glue embolization	0	3	
Relining	1	1	
Conversion to open repair	1	3	
Conversion to aortouniiliac	0	1	
Open/laparoscopic fenestration	0	1	
Thrombolysis and iliac PTA	0	2	
Migration	0	0	…
Device failure	0	0	…
Endoleak during follow-up	0 (0)	38 (44)	<.001
Type Ia	-	4	
Type Ib	-	2	
Type II	-	27	
Type III	-	-	
Type undetermined	-	5	
Sac behavior			.007
Growth	2 (3)	15 (22)	
Stability	25 (40)	25 (36)	
Shrinkage	35 (56)	29 (42)	

Legend: *AAA,* Abdominal aortic aneurysm; *PTA,* percutaneous transluminal angioplasty.

RESULTS

From July 2004 to December 2011, 145 AAA patients were treated with the LP Excluder endograft at our institution. The study excluded 14 patients: seven had previous aortic open reconstruction, three were mycotic aneurysms, two patients with ruptured AAAs died before a postoperative CTA could be performed, and one was treated for traumatic abdominal aortic rupture. Thus, 131 patients were available for analysis.

The follow-up duration of this cohort was a median 4.1 years (IQR, 2.1-6.1; maximum, 8.1 years). During this period, 30 patients (23%) sustained AAA-related adverse events. The median interval between the index operation and the first postoperative CTA was 2.0 days (IQR, 1-9 days) for the low-risk group and 3.5 days (IQR, 2-17 days) for the high-risk group ($P = .081$). In 10 patients (four in the low-risk group), the CTA was delayed >30 days because of concerns about renal function deterioration.

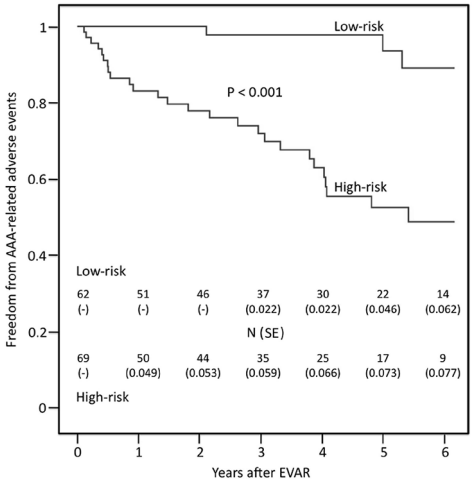

Figure 3. Kaplan-Meier survival curves show freedom from secondary abdominal aortic aneurysm (*AAA*) intervention in low-risk and high-risk patients during follow-up after endovascular aneurysm repair (*EVAR*). *SE,* Standard error.

Univariable analysis of possible risk factors for AAA-related adverse events revealed length of seal <10 mm and presence of endoleak on the first postoperative CTA were significant. These remained significant after multivariable testing (Table 1). These findings were used to divide patients into a low-risk group (proximal and distal seal length ≥10 mm and no endoleak) and a high-risk group (with insufficient seal or presence of endoleak, or both). Baseline characteristics are detailed in Table 2, and the details of inclusion criteria for the high-risk group are presented in Table 3.

Four patients (3%) in the low-risk group and 26 (19%) in the high-risk group sustained AAA-related adverse events ($P < .001$) during the follow-up. Four secondary interventions were required in three patients in the low-risk group, and 31 secondary interventions were required for 23 patients in the high-risk group. Sac growth was observed in two low-risk patients (3%) and in 15 (22%) high-risk patients. No migration or device failure was observed in either group. All AAA-related adverse events are detailed in Table 4.

Kaplan-Meier estimates for freedom from AAA-related adverse events were significantly different between the two groups ($P < .001$, Figure 3), with 5-year estimates of 98% for the low-risk group and 52% for the high-risk group.

Four patients in the low-risk group sustained AAA-related adverse events: one patient was converted to open repair due to aortic rupture as a consequence of endograft infection, 2.11 years after EVAR. No signs of infection were present in the 2-year CTA, and sac shrinkage was noted. Unlike the previous cases, this operation resulted from an additional investigation prompted by the presence of symptoms and not as a result of an image finding.

Table 5. Detailed analysis of adverse events in the low-risk group

Event	Intervention	Time to event, years	Endoleak presence	Loss of seal	Outcome	Follow-up, years
Endograft infection with rupture	Open conversion	2.11	No	No	Postoperative death	2.11
Relining	Sac growth	5.01	No	No	Persistent growth, later identified type Ib endoleak treated with limb extension	7.46
Sac growth	None	5.31	No	No	Continued sac growth	6.31
Limb extension	Short iliac seal	6.81	No	Yes	Successful	7.21

One patient was diagnosed with sac growth after 5 years, in the absence of identifiable endoleak, and was treated by relining the endograft. This treatment was unsuccessful in arresting growth, and a type Ib endoleak became evident 1 year later, which was likely the original cause of growth.

One patient required implantation of an iliac extension (nearly 7 years after EVAR) due to progression of disease and loss of distal seal length.

Lastly, one patient was diagnosed with growth 5 years postoperatively, after a period of shrinkage. This patient was managed conservatively until the end of follow-up. Details of secondary interventions occurring in the low-risk group are provided in Table 5.

In the high-risk group, only patients with type I endoleaks, persistent type II endoleaks associated with sac growth, and progressively shorter seal required an intervention.

During the study period, this patient cohort was subject to intensive periodic imaging, mostly using contrasted examinations (Table 6). For each diagnosis of an AAA-related adverse event over the course of follow-up, 81.7 image examinations had to be performed in the low-risk group and 8.2 in the high-risk group. Imaging was necessary to identify three (75%) of the AAA-related adverse events in the low-risk population, but all occurring after 5 years. In the high-risk group, imaging identified 25 of 26 (96%) of all AAA-related complications.

DISCUSSION

Complications and secondary interventions are frequent after EVAR, and intensive image follow-up is considered mandatory to allow for timely elective treatment of potentially fatal complications that course silently until an acute event occurs, usually rupture or occlusion.[8] Our study suggests, however, that an identifiable subgroup of patients may not

Table 6. Analysis of postoperative image surveillance

Variable[a]	Low-risk (n = 62)	High-risk (n = 69)	*P*
Total follow-up, years	4.0 (1.7-6.1)	4.2 (2.2-6.0)	.42
Total exams performed before first event or end of follow-up	245	205	
CT angiography	183	170	
DUS imaging	55	32	
Noncontrast CT	7	3	
Exams per patient before first event or end of follow-up[b]	3.95 ± 2.45	2.97 ± 2.27	.019
AAA-related adverse events identified from image exams	3 (7)	25 (33)	<.001
Exams needed for each AAA-related adverse event identified	81.7	8.2	

Legend: *AAA,* Abdominal aortic aneurysm; *CT,* computed tomography; *DUS*, duplex ultrasound imaging; *IQR,* interquartile range. a) Continuous data are presented as median (IQR) or mean ± standard deviation and categoric data as number (%). b) Excluding preoperative and first postoperative CT angiography.

benefit from image follow-up for a prolonged period of time, making their surveillance similar to open surgery.

Intensive follow-up imaging may have deleterious effects for patients and health care providers alike. For patients monitored with CTA, radiation exposure and contrast nephropathy are important associated factors that should not be overlooked.[9,10.19] Alternatively, DUS imaging is operator-dependent, laborious, and requires intravenous contrast enhancement to achieve comparable sensitivity.[11.20] Whichever method is used, postoperative image surveillance is costly, requires resource allocation, and may negatively affect a patient's well-being.[21] A recent survey study from the United Kingdom revealed large heterogeneity in surveillance protocols adopted by expert centers.[22] This uncertainty regarding the optimal surveillance program reflects the paucity of evidence regarding risk stratification.

Preoperative anatomic features have been well characterized as risk factors for adverse outcome after EVAR.[12,13,14,15] However, a good proximal or distal landing zone does not guarantee an adequate seal. As an example, it is possible that unintentional low deployment might turn a long proximal neck into a short proximal seal. This is of particular importance in patients with neck angulation, where the distortion of anatomy induced by the deployment systems and parallax error frequently result in oblique positioning of the top stent with a much shorter sealing zone than anticipated. Precise measuring of seal length can be performed quickly and easily using center lumen line reconstruction.

The effect of intraoperative details and on-table imaging on secondary intervention after EVAR has also been investigated. Karthikesalingam et al[23] identified higher risk for patients requiring intraoperative adjuncts and lower risk for those undergoing intraoperative multiplanar CTA. They suggest that these findings may serve as selection criteria for stricter or more "relaxed" imaging follow-up. Like ours, this study relied on the absence of endoleak and adequate sealing zones for prediction of complications. Be-

cause intraoperative adjuncts do not always increase risk and on-table CTA is not widely available, we opted to use standard postoperative CTA and postprocessing software for assessment. We believe this approach provides a more applicable and reliable means of monitoring the end result of EVAR procedures.

The concept of using early postoperative information for risk prediction is not novel. Sternbergh et al[21] showed that freedom from endoleak at 1 month was highly predictive of reduced aneurysm-related morbidity. As a result, they proposed a simplified surveillance program that excluded the 6-month examination and replaced CTA by DUS imaging after the first year. Adaptations of this scheme have been widely accepted in clinical practice.[8] Two studies also identified early postoperative endoleaks as risk factors for adverse outcome.[24,25] Stratifying risk on the basis of absence of endoleak and adequate seal zones on the first postoperative CTA is a less specific but more sensitive method than using endoleak presence alone, as our study demonstrates.

A proportion of patients in our study were considered high risk due to identification of a type II endoleak. If detected, these mandate intensive image surveillance because of the risk of sac growth and, ultimately, rupture.[26,27,28] Detection of these endoleaks using CTA is relatively insensitive, however, as demonstrated by studies using magnetic resonance angiography and blood-pool agents.[29,30] Despite this limitation, a much higher proportion of patients progress to sac growth when type II endoleaks are detected This suggests that the method is still applicable as a predictor.[31] Also, specificity of type II endoleak detection has been questioned, because many are reportedly misinterpreted type I or III endoleaks.[32] This adds strength to the argument of including type II endoleaks as a criterion for high-risk inclusion.

Within the first 5 years, only one AAA-related adverse event occurred in the low-risk group.[33,34,35] This complication resulted from infection, which was not evident on routine CTAs. As such, for our low-risk patient group, the extensive follow-up did not seem to add significant benefit up to 5 years. After 5 years, three additional events occurred in low-risk patients. Two had progressively shortened distal sealing caused by iliac dilatation. The progression of disease can be expected many years after EVAR,[36] and continued surveillance in patients with a prolonged life expectancy is still obligatory, just like in open surgery. The last patient was identified as having sac growth after a period of shrinkage. The cause of growth could not be determined, and the patient remained under close surveillance.[37]

In the low-risk group, 82 image examinations had to be performed for every identified AAA-related adverse event. A cost-benefit analysis is beyond the scope of this study, but this alarmingly high rate of examinations required casts doubt on the benefit for patients and must be acknowledged. Dias et al[38] reported similar findings. Over a median of 54 months, <10% of their cohort of 279 patients actually benefited from CTA surveillance.[38]

Most secondary interventions performed were preventive (preceding complications), even in high-risk patients. Of 31 interventions, only six patients had a demonstrated type 1 endoleak, and no ruptures occurred. Moreover, all secondary procedures in the high-risk group were elective. These findings, in line with previously published data on outcome of secondary interventions,[39] reinforce the importance of continued image surveillance for this group.

The results of this study suggest that a risk-stratified postoperative surveillance protocol could be followed for patients treated with the Excluder endograft (Figure 4). In high-risk patients, standard annual CTA is advised, with DUS imaging an alternative for selected patients with impaired renal function or favorable sac remodeling. For low-risk patients, imaging up to 5 years would only be performed upon clinical suspicion and not for surveillance purposes. This way, the follow-up strategy for low-risk EVAR patients would not differ significantly from the current practice for open surgical patients. Beyond 5 years, annual CTA or DUS imaging seem advisable due to the risk of late complications as a result of disease progression. Because this is only a preliminary study, this proposed scheme should not be adopted for clinical care before the results can be confirmed in large, prospective series.

The retrospective, single-center nature of this study is a limitation that must be acknowledged. Also, selection of patients according to the type of device implanted may be a source of bias and restricts generalization. However, institutional experience with the Excluder endograft was predominant, and only small numbers of patients were treated with other devices for many years. Moreover, most other devices used before 2008 are no longer commercialized. For the Excluder endograft, on the other hand, there is long-term follow-up, and the device is expected to be available for years to come. From 2008, many patients at our center were treated with a fourth-generation Endurant

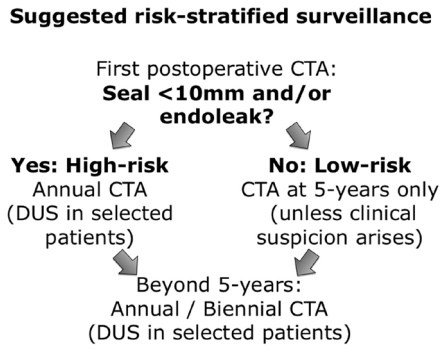

Figure 4. Possible follow-up imaging surveillance with computed tomography angiography (*CTA*) and duplex ultrasound (*DUS*) imaging for patients treated with the Excluder endograft.

endograft (Medtronic Endovascular, Santa Rosa, Calif). Because follow-up duration is very restricted for this group and extrapolation of future results is impossible, we opted not to include them.

The time between the index operation and the first postoperative CTA was not standardized, which could result in variability. However, this would likely affect both groups equally. The distribution of the time to the first CTA was similar between groups, but the median differed by 1.5 days. This difference did not reach statistical significance, perhaps due to sample size, but should be assumed as a limitation.

Lastly, we cannot ensure that the distance from the lowermost renal artery to the start of the graft remained the same after deployment until the CTA was performed. Because migration is possible during this interval, true deployment accuracy is only an approximation and may not reflect the true intraoperative result in all cases.

CONCLUSIONS

The present study suggests that the first postoperative CTA after EVAR can be used to stratify for the risk of AAA-related adverse events, based on the presence of endoleak and the length of proximal and distal seal. On one hand, roughly half of patients in our population were considered low risk, and imaging surveillance up to 5 years could have been waived, making their follow-up similar to patients undergoing open surgical repair. On the other hand, the results emphasize the need for close surveillance of patients at higher risk of complications. This concept requires validation with larger cohorts and a mixed sample of devices before it leads to a significant change in practice but highlights the necessity to re-evaluate current "one-size-fits-all" surveillance protocols.

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Chapter 24

Early sac shrinkage predicts a low risk of late complications after endovascular aortic aneurysm repair

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ABSTRACT

Background

Aneurysm shrinkage has been proposed as a marker of successful endovascular aneurysm repair (EVAR). Patients with early postoperative shrinkage may experience fewer subsequent complications, and consequently require less intensive surveillance.

Methods

Patients undergoing EVAR from 2000 to 2011 at three vascular centres (in 2 countries), who had two imaging examinations (postoperative and after 6–18 months), were included. Maximum diameter, complications and secondary interventions during follow-up were registered. Patients were categorized according to early sac dynamics. The primary endpoint was freedom from late complications. Secondary endpoints were freedom from secondary intervention, postimplant rupture and direct (type I/III) endoleaks.

Results

Some 597 EVARs (71·1 per cent of all EVARs) were included. No shrinkage was observed in 284 patients (47·6 per cent), moderate shrinkage (5–9 mm) in 142 (23·8 per cent) and major shrinkage (at least 10 mm) in 171 patients (28·6 per cent). Four years after the index imaging, the rate of freedom from complications was 84·3 (95 per cent confidence interval 78·7 to 89·8), 88·1 (80·6 to 95·5) and 94·4 (90·1 to 98·7) per cent respectively. No shrinkage was an independent risk factor for late complications compared with major shrinkage (hazard ratio (HR) 3·11; $P < 0·001$). Moderate compared with major shrinkage (HR 2·10; $P = 0·022$), early postoperative complications (HR 3·34; $P < 0·001$) and increasing abdominal aortic aneurysm baseline diameter (HR 1·02; $P = 0·001$) were also risk factors for late complications. Freedom from secondary interventions and direct endoleaks was greater for patients with major sac shrinkage.

Conclusion

Early change in aneurysm sac diameter is a strong predictor of late complications after EVAR. Patients with major sac shrinkage have a very low risk of complications for up to 5 years. This parameter may be used to tailor postoperative surveillance.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is increasingly being used as primary mode for abdominal aortic aneurysm (AAA) repair in suitable patients owing to reduced perioperative mortality compared with open repair.[1] However, EVAR is associated with a significant rate of complications over time.[2] Imaging surveillance is considered mandatory to identify and treat these complications before they result in life-threatening events such as postimplant rupture or graft occlusion. In many countries the burden of post-EVAR surveillance is increasing rapidly.

Currently, there is no consensus on the frequency of post-EVAR surveillance, method of imaging or individual adaptation according to risk.[3,4,5,6,7] Computed tomographic angiography (CTA), which is still regarded as the standard for post-EVAR surveillance, is both costly and associated with potential risks from radiation and iodine contrast exposure, making strategies for reduction of follow-up intensity of interest.[8,9] Patients at low risk of late complications might require less intensive postoperative surveillance. Identification of individual risk factors for stent failure may allow surveillance to be tailored, focusing on patients at higher risk and reducing the surveillance costs for those at lower risk.[4,7,10,11]

Aneurysm sac shrinkage has been proposed as a marker of successful endovascular aneurysm exclusion.[11,12,13] Consequently, it could be expected that patients who have significant shrinkage of the sac in the early postoperative phase would experience fewer complications, and consequently require less intensive imaging surveillance. The aim of this study was to evaluate the role of early AAA sac dynamics in determining long-term outcome after EVAR.

METHODS

This study involved three institutions with experience in EVAR, performing over 50 annual procedures each. Two institutions are university hospitals (Uppsala University Hospital, Uppsala, Sweden, and Erasmus University Medical Centre, Rotterdam, The Netherlands), and the third is a county hospital (Gävle Hospital, Gävle, Sweden). The study complied with the Helsinki declaration on research ethics, and local procedures for ethical clearance were followed at each participating centre.

Patients

All patients treated with EVAR from January 2000 to December 2011 at the three centres were assessed. Patients with a history of aortic reconstructive surgery or mycotic aneurysm were excluded. All three institutions used a 55-mm maximum diameter threshold

for AAA intervention, and operated on smaller aneurysms only in the event of symptoms or accelerated growth. The inclusion criteria were: treatment of infrarenal aortoiliac aneurysm; and availability of two consecutive postoperative image examinations with the same technique (CTA or duplex ultrasound imaging) 6–18 months apart, with the first scan performed within the first 30 days after surgery, as recommended by the Society for Vascular Surgery (SVS) reporting standards for EVAR.[14] Preoperative examinations were used only when no early postoperative imaging was available and if carried out within 60 days before EVAR. The second of the two scans was considered the index examination. The measurement collected was the change in maximum aneurysm sac diameter between the first and second examinations. Patients who had two different imaging modalities during the first 18 months after EVAR were excluded from the assessment of sac dynamics owing to variation between diameter measurements between the tests.

Postoperative image surveillance protocols

Protocols for postoperative surveillance differed between institutions, and also evolved over time. Typically, however, CTA, duplex ultrasonography or both were performed at regular intervals for all patients. All patients were considered eligible independently of the protocol followed, as evaluation of differences in surveillance strategy was not the aim of this study. However, preference was given to CTA-based measurements when CTA and duplex images were available, to reduce observer variability and allow *post hoc* confirmation of diameters. CTA measurements were done using outer-to-outer diameters, and duplex ultrasonography using leading-edge-to-leading-edge measurements. Each institution used the same methodology for assessment of aneurysm diameter throughout the study.

Data management

Data from each institutional database were anonymized and entered into a study-specific database that recorded clinical and anatomical baseline characteristics, and procedural details including date, timing, intraoperative data, as well as endograft model and configuration. All image data were scrutinized by a single experienced vascular surgeon at each centre and the following endpoints were registered: diameter, and follow-up information including all registered complications and secondary interventions. All CTAs included a late arterial phase. Maximum diameter was used for assessment of sac dynamics as recommended in the SVS reporting standards for EVAR.[14]

Definitions

Early sac shrinkage was defined as the difference in maximum diameter between the first (within 30 days) and the second (after 6–18 months) scan. The second was considered the index examination. Intraoperative complications were considered to have

occurred if the device was not deployed at the intended position, if type I or III endoleak or graft obstruction was present, or if E unplanned endovascular or surgical procedures were necessary. Clinical events (complications) were defined as any of the following occurrences after the index examination: direct (type I or III) or undetermined endoleak, endograft occlusion, postimplantation rupture, endograft infection, migration exceeding 10 mm or device integrity failure. Undetermined endoleak was recorded if contrast was visualized outside the endograft and within the aneurysm sac, but the source could not be attributed to failure of a proximal or distal seal or patent aortic branch vessels. Persistent or late-onset type II endoleaks were considered separately, defined as type II endoleaks being present beyond the first postoperative examination, or presenting after a previous endoleak-free examination. Secondary interventions were those performed to resolve or prevent a possible complication, and included endovascular procedures (proximal cuff and stent implant, distal extension implant, catheter-based thrombolysis, iliac stenting, coil or glue embolization of aortic branch vessels) as well as surgical procedures (balloon thrombectomy, femorofemoral crossover, conversion to open repair, open or laparoscopic ligation of collaterals). Early complications were those that occurred before the second (index) examination, and late complications those that occurred after this interval.

Shrinkage categories

Patients were divided into three groups, according to the observed AAA sac dynamics at 1 year. A 5-mm threshold was selected, as suggested by the SVS reporting standards for diameter changes in the aneurysm sac.[14] If the maximum aortic diameter increased, remained stable or decreased by less than 5 mm, patients were included in the no shrinkage group. A reduction in AAA diameter of between 5 and 9 mm was categorized as moderate shrinkage, and a reduction of 10 mm or more as major shrinkage.

Endpoints

The primary endpoint of this study was freedom from any complication. Secondary endpoints were freedom from reintervention, freedom from postimplantation rupture, freedom from direct or undetermined endoleaks, freedom from persistent or late-onset type II endoleaks and freedom from endograft occlusion. Only events occurring after the index imaging, which was used to categorize patients, were considered in this analysis.

Statistical analysis

Categorical variables were compared by means of χ^2 linear-by-linear association tests. Continuous variables are presented as mean(s.d.) if distributed normally and otherwise as median (range or i.q.r.), with analysis using one-way ANOVA for linearity. Estimates for the primary and secondary endpoints were obtained using the Kaplan–Meier method

and compared by means of the log rank test for equality. A multivariable Cox regression model was created to assess the independent influence of early sac dynamics on late complication rates; variables included were: early sac dynamics, baseline AAA diameter, rupture as surgical indication, use of aortomonoiliac stentgraft, occurrence of intraoperative complications, and development of complications before the index examination. Selection bias was explored by comparing baseline characteristics, overall survival, duration of follow-up, and complication and secondary intervention rates in patients included or excluded from the present study; in this analysis the latter patients were those who survived the first 6 months, and were excluded only owing to lack of two consecutive imaging examinations. Similarly, analysis of the primary endpoint was also performed after excluding patients who had surgery for ruptured AAA. To test the validity of categorization, the correlation between absolute and relative diameter changes was tested using Spearman's ρ, and comparison between absolute and proportional shrinkage was performed for the primary endpoint. All tests were two-sided, and $P < 0{\cdot}050$ was considered significant. Statistical analysis was done using SPSS® version 20 (IBM, Armonk, New York, USA).

RESULTS

From 2000 to 2011, 840 patients were treated with EVAR in the three participating institutions. Of these, 45 died within 6 months (27 operated on for ruptured AAA) and 198 were excluded as two equivalent consecutive scans were not available within the specified interval, leaving 597 (71·1 per cent) for assessment of early AAA sac dynamics. In 284 patients (47·6 per cent of the 597) no shrinkage was observed. Among these, growth of 5 mm or more was noted in 14 (2·3 per cent). Moderate shrinkage (5–9 mm) was registered in 142 patients (23·8 per cent) and major shrinkage (at least 10 mm) in the remaining 171 (28·6 per cent). The following endoprostheses were used in this cohort: 202 Excluder® (W. L. Gore and Associates, Flagstaff, Arizona, USA), 189 Endurant™ (Medtronic CardioVascular, Santa Rosa, California, USA), 160 Zenith® (Cook, Bloomington, Indiana, USA), 25 Talent™ (Medtronic CardioVascular) and 21 others. The median interval between the first and second (index) examination was 360 (i.q.r. 264–397) days. Baseline characteristics are described in Table 1.

Freedom from late complications, according to aneurysm sac shrinkage

The total follow-up for the three groups was similar (median 3·1–3·2 years) (Table *2*). The follow-up of interest for this study (after index image examination) was also similar (median 2·2 years). A total of 58 patients (9·7 per cent) developed complications during follow-up. These were more frequent in the no shrinkage group than in the moderate

and major shrinkage groups (12·7, 9·9 and 4·7 per cent respectively; $P = 0{\cdot}038$). Four years after the index imaging, the rate of freedom from complications was estimated at 84·3 (95 per cent confidence interval (c.i.) 78·7 to 89·8), 88·1 (80·6 to 95·5) and 94·4 (90·1 to 98·7) per cent respectively (Figure 1).

Table 1. Baseline characteristics of the three subgroups, based on early sac dynamics

	No shrinkage ($n = 284$)	Moderate shrinkage ($n = 142$)	Major shrinkage ($n = 171$)	$P^{\P}$
Age (years)[a]	74·2(7·2)	73·4(7·3)	72·1(7·6)	0·018#
Sex ratio (M:F)	243:41	114:28	149:22	0·462
Medical history				
Ischaemic heart disease	121 of 274 (44·2)	56 of 137 (40·9)	69 of 162 (42·6)	0·757
Cerebrovascular disease	42 of 273 (15·4)	15 of 137 (10·9)	14 of 163 (8·6)	0·035
eGFR < 60[c]	47 of 184 (25·5)	20 of 86 (23)	36 of 129 (27·9)	0·525
Diabetes mellitus	44 of 274 (16·1)	17 of 137 (12·4)	21 of 163 (12·9)	0·355
Hypertension	175 of 274 (63·9)	86 of 136 (63·2)	107 of 163 (65·6)	0·676
Peripheral arterial disease	38 of 274 (13·9)	21 of 136 (15·4)	23 of 163 (14·1)	0·901
COPD	28 of 273 (10·3)	28 of 137 (20·4)	30 of 158 (19·0)	0·007
Maximum AAA diameter (mm)[b]	59 (36–110)	60 (32–110)	63 (35–139)	< 0·001#
Operative details				
Ruptured aneurysm	14 (4·9)	12 (8·5)	28 (16·4)	< 0·001
Monoiliac stent configuration	11 (3·9)	7 (4·9)	6 (3·5)	0·939
Intraoperative complications	57 (20·1)	35 (24·6)	29 (17·0)	0·710
Proximal cuff/Palmaz®	12	7	9	
Iliac PTA/stenting	20	14	7	
Iliac component extension	6	5	9	
Other endovascular intervention	6	4	2	
Other surgical intervention	4	5	1	
Early postoperative complications§	30 (10·6)	11 (7·7)	6 (3·5)	0·010
Index imaging				
CTA measurements	251 (88·4)	106 (74·6)	148 (86·5)	·445
Interval between two scans used for assessment of sac dynamics (days)[b]	359 (173–541)	364 (170–549)	360 (170–549)	0·698#

Legend: Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.) and †median (range). ‡Estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease formula: eGFR=186×serum creatinine−1·154 ×age −0·203 ×[1·212 if black]×[0·742 if female]. §Before index imaging. COPD, chronic obstructive pulmonary disease; AAA, abdominal aortic aneurysm; PTA, percutaneous transluminal angioplasty; CTA, computed tomographic angiography. Palmaz (Cordis, Bridgewater, New Jersey, USA). ¶$\chi 2$ test, except #one-way ANOVA.

Table 2. Late outcome according to early aneurysm sac shrinkage

	No shrinkage ($n = 284$)	Moderate shrinkage ($n = 142$)	Major shrinkage ($n = 171$)	p[c]
Total follow-up (years)[a]	3·1 (0·5–11·9)	3·2 (0·5–12·2)	3·2 (0·5–12·7)	0·311[d]
Follow-up after index scan (years)[a]	2·2 (0–12·4)	2·2 (0–11·3)	2·2 (0–11·7)	0·277[d]
Complications	36 (12·7)	14 (9·9)	8 (4·7)	0·038
Patients who had secondary interventions	59 (20·8)	17 (12·0)	11 (6·4)	< 0·001
Proximal extension cuff or stent	20	7	2	
Limb component extensions	21	9	3	
Coil/glue embolization	18	1	4	
Open/laparoscopic collateral ligation	9	0	0	
Conversion to open repair	9	2	3	
Postimplantation rupture	3 (1·1)	1 (0·7)	1 (0·6)	0·819
Patients who had direct endoleak[b]	20 (7·0)	11 (7·7)	3 (1·8)	0·040
Type Ia	10	7	1	–
Type Ib	8	4	1	–
Type III	3	1	1	–
Undetermined type	2	1	0	–
Persistent or late-onset type II endoleak	55 (19·4)	9 (6·3)	9 (5·3)	< 0·001[e]
Endograft occlusion	5 (1·8)	3 (2·1)	3 (1·8)	0·979
Endograft infection	2 (0·7)	1 (0·7)	1 (0·6)	0·926

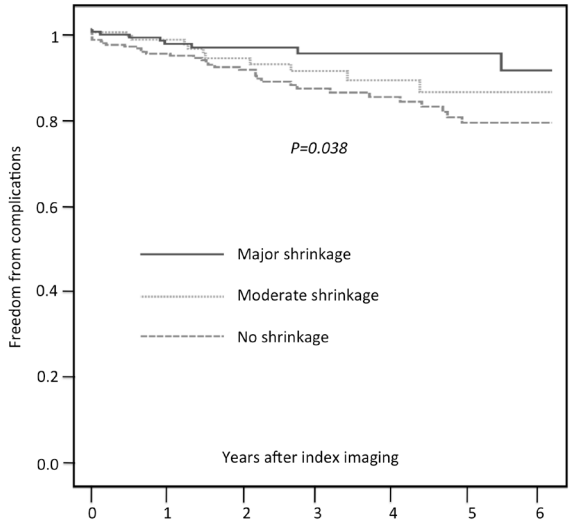
Legend: Values in parentheses are percentages unless indicated otherwise; *values are median (range). Only events after the index scan (at 6–18months) are reported. †More than one endoleak may have occurred in the same patient. ‡Significance derived from univariable time-dependent statistical analysis (Kaplan–Meier analysis and log rank test), except §one-way ANOVA and ¶$\chi 2$ test.

Multivariable testing for potential risk factors for late complications (occurring after the index examination) revealed that, compared with major shrinkage, moderate and no shrinkage increased the risk by 2·1 and 3·1 times respectively (Table 3). Other independent risk factors for late complications were increasing preoperative AAA diameter and a history of early postoperative complications (Table 3). The use of discontinued endograft models did not have independent prognostic influence.

Complications in the major shrinkage group

Eight patients (4·7 per cent) with early shrinkage of the AAA sac of at least 10 mm had late complications. Three developed acute limb ischaemia owing to endograft limb thrombosis, at 1, 11 and 16 months after the index imaging (17, 18 and 26 months after EVAR). There were no imaging changes suggesting an increased risk of these events. Two

patients had type I endoleaks: one type Ia 6 months after the index scan (1·0 year after EVAR) and one type Ib 2·7 years after the index scan (3·3 years after EVAR). The patient with a type Ia endoleak had a very short proximal seal zone (7 mm) at the 30-day CTA, despite a long proximal neck. The patient with a type Ib endoleak had dilatation of an iliac artery that was already wide (24 mm) before surgery. One patient developed a type III endoleak 12 months after the index examination (2 years after EVAR), owing to insufficient component overlap at implantation. One patient had an aneurysm rupture 5·5 years after the index examination (6·5 years after EVAR), without a previously visible endoleak, which was treated successfully by urgent conversion to open repair. Finally, one patient had endograft infection diagnosed at the time of the index examination and died from sepsis before graft excision. This patient had low-grade fever before surgery, and was considered to have had an inflammatory aneurysm; a mycotic primary aetiology was suggested retrospectively.



N at risk, % free of complications, (Standard Error)

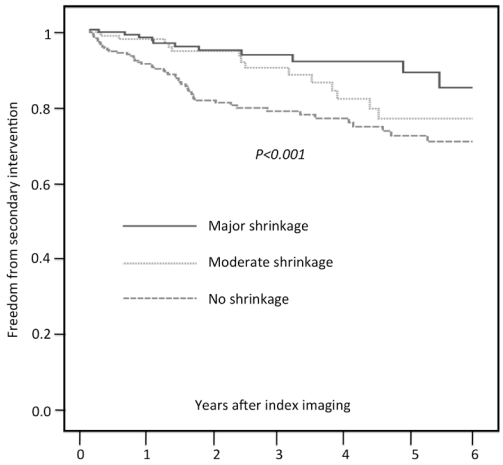
Major shrinkage	171	94	44	22
	-	95.7%	94.4%	90.5%
	(-)	(0.017)	(0.022)	(0.044)
Moderate shrinkage	142	73	38	12
	-	93.2%	88.1%	85.4%
	(-)	(0.025)	(0.038)	(0.045)
No shrinkage	284	151	79	44
	-	90.6%	84.3%	78.3%
	(-)	(0.019)	(0.028)	(0.037)

Figure 1. Kaplan–Meier plot for freedom from late complications, according to early sac shrinkage. $P < 0{\cdot}038$ (log rank test)

Freedom from late secondary intervention, direct endoleak, persistent or late-onset type II endoleak, postimplant rupture and endograft occlusion according to early sac shrinkage

Late secondary interventions after the index imaging were needed in 87 patients overall (14·6 per cent). Patients with no shrinkage had significantly more secondary interventions than those with moderate and major shrinkage (20·8, 12·0 and 6·4 per cent respectively; $P < 0{\cdot}001$) (Table 2). The estimated rate of freedom from secondary intervention 4 years after the index imaging examination (5 years after EVAR) was 76·6 (95 per cent c.i. 70·5 to 82·7), 81·8 (72·2 to 91·4) and 91·6 (85·9 to 97·3) per cent for no, moderate and major shrinkage groups respectively (Figure 2).

Late direct (or undetermined) endoleaks also occurred less frequently in patients with major shrinkage, but no significant difference was observed for patients with moderate or no shrinkage. Estimates for rates of freedom of direct or undetermined endoleaks 4 years after the index imaging were 89·4 (95 per cent c.i. 84·1 to 94·6), 90·7 (83·8 to 97·6) and 97·2 (93·9 to 100) per cent for no, moderate and major shrinkage groups respectively (Figure 3).



N at risk, % free from secondary intervention, (Standard Error)

Major shrinkage	171	92	43	20
	-	94.6%	91.6%	84.7%
	(-)	(0.020)	(0.029)	(0.055)
Moderate shrinkage	142	75	38	12
	-	94.3%	81.8%	76.6%
	(-)	(0.023)	(0.049)	(0.058)
No shrinkage	284	135	72	38
	-	80.8%	76.6%	70.5%
	(-)	(0.027)	(0.031)	(0.039)

Figure 2. Kaplan–Meier plot for freedom from late secondary intervention, according to early sac shrinkage. $P < 0{\cdot}001$ (log rank test)

Table 3. Cox regression analysis of risk factors for late complications

	Hazard ratio	*P*
Moderate shrinkage (*versus* major shrinkage)	2·10 (1·11, 3·98)	0·022
No shrinkage (*versus* major shrinkage)	3·11 (1·75, 5·53)	< 0·001
AAA diameter (per mm increase)	1·02 (1·01, 1·04)	0·001
Treatment of intact (*versus* ruptured) AAA	0·87 (0·43, 1·79)	0·712
Aortomonoiliac stent design	2·00 (0·77, 5·23)	0·156
Intraoperative complications	1·32 (0·85, 2·04)	0·219
Complications before index examination	3·34 (2·21, 5·04)	< 0·001

Legend: Values in parentheses are 95 per cent confidence intervals. AAA, abdominal aortic aneurysm.

Table 4. Selection bias assessment

	Included ($n = 597$)	Excluded[c] ($n = 198$)	P[d]
Total follow-up after EVAR (years)[a]	3·2 (0·6–12·7)	2·8 (0·6–12·1)	< 0·001[e]
Age (years)[b]	73·4(7·4)	73·2(8·0)	0·658[e]
Preoperative AAA diameter (mm)[b]	63(14)	64(15)	0·303[e]
Deaths	156 (26·1)	45 (22·7)	0·396
Total no. of secondary complications	106 (17·7)	31 (15·7)	0·587
Total no. of secondary interventions	109 (18·3)	32 (16·2)	0·591

Legend: Values in parentheses are percentages unless indicated otherwise; *values are median (range) and †mean(s.d.). ‡Owing to image availability. §$\chi 2$ test, except ¶one-way ANOVA.

Persistent or late-onset type II endoleaks were more frequent in the no shrinkage group (19·4 per cent). No difference was observed in the rate of persistent type II endoleaks for the moderate and major shrinkage groups (6·3 and 5·3 per cent respectively). Persistent or late-onset type II endoleaks were associated with sac growth in 24 patients, of whom eight also had type I endoleaks. One patient in each of the moderate and major shrinkage groups had subsequent sac growth associated with a persistent, isolated type II endoleak. No differences between groups were observed in late postimplant rupture or endograft occlusion.

Assessment of selection bias and sensitivity analysis

There were no differences in age and AAA diameter between patients included in, or excluded from the study (Table 4). Included patients had longer follow-up (median 3·2 *versus* 2·8 months after EVAR; $P < 0·001$), but the overall mortality rate did not differ significantly (26·1 *versus* 22·7 per cent; $P = 0·396$). However, similar numbers of overall complications and secondary procedures were observed in both groups.

In 18 patients (3·0 per cent) a preoperative examination was used to determine baseline diameter. No differences were observed in median shrinkage (5 *versus* 4 mm;

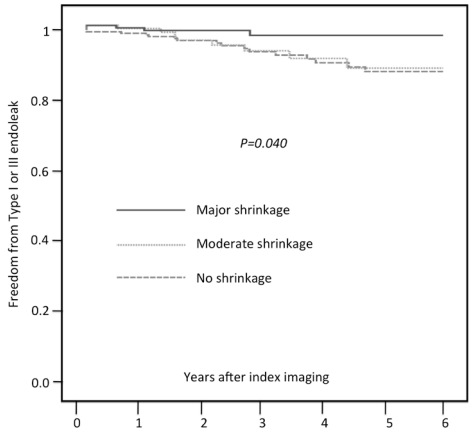
Table 5. Sensitivity analysis based on absolute *versus* proportional categorization

	Proportional categorization of shrinkage (%)		
Absolute shrinkage (mm)	< 10	10–20	> 20
< 5	281 (98·9)	3 (1·1)	0 (0)
5–9	68 (47·9)	73 (51·4)	1 (0·7)
≥ 10	2 (1·2)	55 (32·2)	114 (66·7)

Legend: Values in parentheses are percentages.

$P = 0{\cdot}769$) or group allocations ($P = 0{\cdot}226$) for patients with baseline diameters measured before or after surgery.

There was a strong correlation between proportional and absolute categorization of shrinkage ($\rho = 0{\cdot}988$, $P < 0{\cdot}001$). Proportional categorization of groups (less than 10, 10–20 and more than 20 per cent shrinkage) would have resulted in misclassification of shrinkage in 48·6 per cent of patients with moderate shrinkage defined according to absolute measurements (47·9 per cent misclassified as no shrinkage and 0·7 per cent as major shrinkage) and misclassification of major shrinkage in 33·3 per cent (32·2 per cent as moderate shrinkage and 1·2 per cent as no shrinkage). Importantly, concordance in



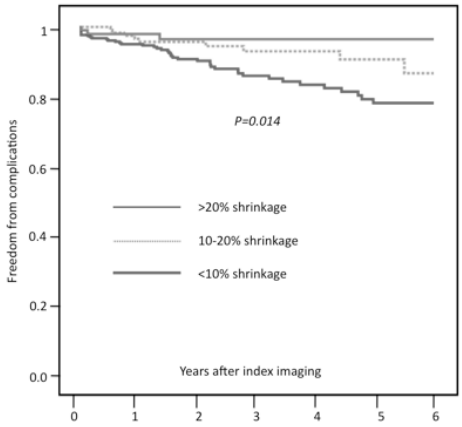
N at risk, % free from type I or III endoleak, (Standard Error)

Major shrinkage	171	97	45	22
	-	98.6%	97.2%	97.2%
	(-)	(0.010)	(0.017)	(0.017)
Moderate shrinkage	142	74	39	12
	-	95.8%	90.7%	87.9%
	(-)	(0.021)	(0.035)	(0.044)
No shrinkage	284	148	80	46
	-	95.8%	89.4%	87.0%
	(-)	(0.013)	(0.027)	(0.031)

Figure 3. Kaplan–Meier plot for freedom from direct or undetermined endoleaks, according to early sac shrinkage. $P = 0{\cdot}040$ (log rank test)

the no shrinkage group was 98·9 per cent (Table 5). Crude complication rates among patients with less than 10, 10–20 and over 20 per cent shrinkage were 12·5, 7·8 and 2·9 per cent respectively ($P = 0{\cdot}002$). Four years after the index scan, the rate of freedom from complications was estimated at 83·5, 93·1 and 96·5 per cent respectively (Figure 4). In a multivariable model, less than 10 per cent shrinkage was associated with an increased risk of complications (HR 2·95, 95 per cent c.i. 1·48 to 6·16) compared with more than 20 per cent shrinkage. Had patients treated for ruptured AAA been excluded, the proportion of patients with complications in each group would not have differed (13·3 per cent for no shrinkage, 9·3 per cent for moderate shrinkage and 4·5 per cent for major shrinkage). Similarly, the Cox regression model did not change when patients with ruptured AAA were excluded from the analysis.

If the definition of shrinkage extended beyond the first year, 46 additional patients (7·7 per cent of all those eligible) would have been classified as having either moderate or major shrinkage. Intervention in one of these patients for an isolated type II endoleak, despite absence of growth, potentially interfered with the natural evolution of the aneurysm sac. One patient was identified as having a type Ib endoleak 6 months after the index procedure, with an uneventful subsequent follow-up. One patient was identified



N at risk, % with clinical success, (Standard Error)

>20% shrinkage	105 - (-)	55 96.5% (0.020)	26 96.5% (0.020)	12 96.5% (0.020)
10-20% shrinkage	141 - (-)	73 95.8% (0,019)	46 93.1% (0.026)	18 86.8% (0.051)
<10% shrinkage	351 - (-)	179 90.3% (0.018)	91 83.5% (0.027)	42 78.2% (0.034)

Figure 4. Kaplan–Meier plot for freedom from late complications, according to early sac shrinkage based on proportional changes (sensitivity analysis)

as having proximal stent migration 5 years after the index procedure, but there was no need for secondary intervention because the proximal seal was sufficient. Two patients had endograft limb occlusion during follow-up. No other complications were noted for this group of patients.

DISCUSSION

The present study confirms that early sac shrinkage is an important prognostic factor for improved late outcome after EVAR. Patients with major sac shrinkage during the early postoperative phase have a low risk of subsequent complications for up to 5 years. Conversely, patients in whom early shrinkage does not occur are at higher risk of complications and more often require secondary interventions. These results may have important implications for individualization of postoperative surveillance.

The importance of sac shrinkage has been investigated previously, and contraction of the aneurysm sac has been suggested as a marker for success after EVAR. In a recent publication involving 1450 procedures, Cieri and colleagues[15] reported that persistent shrinkage of the AAA sac (over 5 mm) was associated with rates of freedom from AAA-related death at 3 and 10 years of 100 and 99·7 per cent respectively. Houbballah and co-workers[11] reported no postimplant ruptures or conversions, and very low rates of type I leak (2·2 per cent) and secondary intervention (3·3 per cent) at a mean follow-up of 4·2 years, for patients with significant sac contraction. Both authors concluded that significant contraction of the aneurysm sac is a robust predictor of success, which is in line with the present findings. However, these studies did not specifically investigate aneurysm sac shrinkage in the early postoperative phase, which limits the potential to apply their findings to individualized surveillance algorithms defined at an early stage.

Lee *et al.*[12] showed that a volume reduction of greater than 10 per cent 6 months after EVAR was a strong predictor of clinical success. The present study confirms this in a larger, contemporary series, adding that different degrees of shrinkage have different prognostic impact. Although measuring volume improved the accuracy of sac dynamics,[16] the added value is still undetermined and it is impractical in a clinical setting, compared with diameter measurement.

The observed differences in type and number of postoperative complications according to sac shrinkage could potentially be related to the preoperative aneurysm anatomy and the sealing length achieved at time of stent implantation. The importance of adequate seal length as verified on early postoperative imaging was confirmed previously as a strong prognostic factor for late EVAR outcome.[10] In the present study, early postoperative complications were more common in the no shrinkage group. Lack of early complications may be interpreted as a surrogate for adequate implantation, which

is in line with previous research. For the present study, however, this hypothesis could not be tested, as detailed baseline anatomical variables and postoperative seal length were not available for all patients.

Using sac shrinkage as a marker for success may not be applicable to limb occlusion complications. Late limb occlusion occurred uniformly in approximately 2 per cent of patients of all groups (Table 2), suggesting that shrinkage did not affect the risk of this complication in the long term. Most early limb occlusions are detectable on imaging and the result of a technical flaw, whereas late occlusions occur mostly without prior image findings.[17]

The present results have implications for post-EVAR surveillance. After 1 year, patients may be stratified on the basis of sac shrinkage, and postoperative surveillance may be tailored to the expected risk of complications. Here, only 4·7 per cent of the patients with at least 10 mm sac shrinkage at 1 year had late complications, of which only three of eight were potentially preventable or predictable with surveillance imaging (2 type I and 1 type III endoleaks). Early postoperative characteristics could have predicted an increased risk of late complications in these three patients (very short seal or insufficient component overlap). Patients with major shrinkage of the aneurysm sac may benefit from adapted surveillance towards symptom-based investigations only, avoiding the need for routine investigations.[4,8,9]

This study has several limitations, restricting firm conclusions. First, it is a retrospective study and may be subject to selection bias; compliance with institutional surveillance protocols is unknown. Furthermore, thresholds for intervention may have differed between institutions and over time. On the other hand, the results are based on a large international sample derived from prospectively collected data from three different hospitals, using a real-world variety of different endoprostheses. Another limitation is that the population is essentially northern European, and the results may not be generalizable to all ethnic groups. Patient categorization was based on an absolute (not proportional) reduction in diameter. As a result, patients with a smaller preoperative AAA were less likely to show sac shrinkage at 1 year, and similarly patients with ruptured AAAs were more likely to be included in the major shrinkage group (as their preoperative maximum AAA diameter was generally greater). The use of absolute reduction in sac diameter for definition of groups could potentially have resulted in misclassification of smaller or very large AAAs. The sensitivity analysis showed that classification of patients based on proportional diameter decrease would have yielded similar results. Interesting differences at baseline between groups suggest a possible prognostic influence of age, chronic obstructive pulmonary disease, maximum AAA diameter and type of presentation (intact *versus* ruptured AAA). Detailed anatomical baseline characteristics with known prognostic impact (such as iliac diameter or tortuosity) were not available for all patients and could not be integrated into the multivariable model. Furthermore, as not

all patients had the necessary imaging for inclusion, a chance of selection bias remains. The authors assessed the risk of bias by analysing the baseline characteristics and complication rates of patients excluded or included and found no differences, although the duration of follow-up differed slightly. Finally, the temporal restriction on categorization of patients may have resulted in misclassification. In the sensitivity analysis, it was found that a further 7·7 per cent of patients could have been classified as having major sac shrinkage if the difference between scans had been extended beyond 1 year; these patients developed few complications over the course of follow-up. However, the authors opted to restrict the classification interval to allow early stratification.

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Chapter 25

Standard vs. individualized surveillance after EVAR – Study protolol

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BACKGROUND

Endovascular aneurysm repair (EVAR) has gained acceptance as a primary treatment option for elective abdominal aortic aneurysms (AAA). Compared to open surgical repair, EVAR is less invasive and reduces perioperative mortality to approximately one-third.[1] However, a significant number of patients require secondary interventions to maintain adequate aneurysm exclusion and ultimately prevent death from AAA rupture. Post-EVAR complication rates are inconsistently reported to range from 10-30% within the first 5-years, and a persistent risk of rupture is reported at 0.5-1%/yearly. To maintain success and offer timely secondary intervention, intensive image surveillance by either Computed Tomography Angiography (CTA) or Duplex Ultrasound (DUS) has been recommended.[2]

Uncertainty over the adequate surveillance was led to great discrepancy in surveillance protocols.[3] With current surveillance regimens, a large number of post-operative examinations are required to detect complications that prompt treatment.[4] Even when strict imaging protocols are followed, a significant number of secondary interventions are still driven by the presence of symptoms and not by imaging findings. Dias et al., in a cohort of 279 patients, suggested that only 9% of patients actually benefited from yearly CTAs, since only these were subjected to secondary interventions based on asymptomatic image findings.

Surveillance may also have deleterious effects. Cumulative radiation[5] and contrast-induced nephropathy[6] are two potential caveats of CTA-based strategies. DUS-based strategies may be limited by operator-dependence/reproducibility and offer no opportunity for "preventive" treatment of patients with progressive loss of seal or component separation before endoleaks actually occur. Both strategies require significant resource allocation and increase post-implant costs significantly.[7] It is also unclear to what extent secondary interventions in asymptomatic patients are justified.

The difficulty or unwillingness to apply the recommended surveillance strategies is well expressed in a recent publication by Schanzer et al.[8] In this study, half of 20.000 Medicare beneficiaries treated by EVAR were lost to image follow-up at 5-years. Reducing the burden of image surveillance may help resolve this serious failure to comply with current guidelines.

Clarification of risk factors and predictors for late complications has led researchers to suggest stratification of surveillance strategies. Sternberg et al. reported a sub-study of the pivotal and continued-access US Zenith Endovascular trial, retrospectively including 739 patients.[9] Using absence of endoleak on the first postoperative CTA as discriminator, significant differences were found in between groups (aneurysm related morbidity was 83.5% *vs* 55.9% at 5-years). This difference was further enhanced by adding absence of endoleak at 1-year (85.8% *vs* 52.5%). Based on this, the authors suggested that in

patients without early endoleak, the 6-month examination may be waived and duplex surveillance may replace yearly CTA.

Our group has published a study investigating the predictive value of the first postoperative CTA, in resemblance to the prior study by Sternberg et al.[4] The fundamental difference was that seal length was investigated, using centre-lumen line reconstruction. Patients were discriminated on basis of absence of endoleak and sufficient seal. Of the 131 patients included 62 were considered low-risk. In that group, only one aneurysm-related adverse event was registered, (undetected in the immediately prior routine CTA) compared to 19% of patients in the high-risk group. Although limited by the use of a single endovascular device (Gore Excluder), these results suggested that a subgroup of patients could do without routine imaging for the first 5-years (as recommended for open surgical repair patients).[10]

Gill et al recently published a similar study, where 134 patients were included. Absence of endoleak alone on the first postoperative CTA was used as discriminator. Hazard ratio for secondary intervention in patients with endoleaks was 6.01 (95% CI: 2.24 – 16.17). Based on this cohort using several different endovascular devices, the authors conclude that absence of endoleak on early imaging is a strong predictor of the need for secondary intervention.

In another recent study, Troutman et al. reported on 410 patients followed with DUS. In line with the previous observations, the authors suggest that a negative 30-day DUS examination (no endoleak or graft limb stenosis) is highly predictive of the need of secondary intervention. In this study, only 2.2% of patients at low risk (7/325) eventually required treatment during the first 3 years post EVAR, compared to 25% of patients with abnormal findings on DUS.

In cases where doubt subsists regarding the efficacy of the primary repair, comparison to a second postoperative examination could be used as tiebreaker. In another publication by our group, the role of early sac dynamics was investigated by comparison of maximum diameter of two similar postoperative examinations (CTA or DUS) with an interval of 6 to 18 months. No shrinkage was associated with a three-fold risk compared to significant shrinkage (10mm or more), and a two-fold risk compared to moderate shrinkage (5-9mm). Others had proposed that positive sac remodelling could be used as a surrogate for success,[11,12] but none proposed a link between early dynamics with late events.

Although current guidelines suggest a small degree of adaptation of surveillance strategy according to risk,[2] all published data on the subject is retrospective, mostly single-centre and may suffer from significant bias. High quality data, in the format of a randomized controlled trial is necessary to determine if risk-adaptation of postoperative surveillance is a safe and efficient strategy.

RESEARCH QUESTION

In patients submitted to elective endovascular abdominal aneurysm repair, a risk-adapted, low-intensity strategy for postoperative image surveillance is non-inferior to standard surveillance in identifying the need for secondary interventions within the first 5-years after operation.

METHODS/DESIGN

General

This study is a multicentre open randomized controlled non-inferiority trial comparing standard and individualized postoperative surveillance strategies after EVAR. Participating researchers must be vascular surgeons or interventional radiologists certified by national entities. Recruitment is expected to begin in the second semester of 2015.

The trial will follow the recommendations from the Dutch Good Practice Guidelines. Reporting will be done according to the CONSORT 2010 guidelines. Site inclusion requires local Institutional Review Board approval. Written informed consent is mandatory for all patients, and protocol, information and consent forms must be approved by local Research Ethics Committees at each site.

Eligibility criteria

All patients treated in a participating centre for infra-renal degenerative AAA by implant of an aorto-biiliac or aorto-monoiliac stentgraft are eligible for this study. Patients treated for infectious aneurysms, aortic dissection or isolated iliac aneurysms are not eligible for randomization. Patients treated with stentgrafts that do not rely on proximal and distal fixation for success (such as Nellix) are also excluded. In order to reproduce the local reality of recruitment centres, there is no recommendation against recruitment of patients with adverse anatomical features or impaired renal function.

Site recruitment

Study investigators will send invitations to potential recruitment sites, preferentially via national and regional societies throughout Europe. Before the first randomization, each site is given instructions for conducting postoperative surveillance for patients in the study and control groups. Each participating site is expected to provide a checklist for study requirements before the first patient may be randomized.

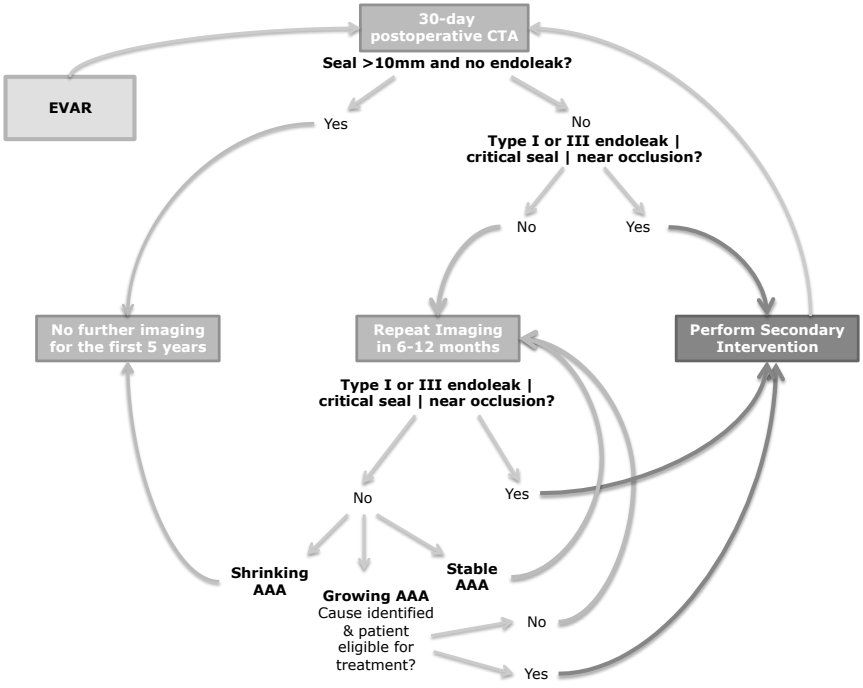

Figure 1. Three way decision model (study group)

Randomization

After informed consent is provided, patients are randomized to either standard or individualized surveillance on a 1:1 ratio. Randomization is expected to occur before the operation, to minimize the chance of selection bias (resulting in patients more likely to have complications are not being offered randomization). Randomization is performed using web-based computer-generated assignment. Blinding of group assignment is not possible, so physician and patient will be made aware of the result of randomization.

Selection of the restricted surveillance strategy

For this study, the investigators gathered current evidence and defined a guide for patient stratification. When randomized for the restricted surveillance strategy, the decision process will depend on individual physician's evaluation of the adequateness of sealing zones and on the presence and characteristics of endoleaks. A thee-way decision model is adopted and applicable after any given image exam (Figure 1). Shortly, physicians must decide if no imaging is necessary up to 5-years, if secondary intervention is necessary or if doubt subsists and another image exam is necessary in 6 to 12 months. After the index operation, patients with >10mm seal zones and absence of endoleaks

will receive no further imaging. Patients with direct (type I or III) endoleaks, critical seal (impending endoleak) or near occlusion will be considered for secondary intervention, unless contra-indicated or refused by the patient. The remainder (patients with type-II endoleaks or short seal zones) will perform a subsequent examination in 6-12 months. After this examination, patients with direct endoleaks, critical seal or near occlusion will be considered for secondary intervention. In the absence of these criteria, sac dynamics will determine the need for subsequent examinations: patients with shrinkage will receive no further imaging, those with stable, non-shrinking sacs will perform a subsequent 6-12 month examination and those with growth will be subject to further studies to determine the cause. If cause of growth can be determined and treatment is feasible, patients should receive secondary intervention. If not, a subsequent 6-12 month examination is recommended. After secondary intervention, the immediate post-operative examination will again determine the need for further imaging.

At any time-point during the 5-year study period a patient randomized to the study group may be considered for no further imaging. The expected proportional reduction in the number of routine postoperative examinations within the first 5 years is calculated in the following manner: 60% of patients assigned to no further imaging at 30-days (67% reduction), 20% after 1 year (50% reduction), and 10% after year 2 (33% reduction): in total 53% reduction ([0.6x67%]+[0.2x50%]+[0.1x33%]). No reduction is expected in 10% of patients. This calculation includes the mandatory 30-day and 5-year examinations. If these are not considered, the expected proportional reduction is (0.6x100%)+(0.2x75%)+(0.1x50%) or 80%.

Choice between CTA and DUS is made according to local practice of recruiting sites, but sub-analysis for CTA-based, DUS-based surveillance will be performed. However, if a DUS-based strategy is followed, an early contrast CT is still suggested to allow sealing zone analysis, only replaced by non-contrast CT if there is renal impairment. All symptom-driven examinations and their findings are documented and associated procedures registered.

Selection of the appropriate active control

Postoperative image surveillance after EVAR is a topic of much controversy and many disparities between centres. In an attempt to provide guidance, both the European Society of Vascular Surgery (ESVS)[2] and the North-American Society of Vascular Surgery (SVS)[10] have issued recommendations, which are not entirely equivalent. The ESVS recommendations are more recent and closer to the common practice in Europe, and were selected as the active control (standard surveillance). The following adaptations were made: plain radiographs were waived, as it is possible to obtain similar information from CTA; all patients should undergo a 5-year CTA, as recommended by the SVS Guidelines.

Image interpretation and analysis

To simulate real practice, no strict protocols for imaging are defined in the study protocol. There is, however, a pre-requisite for DUS accreditation for vascular laboratories in centres performing DUS-based surveillance. A recommendation is made for CTA protocols to use minimum 16-slice detectors and either dual or late-phase runs allowing optimal identification of endoleaks. Although this is not mandatory, recruiting sites are advised to use CT image post-processing software including centre-lumen line reconstructions for improved assessment of seal length, especially in tortuous anatomy.

Primary endpoint

The chosen primary endpoint is freedom from secondary intervention. Asymptomatic image findings (included in the definition of clinical failure[13]) are not included in the primary endpoint to avoid bias favouring patients in the intervention group.

Secondary endpoints

Safety endpoints

AAA-related mortality and post-implant rupture are the two chosen endpoints. Interim analysis at 2 and 4 years will aim to determine if there are differences in these endpoints, motivated by patients' safety. Continuation of the study will depend on absence of difference in these endpoints.

Efficacy endpoints

Clinical success, as defined by the reporting standards for EVAR.[13] The comparison will be made after 5-years, when possible occult asymptomatic complications will become evident in both groups.

Overall survival will also be studied as a secondary endpoint because it is important to understand how the strategy of surveillance may influence survival.

Additionally, changes in renal function will be evaluated to determine the effect of cumulative administration of nephrotoxic contrast agents.

Health economics analysis

In addition to clinical endpoints, a cost-effectiveness and cost-efficiency analysis will be performed, to determine if there is a relevant economical benefit in a using a routine or selective imaging strategy. This will account for the cost of examinations, the cost of routine follow-up visits, the cost of re-admissions and secondary interventions and QUALYs.

Quality of life and patient reported outcomes

Sub-studies are expected to identify possible influence in quality of life and patient-reported outcomes. There are complex and poorly understood issues that may be influenced significantly by restricting image surveillance. These should occur in selected recruitment centres and will require additional workload and separate informed consent.

Sample size

Sample size calculation was based using the following premises:

1. A 30% mortality is expected at 5-years[14]
2. An 80% freedom from secondary intervention is expected at 5-years in the control group[1,15]
3. A 5% reduction is expected in the rate of (image-driven) secondary intervention for the study group, due to the restricted imaging.
4. A 3% non-inferiority limit is the maximum acceptable difference.
5. An 80% power level is selected.
6. A 5% significance level is selected.

Having these premises in mind, 794 patients (397 for each arm) would be required to be 80% sure that the upper limit of a one-sided 95% confidence-interval will exclude a difference in favour of the standard group by more than 3%.

Study duration and follow-up methods

The study is intended to last for 5-years after EVAR. Patients are to be followed by either hospital visits or telephone interviews, scheduled annually. In each visit, CRFs should be completed including health condition, presence of symptoms, all secondary events and interventions. Determination of cause of death should be primarily obtained by autopsy. When unavailable, death certificates should be obtained from local authorities and the patient's family interviewed. All unscheduled visits should be registered, including cause, findings and interventions.

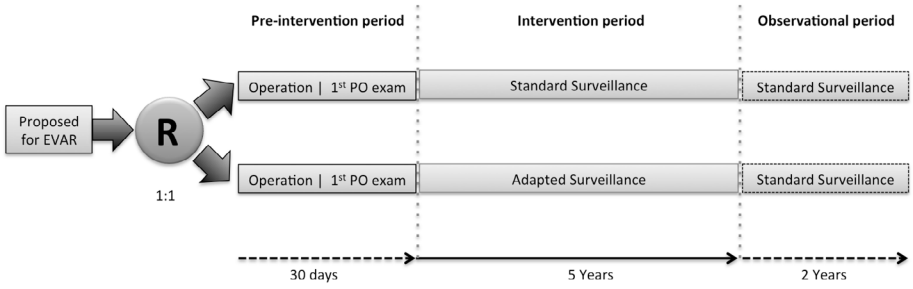

Figure 2 – Study timeline

A local study coordinator per site will be responsible for protocol adherence and all data collection. A national coordinator for each participating country will be responsible for regional logistics and communication with other sites.

To determine if consequences of restricting image surveillance up to 5-years are not simply delaying inevitable secondary intervention, a 2-year follow-up observational analysis after the termination of the study is projected. The study timeline is summarized in Figure 2.

Statistical Analysis

Analysis will include intention to treat (ITT) and per protocol (PP) analysis. All tests will be two-sided, and $P < 0.05$ will be considered statistically significant. If variation in results across recruiting sites is detected, clustering effect by site will be determined using generalized estimating equations.

DISCUSSION

The need to reduce surveillance after EVAR for patients at lower risk of complications has been recognized by numerous publications and by the latest recommendations issued by the European Society for Vascular Surgery and the Society for Vascular Surgery alike.[2,4,10,16,17,18,19] This study aims to provide high-level evidence on the applicability of risk-adaptation of image surveillance after EVAR. It is expected that similar secondary intervention rates occur without compromise of patient safety, but with a significant reduction of image exams for the study group. Health economical analysis is expected to demonstrate a significant reduction in post-placement costs, a relevant contributor to the overall cost surplus of EVAR over open repair.[7] The impact on quality of life is unpredictable, given the complexity of the subject.

Conceptually, this study is designed to be as close to a registry as possible, to reduce the possible bias of strict inclusion criteria or complex protocols, which frequently restrict the external validity of randomized controlled trials.[20] The participating centres that are part of a national or regional vascular registry are encouraged to link registry data to the study so that the proportion of non-randomized patients can be validated. It is also possible to link the randomization procedure, mimicking a registry based randomized control trial (RRCT), such as the TASTE study.[21] Other centres will register non-randomized patients on a log-list.The standard of care used for the control group is the recently published recommended strategy of the ESVS, and the selective strategy relies on the evaluation of the quality of seal achieved after EVAR and the estimated chance of major complications leading to failure and consequent rupture, performed by treating physicians according to the study recommendations, summarized in Figure 1.

Application of the suggested stratified surveillance strategy requires technical imaging skills that may not be generalized or readily available. Specifically, centre-lumen line reconstruction is recommended to adequately determine sealing length. However, most centres routinely performing EVAR prepare cases using this technology, and can easily adapt local logistics to perform similar reconstructions for the first postoperative CTA. Another potential limitation is the limited use of iodinated contrast in patients with renal insufficiency. It is possible to measure seal length using non-contrast CT, but not visualization of endoleaks. However, a combination of non-contrast CT and DUS may provide similar information as an early post-operative CTA and the protocol could therefore be followed accordingly.

The chosen reference standard is based on recommendations issued by the ESVS and SVS (Supplement).[2,10] However, many centres adopt different surveillance strategies, depending on local resources and experience. Also, it is possible that recommendations may change over the course of the study. However, due to the great discrepancy and lack of consensus currently observed regarding optimal surveillance, it is preferable to maintain the societies' recommendations at baseline as the reference standard.

The choice of the primary endpoint is a critical issue of the study. The endpoint of freedom from secondary intervention was chosen based on the assumption that correct identification of patients at risk of complications will not change the rate of secondary interventions significantly, but result in the need for less examinations overall. It is also assumed that restricted imaging for low-risk patients does not result in increased AAA-related death or post-implant rupture. This is supported by several retrospective studies providing homogeneous results. Although prevention of any aneurysm related morbidity is the primary goal of AAA repair, a composite endpoint including both secondary interventions (aimed to reduce the risk of complications) and the complications themselves (including rupture) would result in a conflicting composite endpoint, creating an unacceptable study design. Utilization of only AAA-related deaths or post-implant rupture as primary endpoints would make the study unfeasible due to the expected low rate of events and chance of missing important and determinant events - AAA-related deaths may be missed if patients died before diagnosis and no autopsy was performed. An interesting alternative would be to use the comprehensive complication index, as proposed by Slankamenac et al. The potential advantage of this would be to account for compounding complications in individual patients and also for patient's perceived importance of complications.[22] This method, however, has only been used in retrospective general surgery studies, and therefore we opted for a more conventional dichotomous endpoint. Another alternative would have been to select overall mortality as the primary endpoint. This would account for any possible negative influence of performing more imaging in low-risk patients, but the expected small difference would also make the study unfeasible due to the power sample required.

In non-inferiority studies, selection of the non-inferiority margin is of major importance. Since it is not ethical to create a third arm with "placebo", or no surveillance, the authors have estimated the likelihood of events fitting the primary endpoint had no surveillance been performed based on current literature. The caveat is that this may vary significantly depending on local expertise, complexity of case-mix, time period or device selection. Sample size was also based on the assumption of a 5% difference in the primary endpoint between groups. This is expectable due to the expected lower rate of image-driven secondary interventions in the study group.

The trial is expected to start randomization in the second semester of 2015, and enrolment complete in 2017. Interim analysis is expected to occur after 2 and 4 years, including assessment of safety endpoints, and the definitive results when all patients reach the end of the study. The publication plan is as follows: a first publication will report the study design when inclusion starts, as a letter. A second publication will report cohort data (irrespectable of the randomization) regarding reinterventions and complication during the first year after EVAR, based on data collected at 12 months after inclusion of the last patient. A third publication will be the main publication of the study, based on the data after the 5-year follow-up of all patients. A fourth publication will report on the outcome after the final two-year observation period. Two separate publications will report the results of the health economics and quality of life sub-studies.

In conclusion, there is a clear and urgent need to reduce postoperative surveillance after AAA repair. Retrospective data suggests that risk-adapted strategies are safe and may reduce routine imaging significantly without missing clinically relevant complications. High-quality evidence is lacking, however. We propose the design of a two-arm open randomized controlled trial to determine if a risk-adapted, low-intensity imaging strategy for postoperative surveillance is non-inferior to standard surveillance in identifying the need for secondary interventions within the first 5-years after operation. Additionally, the study will determine the impact of a reduced strategy on quality of life and on healthcare expenses.

SUPPLEMENT

Clinical practice guidelines ESVS (EJVES 2010, Moll et al)

All patients should have a CTA and plain radiographs with anteroposterior and lateral projections at 30 days post- procedure. Level 2c, Recommendation A.

If there is any endoleak or less than one stent component or iliac overlap, CTA at 6 months and 12 months with plain radiographs should be done with adequate treatment if indicated. Level 2b, Recommendation B.

In patients with no early endoleak and good component overlap, the traditional 6-month CTA could be omitted, but a CTA and plain radiographs should be done at 12-month. Level 2b, Recommendation B.

At 12 months, if there is no endoleak and a stable or shrinking AAA, a yearly DU is recommended with plain radiographs using a standardised protocol with anteroeposterior and lateral projections to assess device migration, stent fractures and modular disconnections. If the patient's body habitus preclude an adequate DU, then a non-contrast CT with plain radiographs can be substituted. Level 2b, Recommendation B.

Any increasing aneurysm diameter or new endoleak, after prior imaging studies have suggested complete aneurysm sac exclusion, should prompt complete imaging with CTA and plain radiographs. Level 2b, Recommendation B.

Follow-up with DU, non-contrast CT imaging, and plain radiographs seems reasonable for patients with renal insufficiency at any time after EVAR. Level 3b, Recommendation C.

SVS practice guidelines (JVS, 2009, Chaikof et al)

Surveillance during the first year after EVAR should consist of contrast enhanced CT imaging at one and 12 months. Level of recommendation: Strong Quality of evidence: High

If a Type II endoleak or other abnormality of concern is observed on contrast enhanced CT imaging at one month after EVAR, postoperative imaging at six months is recommended. Level of recommendation: Strong Quality of evidence: High

If neither endoleak nor AAA enlargement is documented during first year after EVAR, Color Duplex ultrasonography is suggested as an alternative to CT imaging for annual postoperative surveillance. Level of recommendation: Weak Quality of evidence: Low

The presence of a type II endoleak should initially prompt continued CT surveillance to ascertain whether the aneurysm is increasing in size. If the aneurysm is shrinking or stable in size, follow-up with CDU is suggested as an alternative to continued CT imaging. Level of recommendation: Weak Quality of evidence: Low

A new endoleak that is detected after prior imaging studies have suggested complete aneurysm sac exclusion should prompt evaluation for a Type I or Type III endoleak. Level of recommendation: Strong Quality of evidence: High

Color Duplex ultrasonography and a non-contrast CT scan are recommended as a substitute for contrast enhanced CT imaging for post-EVAR surveillance of patients with renal insufficiency. Level of recommendation: Strong Quality of evidence: High

Non-contrast CT imaging of the entire aorta is recommended at five year intervals after OSR or EVAR. Level of recommendation: Strong Quality of evidence: High

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SUMMARY

Endovascular aortic repair is a widespread alternative for a multitude of aortic pathologies. The aim of this thesis is to increase the current knowledge on risk factors for endovascular aortic repair – exploring the binomial patient-device – to clarify endovascular-specific complications and to contribute towards a risk-based strategy of postoperative surveillance.

In Part I, the authors addressed controversial issues related to endovascular repair of the thoracic aorta (TEVAR). Chapter 1 elucidates the complexity of type-B aortic dissection, focusing on differences in clinical presentation and pathological mechanisms. A summary of evidence suggests medical treatment with immediate ß-blockade, and intervention for those with complications and possibly for a selected subgroup at high risk of complications. Evidence also suggests endovascular repair is preferable to open surgery, and life-long surveillance is required (irrespective of strategy) due to the persistent risk of aortic complications. In Chapter 2 the authors explored the strengths and weaknesses of the ABSORB (efficacy of endovascular grafting in uncomplicated acute dissection of the descending aorta) trial protocol. Importantly, the primary endpoint is a composite of clinical and image findings (false lumen thrombosis), and the latter may be the dominant but clinically less relevant component. Chapter 3 concerns the critical issue of spinal chord ischemia after thoracic endovascular repair. In the presented case, a patient suffered from paraplegia despite prompt spinal drainage and blood pressure augmentation. Although there was evidence of spinal cord injury, functional recovery occurred months later after intense rehabilitation. Another dreaded complication of TEVAR is addressed in Chapter 4. In response to a publication regarding prevention of endograft collapse, the authors point out that the rarity of this complication does not allow for definite conclusions.

In Part II, the risk factors for endovascular aneurysm repair (EVAR) of the abdominal aorta are explored. Chapters 5 through 8 address the proximal attachment site. Chapter 5 concludes that neck-related risk factors have separable proportional risks, and confirms neck length to be the most important individual contributor to proximal seal failure, in a worldwide cohort of patients treated with a late generation (Medtronic Endurant) device. Chapters 6, 7 and 8 demonstrate reduced significance for proximal angulation and thrombus in early and late outcome, with similar outcomes for patients with and without severe angulation or heavily thrombotic proximal neck. Chapter 9 analyses the influence of family history on the chance of complications after EVAR. Patients with strong familiar association have similar preoperative anatomical features to those without, but have a two-fold increased risk of complications, especially secondary interventions and aneurysm growth.

In Part III, the authors explored the institutional experience on endovascular treatment of aortic aneurysm rupture. In Chapter 10, the authors show that endovascular repair is associated with a early mortality risk reduction III, maintained over mid-term. The study also suggests that endovascular repair may be particularly beneficial for older patients and for those presenting haemodynamic instability. In Chapter 11 the authors demonstrate that prognosis of patients who survive aneurysm rupture is similar to those operated electively. In this study, rupture is associated with an overall 10-fold increase in perioperative mortality, and endovascular repair with a decrease to one-third. The results also show a trend towards improved overall and cardiovascular related survival after EVAR, with malignancy assuming growing preponderance as cause of death.

In Part IV, mid- to long-term device-specific outcomes are reported. In Chapter 12 the evidence on device-specific outcomes is compiled, revealing the paucity in direct comparisons and evidence to support device selection. In Chapters 13 and 14 long-term results of two widely used endovascular devices for AAAs are presented (Gore Excluder and Medtronic Endurant). Chapter 13 focuses on clinical success and morphological changes up to 11 years of follow-up. Although 10-year clinical success (as defined in the SVS Reporting Standards for EVAR)[1] is only 58% and one-fifth require secondary intervention, AAA-related mortality and post-implant rupture rates are very low (2% at 10-years). In Chapter 14 the authors report on the longest follow-up to date (median 48 months) using the Endurant device. Although many patients were treated outside instructions for use in this series, primary clinical success is high and the 4-year estimate of AAA-related mortality is 3%.

In Part IV, possible complications of EVAR are scrutinized, aiming to clarify their significance and potential treatment strategies. In Chapter 15, the incidence, associations and consequences of the post-implantation syndrome are explored. Device fabric is found to be the major contributor to the occurrence of post-implant syndrome (56% for polyester vs. 18% for ePTFE). Other demographic, anatomical or procedural factors did not emerge as risk factors. Importantly, the study also identifies no long-term consequences for affected patients. Chapters 16, 17 and 18 concern the problematic of endoleaks. In Chapter 16, the authors address the conservative management of primary type-1a endoleaks. Under strict conditions – adequate anatomy, correct device oversizing and optimal planning – a conservative approach may yield satisfactory results without exposing patients to unnecessary risk. Chapter 17 is a critical assessment of a systematic review regarding the risk of type-II endoleaks after EVAR. In this publication, the authors point out that rupture associated with isolated type-II endoleaks affects less than 0.1% of EVAR patients, and the connexion is most frequently circumstantial or speculative. Also, there is no hard evidence to show benefit in treatment directed at type-II endoleaks since these therapies are frequently unsuccessful or potentially harmful. In Chapter 18,

the authors show that conservative management of aorto-caval fistula with associated type-II endoleak is possible and may result in positive sac remodelling. In Chapter 19, the authors report long-term outcomes of laparoscopic sac fenestration to treat stable or expanding aneurysms after EVAR. The results suggest a degree of unpredictability for attaining lasting success, with additional treatment being frequently necessary. Chapters 20 and 21 relate to the issue of thrombus deposits and graft occlusion. In the former, the authors show that thrombotic deposits within endografts are common, occurring in 16% of patients over time. Smoking, aorto-uni-iliac devices, barrel-shaped main body and polyester composition all increase the risk of thrombotic deposits. However, no association with thromboembolic events is identified. In Chapter 21, incidence and consequences of graft occlusion are explored. At a median follow-up of 1.7 years, Endurant endograft occlusion occurred in 4% of patients, mostly within 2 months of operation. A technical cause is found in 60% of cases. Lastly, Chapter 22 reveals the dynamics of the iliac seal zone, suggesting iliac dilatation and retraction are common events, and may have clinical consequences. Short seal at 30 days and occurrence of both dilatation and retraction are independent predictors for seal-related complications, while only dilatation over follow-up is a predictor for occlusive complications.

In Part VI, the authors contribute to optimize postoperative surveillance. In Chapter 23 the authors show that evaluation of sealing zones and endoleak presence at the first post-operative CTA is highly predictive of complications over the subsequent 5-years. In the group with adequate seal and no endoleak, 98% of patients were free from complications and over 80 examinations were necessary to identify a potential problem. In Chapter 24 early sac dynamics are used as proxy for successful repair. Those with significant shrinkage were at very low risk of complications for the first 5-years. Chapter 25 is a protocol for a randomized controlled trial testing the safety and efficacy of a risk adapted strategy for surveillance after EVAR in comparison to standard of care.

DISCUSSION

Treatment of aortic pathology by means of endovascular implantation of covered stents is generally associated with improved early outcome.[2,3] The caveat is a higher risk of late complications, which lead to a small but significant persistent risk of disease-related mortality or morbidity. Fine-tuning the binomial patient-device and expanding our understanding of endovascular-specific complications are necessary steps to improve treatment allocation, reduce late morbidity and increase durability, consequently reducing the need for intensive surveillance.

Thoracic aorta: challenges and controversies

Thoracic aortic disease is diverse and complex, and simultaneously infrequent. Aortic type-B dissections have an incidence of 1-2:100.000, and intra-mural haematoma and penetrating aortic ulcer are even less frequent.[4] Consequently, there is a lack of evidence to support decisions as expressed in current guidelines. In acute aortic dissections, the dynamic behaviour and fragility of wall elements are paramount. While aggressive blood-pressure heart rate control seems undisputed,[5,6] dynamic non-invasive imaging performed timely may be a key element for appropriate patient selection and planning for invasive therapy, as Chapter 1 suggests. Also, specific device designs may improve the outcome further.

Current evidence points towards favourable aortic remodelling after endovascular closure of the primary entry tear. This, in turn, may help prevent late aortic-related morbidity and mortality for acute uncomplicated type-B dissections. In Chapter 2, the role of false lumen thrombosis on the natural history of the disease is questioned.[7,8] Consequently, the ABSORB trial[9] future results may lack validity – *i.e.,* statistical significance obtained at the cost of clinical significance. Furthermore, a bias may be present in the definition of false lumen thrombosis, where patients in the intervention group are more likely to be considered as having false lumen thrombosis.

Paraplegia remains a devastating consequence of thoracic aortic repair, particularly when long coverage of aortic segments is necessary and/or collateral pathways (mainly from the subclavian and hypogastric arteries) are absent or sacrificed.[10] Despite optimal prevention strategies, the post repair incidence may be as high as 4%.[11] Generally considered irreversible, Chapter 3 reports partial functional recovery several months after onset of flaccid paresis (SCID category I). This may be explained by brain reorganization due to increased activation of secondary motor brain areas and spatial shift in activation, neural plasticity or progenitor cell-induced spinal chord regeneration.[12,13] Although rare, this case-report suggests that intense rehabilitation programs may be justified to increase the chance of functional recovery.

Endovascular device collapse is another rare yet devastating complication of thoracic aortic repair. The aetiology of collapse may be multifactorial, and underreporting is likely. Since aortic pulsatility is greater in younger subjects and most traumatic cases are performed urgently, a chance of inappropriate sizing (a strong risk factor for collapse) is possible in many cases.[14] Intra-operative confirmation of aortic diameter using calibrated catheters may aid in this setting. Lastly, the influence of device selection on collapse may result from selection bias, due to the preferential use of some devices in cases of non-aneurismal disease. The authors recommend therefore mandatory close observation of patients at higher risk of collapse, and prompt re-intervention should be considered when signs of collapse are identified, by means of implantation of a second endovascular device or conversion to open repair.

Clarifying risk factors for EVAR

The picture is more defined regarding the abdominal aorta, and in particular infra-renal aneurismal disease. However, the multiplicity of variables that potentially influence outcome and sequential introduction of technological advances, many of which device-specific, still result in significant complexity. Data from the United States suggest that a paradigm shift in the treatment of this disease has occurred in the last decade – 4 in every 5 AAA patients are now treated by EVAR.[15] This highlights the necessity to improve the understanding of risk factors and improve selection of patient and devices. Patient-related risk factors are mainly associated with aneurysm anatomy, and particularly with the proximal attachment site.[16] Proximal neck length remains the strongest determinant of failure at short and long-term, even with the use of modern devices that optimize accurate delivery, as shown in Chapter 5. However, there is a decline in the need for secondary interventions at mid-term in a large cohort of over 1200 patients, suggesting improvement when comparing to the pivotal randomized trials.[17,18,19] Aside from this, Chapter 5 also provides relative importance to individual risk factors, which may aid in decision-making and informed consent.

Proximal neck angulation and thrombus are also considered important risk factors for EVAR,[20-22] but their importance is challenged in this thesis. The results of Chapters 6, 7 and 8, complemented by Chapter 5, may impact practice significantly by suggesting similar mid- to long-term outcome for patients with heavily angulated or thrombotic proximal anatomy, compared to those without. It is important to note, however, a higher risk of intra-operative complications. Chapter 8 also dissipates doubts on the durability of EVAR in heavily thrombotic proximal necks, by demonstrating favourable neck remodelling and complete dissolution of thrombus in virtually all patients over time. Caution however is necessary when interpreting the results, due to the fact that most patients were selected and treated by skilled endovascular surgeons who are aware of device characteristics and limitations and optimize pre-operative planning. Therefore, these outcomes may not be reproducible in less experienced settings.

In this thesis, a non-anatomical risk factor for EVAR is also suggested. Chapter 9 finds a two-fold higher risk of complications in patients with a strong familiar association. These novel findings may represent an indirect demonstration of distinct mechanisms in familial aneurismal disease, and suggest that family history should be considered in patient selection and subsequent surveillance. Also noteworthy is that standard anatomical characteristics cannot be used to distinguish between "sporadic" and "familial" groups, since there are no identified differences at baseline.

Applicability of EVAR in the setting of aneurysm rupture

The use of EVAR for ruptured aneurysms is still controversial. Although an endovascular-first strategy has failed to demonstrate benefit in randomized trials,[23,24] the reported

crude mortality for EVAR (around 24%) was consistent and strikingly similar to the mortality rate presented in Chapter 10. These results imply a potential improvement in risk prediction by introducing type of repair into the equation. Also, and comparably to the IMPROVE trial results,[24] older or more unstable patients benefited most from EVAR. The results of Chapter 10 also suggest that pre-operative risk factors have different degrees of influence depending on type of repair, which may improve selection of treatment for individual patients.

The long-term prognosis of patients surviving ruptured AAA repair has been shown to reflect the outcome of electively treated patients.[25] This awareness reinforces the need for optimization of management for ruptured aneurysms. Chapter 11 confirmes this in a more recent cohort, and additionally reveals a shift towards cancer as a dominant cause of late mortality. Consequently, care should focus not only on secondary cardiovascular prevention but also on early detection and referral of malignancies.

Device-specific outcomes after EVAR

The exact influence of the implanted device on outcome is difficult to obtain, due to the multiple variables involved in device selection. To date, there is no randomized trial directly comparing devices, and it is not expectable that there will ever be one. Indirect comparison, which is presented in Chapter 12, is therefore necessary to understand the potential benefits and pitfalls of each design, and its influence on early and long-term outcome. While results are generally good for patients with friendly anatomy using any modern device, adequate selection is critical for challenging cases.

Chapters 6 and 7 test the performance of the Endurant device in heavily angulated proximal neck anatomy, an indication that seems particularly suited for this device. Chapter 13 offers the longest follow-up in literature (up to 11 years) using a device that is virtually unchanged since its introduction (Gore Excluder). Outcomes with the newer Endurant are reported in Chapter 14. Similarly to the previous chapter, these are the longest-term data available (4-years) with this particular device. The very low AAA-related mortality in both cohorts is reassuring, conferring evidence of lasting performance. The additional morphological analysis performed contributes to improve understanding of the post-implantation dynamics.

Other chapters include direct comparison of devices or device characteristics. In Chapter 8, the presence of active fixation was protective against migration in patients with heavily thrombotic proximal necks. The authors consequently recommend use of supra-renal active fixation for these patients. A difference in post-implantation syndrome for polyester and ePTFE based devices is the key finding in Chapter 15, discussed below. Similarly, Chapter 20 confirms that polyster devices are more likely to accumulate thrombotic deposits than ePTFE, in line with findings from others.[26,27]

Endovascular-specific complications after EVAR

Since late complications potentially leading to rupture and/or death are the major limitation of EVAR,[2,28] it is mandatory to have a clear understanding of the true significance. Chapter 15 confirmed the influence of graft fabric on triggering an inflammatory foreign body response, which had only been previously suggested in one small study.[29] The present study adds to contemporary knowledge by providing incidence and clinical impact of this syndrome, improving informed consent. Clarification on the absence of clinical sequelae is also important, suggesting this is a transitory and benign condition. A recent publication has suggested that elevated high-sensitivity CRP levels may be caused by the post-implant syndrome, and are associated with major adverse cardiac events after surgery.[30] This effect, however, is difficult do dissociate with the rise of inflammatory markers generally observed in cardiac events. The study also confirms that polyester grafts are more frequently associated with the post-implant syndrome.

It is consensual that type-I endoleaks require prompt resolution, since the aneurysm remains pressurized and risk of rupture persists.[31] The results of Chapter 16 are, in this sense, counter-intuitive. However, the current study is the first to assess the natural history of untreated primary type-Ia endoleaks, and suggests that there is a role for conservative management as long as there is favourable anatomy for EVAR, planning and sizing were correctly performed and the device is deployed at the intended position. In these conditions, most endoleaks will seal spontaneously once coagulation is normalized and early neck remodelling occurs. This knowledge is particularly relevant when faced with the intraoperative decision to accept a type-Ia endoleak or submit the patient to complex off-label procedures[32] or acute conversion, which carries significant risk.[33]

Regarding type-II endoleaks, Chapter 17 points out that there is no hard evidence to show benefit in treatment directed at type-II endoleaks and these therapies are frequently unsuccessful or even harmful.[34] When sac expansion is observed, efforts should be directed at excluding direct (type I or III) endoleaks, correction of insufficient seal and possibly graft relining.[35,36,37] Following on the subject, Chapter 18 shows that conservative management of type-II endoleaks associated with aorto-cava fistulae is possible and results in favourable aneurysm remodelling. This is contrary to previous reports where prompt closure of the arterio-venous communication has been advocated,[38,39] and suggests that secondary intervention should be reserved for patients with systemic repercussions.

Post-implant sac growth is another concerning complication, as it suggests the aneurysm sac remains pressurized and at risk of rupture.[40] Treatment of these patients may be very challenging, especially in the absence of visible endoleak or after failed percutaneous attempts to treat type-II endoleaks. Chapter 19 represents the largest, even if small (eight patients), published series using a laparoscopic fenestration alternative to

open conversion. The results, although safe in the early period,[41] were disappointing at long-term and should not be used as first-line therapy. This therapeutic option may be reserved for very selected cases only.

Thrombotic complications are also important determinants of success after EVAR. In-graft thrombotic deposits are common and seem to have no clinical consequences, as outlined in Chapter 20, confirming the results of a smaller prior study[27] and refuting the outcome of another.[26] Occlusion, however, seems to be of concern with newer generation devices that feature more flexible limbs and improved delivery systems. Chapter 21 identifies technical causes for most occlusions. Extra attention to avoid and detect technical flaws and more liberal intraoperative and early postoperative (re)intervention strategy may reduce the occlusion rates and improve outcome. Lastly, Chapter 22 calls attention to the importance of sufficient distal seal length. Iliac dilatation has been described before,[42,43] but iliac limb retraction was only suspected in extreme cases.[44] Insufficient seal will result in a higher chance of retraction and facilitate the occurrence of type Ib endoleaks, and consequently optimization of the iliac seal zone is mandatory for prevention of iliac-related complications.

Risk-adapted strategy for postoperative surveillance

After EVAR, intensive image surveillance is recommended to identify potential complications and offer the chance of timely secondary intervention.[45] Uncertainty over the ideal surveillance strategy has led to significant discrepancy between locally adopted surveillance protocols.[46,47,48] Currently, a large number of post-operative examinations are required to detect complications requiring treatment, as expressed in Chapters 23 and 24. Even when strict imaging protocols are followed, a significant number of secondary interventions are still driven by the presence of symptoms and not by image findings.[49] It is also unclear to what extent secondary interventions in asymptomatic patients are justified.

Chapter 23 suggests that the post-operative CTA is a strong discriminator, which may be used to stratify patients for standard or restricted surveillance. This is in line with other retrospective research, also pointing out the predictive value of the first postoperative investigation.[50,51] Chapter 24 conceptually differs from the former in the sense that it requires two consecutive postoperative examinations and stratifies patients according to the early aneurysm sac dynamics. Shrinkage of the aneurysm sac has previously been identified as a surrogate for success,[52,53] but not seen as a tool for risk stratification and consequent adaptation of surveillance strategy.

Based on current evidence, it is clear that contemporary postoperative surveillance strategies are inefficient and excessive. After EVAR, up to 50% of patients are lost to image follow-up, reflecting the difficulty or unwillingness to comply to recommendations.[54] Selection of patients at higher risk and focus image surveillance on these may

reduce the overall burden and improve compliance, with no additional risk for patients. To determine the safety and efficacy of a risk-adapted strategy, a multicentre open non-inferiority randomized controlled trial is under development. All patients electively treated for degenerative infra-renal AAA with an endovascular device that relies on proximal and distal fixation are eligible for randomization. Recruitment is planned to occur in European medical facilities with endovascular experience, provided a checklist of requirements is fulfilled. Randomization to a standard or risk-adapted surveillance is performed before operation to minimize the chance of bias, where patients more likely to suffer from complications are not included. The chosen primary endpoint of this study is freedom from secondary intervention. Secondary endpoints will include safety endpoints (AAA-related death and post-implantation rupture) and efficacy endpoints: clinical success (as defined in the SVS Reporting Standards for EVAR), overall mortality. Quality of life assessment and health economics analysis will be performed in parallel as sub-studies. The duration of the study will be 5-years (intervention period) followed by an extra 2-years (observation period). Although the necessary duration of this trial will be an important shortcoming, the outcome may provide a solution for the challenge of surveillance after EVAR.

In conclusion, endovascular repair has become a valid alternative for thoracic and abdominal aortic diseases, but clarification of risk factors and complications is still necessary. In this thesis, several aspects of patient and device selection are analysed, and complications and their possible treatments scrutinized with the objective of improving outcome. With this knowledge, management of patients with aortic disease may be improved and postoperative surveillance may be adapted to individual risk.

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SAMENVATTING

Endovasculair herstel is een veelvuldig gebruikt alternatief voor een verscheidenheid aan aandoeningen van de aorta met een snelle ontwikkeling in mogelijkheden. Het doel van dit proefschrift is een bijdrage te leveren aan de huidige kennis van risicofactoren voor endovasculair herstel, specifiek gericht op de interactie tussen patiënt en device, om inzicht te krijgen in de complicaties en om een bijdrage te leveren aan een op risico's gebaseerde strategie voor postoperatieve follow-up.

In Deel I worden controversiële onderwerpen behandeld welke gerelateerd zijn aan de endovasculaire behandeling van thoracale aortapathologie (TEVAR). Hoofdstuk 1 behandelt de complexiteit van type B dissecties waarbij specifiek gekeken wordt naar de verschillen in klinische presentatie en onderliggende pathologie. Gebaseerd op de literatuur lijkt momenteel dat conservatieve behandeling met bètablokkers de beste behandeling is voor een ongecompliceerde type B dissectie terwijl een interventie de beste behandeling is voor een geselecteerde subgroep patiënten welke een hoog risico op complicaties hebben. Verder is er ook bewijs dat endovasculair herstel de voorkeur geniet boven open herstel. Levenslange follow-up is noodzakelijk (onafhankelijk van het type behandeling) vanwege het aanhoudende risico op complicaties. In hoofdstuk 2 beschrijven de auteurs de sterke en zwakke kanten van het protocol van de ABSORB-studie (efficacy of endovascular grafting in uncomplicated acute dissection of the descending aorta). Het is belangrijk te realiseren dat het primaire eindpunt van deze studie een samenvoegsel is van zowel klinische als imaging uitkomsten (trombose van het valse lumen) waarbij de laatste van de twee de belangrijkste, maar klinisch minder relevante component is. Hoofdstuk 3 gaat over ruggenmergsischemie na een thoracale endovasculaire behandeling. Er wordt een patiënt besproken met een paraplegie ondanks het direct inbrengen van een spinale drain en het verhogen van de bloeddruk. Hoewel er bewijs was van schade aan het ruggenmerg werd, na een maand van paraplegie, toch een functioneel herstel gezien na maanden van intensieve revalidatie. Een andere gevreesde complicatie na TEVAR wordt beschreven in hoofdstuk 4. Als antwoord op een publicatie over het voorkomen van het collaberen van een endograft hebben de auteurs beschreven dat door de zeldzaamheid van deze complicatie duidelijke conclusies niet kunnen worden getrokken.

In Deel II worden de risicofactoren voor de endovasculaire behandeling van een aneurysma (EVAR) bestudeerd. In hoofdstuk 5 t/m 8 wordt specifiek gekeken naar het proximale deel van de behandeling. De conclusie van hoofdstuk 5 is dat de nek gerelateerde risicofactoren niet allemaal even zwaar wegen en dat de lengte van de nek de allerbelangrijkste factor is voor het falen van de proximale seal. Voor deze studie is een wereldwijd cohort van patiënten gebruikt, welke behandeld zijn met de laatste

generatie endografts (Metronic Endurant). In hoofdstuk 6, 7 en 8 wordt aangetoond dat het belang van angulatie van de nek en aanwezigheid van trombus in de nek minder belangrijk is dan gedacht en dat de resultaten op termijn van deze op zich ongunstige karakteristieken, hetzelfde zijn als voor patiënten met een standaard anatomie. Hoofdstuk 9 analyseert de invloed van de familieanamnese op de kans op complicaties na EVAR. Patiënten met een sterk positieve familieanamnese voor het voorkomen van aneurysmas hebben dezelfde preoperatieve anatomische karakteristieken als de patiënten met een negatieve familieanamnese, terwijl zij wel een tweemaal verhoogd risico op complicaties laten zien. Met name komen meer secundaire interventies en groei van het aneurysma voor.

In Deel III worden de resultaten besproken van de patiënten welke endovasculair behandeld zijn voor een ruptuur van een infrarenaal aneurysma van de aorta abdominalis in het Erasmus Medisch Centrum te Rotterdam. In hoofdstuk 10 beschrijven de auteurs dat een endovasculaire behandeling een twee keer zo kleine kans geeft op vroege mortaliteit en dat dit voordeel enoge jaren behouden blijft. . Tevens werd gevonden dat endovasculair herstel waarschijnlijk het meest gunstig is voor oudere patiënten en voor die patiënten welke zich presenteren met hemodynamische instabiliteit. In hoofdstuk 11 laten de auteurs zien dat de prognose van patiënten die succesvol geopereerd zijn aan een ruptuur van een aneurysma, hetzelfde is als die van patiënten welke electief geopereerd zijn. In deze studie wordt een ruptuur geassocieerd met een tienvoudige toename in perioperatieve mortaliteit, terwijl endovasculair herstel een drievoudige vermindering van mortaliteit laat zien ten opzichte van een open conventioneel herstel. De resultaten laten ook een trend zien richting een verbetering van de overleving in het algemeen en van een cardiovasculair gerelateerde overleving met een verhoging van de kanker gerelateerde overleving.

In Deel IV worden de midden - en lange termijn uitkomsten besproken van de verschillende merken endografts. In hoofdstuk 12 worden de uitkomsten per type endoprothese beschreven waarbij naar voren komt dat er nauwelijks vergelijkingen tussen verschillende devices in de literatuur worden gedaan. In hoofdstuk 13 en 14 worden de lange termijn resultaten beschreven van twee endografts welke wereldwijd veelvuldig gebruikt worden voor de behandeling van abdominale aneurysma's (Gore Excluder en Metronic Endurant). Hoofdstuk 13 richt zich specifiek op het klinische succes en op de morfologische veranderingen tijdens een lange follow-up tot elf jaar. Hoewel het klinisch succes na tien jaar (zoals gedefinieerd in de SVS reporting standards for EVAR)[1] slechts 58% is en een vijfde van de patiënten secundaire interventies ondergaat, is de aneurysma-gerelateerde mortaliteit en de postoperatieve ruptuurkans erg laag (2% na tien jaar). In hoofdstuk 14 worden de resultaten beschreven van de langst beschikbare follow-up (mediaan 48 maanden) van de Endurant endoprothese. Ondanks het feit dat

veel patiënten behandeld werden buiten de instructions for use (IFU), was het primaire klinische succes hoog en de vierjaars aneurysma gerelateerde mortaliteit slechts 3%.

In Deel V worden de mogelijke complicaties na EVAR onder de loep genomen om hun klinisch belang te bepalen en om te zien wat de beste behandeling is. In hoofdstuk 15 wordt de incidentie en de consequentie van het postimplantatiesyndroom (PIS) beschreven. De belangrijkste factor hierin bleek het materiaal van de endoprothese te zijn (56% bij polyester graft vs. 18% bij ePTFE). Andere demografische, anatomische of procedure gerelateerde factoren werden niet als risicofactor gevonden. Er bleken geen consequenties op lange termijn te zijn voor patiënten met het postimplantatie-syndroom. Hoofdstuk 16, 17 en 18 concentreren zich op het probleem van endoleaks. In hoofdstuk 16 beschrijven de auteurs de conservatieve behandeling van primaire type 1A endoleaks. Als aan strikte voorwaarden wordt voldaan gunstige anatomie, voldoende oversizing en optimale uitvoering – kan een conservatieve behandeling bevredigende resultaten geven zonder dat de patiënt blootgesteld wordt aan onnodige risico s. hoofdstuk 17 is een kritische beoordeling van een systematisch review over het risico van type 2 endoleaks na EVAR. In deze publicatie beschrijven de auteurs dat de kans op een ruptuur geassocieerd met een geïsoleerd type 2 endoleak lager is dan 0.01% voor alle EVAR-patiënten en dat de relatie type 2 endoleak-ruptuur vrijwel altijd speculatief is. Tevens is er geen hard bewijs dat de behandeling van type 2 endoleaks zinvol is, aangezien deze behandeling meestal niet succesvol is, maar wel potentieel schadelijk voor de patiënt blijkt te zijn. In hoofdstuk 18 laten de auteurs zien dat de conservatieve behandeling van een aortocavale fistel na EVAR in aanwezigheid van een type 2 endoleak tot goed resultaat leidt en resulteert in een krimp van de aneurysmazak. In hoofdstuk 19 rapporteren de auteurs de lange termijn uitkomsten van laparoscopische aneurysmazakfenestratie bij patiënten met een stabiele of groeiende diameter van het aneurysma na EVAR. De resultaten laten zien dat het succes onvoorspelbaar is waarbij de behandeling meestal gevolgd moet worden door aanvullende behandelingen. Hoofdstuk 20 en 21 beschrijven het fenomeen van ophoping van trombus en occlusie van de endograft. De ophoping van trombus in een endograft komt veel voor, bij 16% van de patiënten. Roken, implantatie van een aortomono-iliacale(AUI) endograft, een wisselende diameter van het lijfje van de endograft en polyester als materiaal van de endoprothese verhogen allemaal het risico op deze trombusformatie. De aanwezigheid van trombus in de endograft was niet geassocieerd met trombo-embolische complicaties. In hoofdstuk 21 wordt de incidentie van endograft occlusies beschreven en het klinische gevolg. Na een mediane follow-up van 1.7 jaar werd een occlusie van een endurant endoprothese gevonden bij 4.7% van de patiënten, deze occlusie trad meestal binnen twee maanden na de operatie op. In 60% van de gevallen bleek er een technische oorzaak aan ten grondslag te liggen. In hoofdstuk 22 wordt de dynamiek van de iliacale sealingzone beschreven waarbij naar voren komt dat iliacale dilatatie en retractie van

de endoprothesepoot vrij veel voorkomen en dat dit klinische consequenties heeft. Een korte seal, dertig dagen na de operatie, is een predictor voor complicaties.

In Deel VI leveren de auteurs een bijdrage aan de optimalisatie van postoperatieve follow-up na EVAR. In hoofdstuk 23 laten de auteurs zien dat de sealingzone en de aanwezigheid van endoleaks op de eerste postoperatieve CT-scan een hoge voorspellende waarde hebben voor het optreden van complicaties binnen de eerste vijf jaar. Indien een patiënt adequate seal heeft en geen endoleak, blijkt de kans 98% te zijn dat er de eerstvolgende vijf jaar geen complicaties optreden. In dit geval blijkt tevens dat er 80 onderzoeken nodig waren voordat één potentiele complicatie gevonden werd. In hoofdstuk 24 wordt de dynamiek van de diameter van de aneurysmazak gebruikt als proxy voor een succesvolle uitkomst. De patiënten die een significante krimp van hun aneurysma lieten zien gedurende het eerste postoperatieve jaar bleken een zeer laag risico te hebben op complicaties binnen vijf jaar. In hoofdstuk 25 wordt een protocol beschreven voor een op te zetten, gerandomiseerde multicentrische studie (RCT) om de veiligheid en efficiëntie van een risicogestuurde surveillance na EVAR te bestuderen in vergelijking met de "standard of care".

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54. **Bastos Gonçalves F**, Oliveira NF, Ultee KH, Hoeks SE, Stolker RJ, Verhagen HJ. Iliac seal zone dynamics and clinical consequences after endovascular aneurysm repair (submitted)

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2. **Bastos Gonçalves F**, White GF, Perdikides T, Verhagen HJM. Endoluminal Treatment of Infra-renal Abdominal Aortic Aneurysm. In: Vascular Surgery: Cases, Questions and Commentaries – 3rd edition. George Geroulakos, Bauer Sumpio, editors. London: Springer-Verlag London Limited, 2011, p.25-42
3. **Bastos Gonçalves F**, Metz R, Hendriks JM, Rouwet EV, Verhagen HJM. Natural history (of type B-dissections). Which patients whould be treated and how? In: Jean-Pierre Bequemin, editor. Controversies and Updates in Vascular Surgery. Torino: Edizioni Minerva Medica SPA; 2011, p.415-420
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6. **Gonçalves FB**, Voûte MT, de Vries JPPM, van Keulen JW, Moll FL, van Herwaarden JA, Verhagen HJM. About fitness, safety and risk of AAA repair,what is the best... in extremely angulated proxi-

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PhD PORTFOLIO

Summary of PhD training and teaching activities

PhD student:	Frederico M. V. Bastos Gonçalves	PhD Period: 2010-2014
Department:	Vascular Surgery / Anaesthesiology	Promotors:
Research School:	COEUR	H.J.M. Verhagen & R.J. Stolker

1. PhD Training		
Courses and academic skills	**Year**	**ECTS**
- Associate Editor - Rev Port Cir Cardiotorac Vasc	2011-2014	2.0
- Coordinator of the Vascular Biology Working Group of the Portuguese Society of Angiology and Vascular Surgery	2010-2014	4.0
- Reviewer of the European Journal of Vascular and Endovascular Surgery	2010-2014	2.5
- Reviewer of the Journal of Vascular Surgery	2012-2014	1.5
- Reviewer of the Journal of Endovascular Therapy	2012-2014	1.5
- Endovascular aortic procedures – Advanced (Rotterdam)	2011	0.3
Seminars & Workshops		
- Journal club, Research meetings, Vascular Rounds (Rotterdam, Lisbon)	2010-2014	5.7
- COEUR PhD Day	2011	0.8
- Global Science Forum (Berlin)	2014	1.6
- Aortic Endovascular Therapies – Faculty Education Program (New York)		1.6
Presentations (0.5 points/each)		
- National lectures	2010-2014	4.5
- International lectures	2010-2014	5.0
Symposia & Meetings (0.3 points/day)		
- National conferences	2010-2014	12.0
- International conferences	2010-2014	12.6
2. Teaching		
Supervising	**Year**	**ECTS**
- MSc students at the Erasmus medical Centre	2013-2012	1.2
- MSc students at Centro Hospitalar de Lisboa Central (Portugal)	2012-2014	1.2
- Supervisor of Residency in Vascular Surgery (Portugal)	2013-2014	1.2
- Supervisor of Master Thesis	2013-2014	1.2
- Lecturing	2013-2014	3.0
Other activities		
- Organization: Haemorrheology, Haemostasis and Inflammation in Vascular Pathology Meeting (Lisbon)	2012	1.5
- Organization: Advanced Course on Deep Vein Thrombosis (Lisbon)	2014	1.5

CURRICULUM VITAE

Frederico Miguel Valido Bastos Gonçalves was born January 6th, 1977 in Lisbon, Portugal. He studied in Lisbon until 1991 and subsequently at the American Community School of Abu-Dhabi, UAE. He attended the Medical School of the University of Lisbon from 1995-2001, where be became interested in the field of vascular disease. After a 2-year general residency at the Santa Maria Hospital in Lisbon, he started his specialized training in Angiology and Vascular Surgery at the Santa Marta Hospital in Lisbon in 2003. In 2009 he spent three months as a fellow at the Erasmus Medical Centre, in Rotterdam. Since 2010 he is a staff member at the Department of Angiology and Vascular Surgery of Santa Marta.

In February 2010 he passed the national exam for the degree of Specialist in Angiology and Vascular Surgery with distinction. In September the same year he passed the European Board of Vascular Surgery Exam and obtained the degree of Fellow of the European Board of Vascular Surgery.

In 2010 he joined a PhD program at the Erasmus Medical Centre, under the supervision of Professors Hence J. M. Verhagen and Robert J. Stolker, on the topic of endovascular treatment of the aorta. Aside from the Erasmus Medical Centre, the departments of Vascular Surgery of the Utrecht University Medical Centre, of the Antonius Ziekenhuis in Nieuwegein and of the Uppsala Academic Medical Centre (Sweden) also contributed to the fulfilment of his research. From 2010 to 2013, he divided his time being a researcher in The Netherlands, and a surgeon in Lisbon. Since 2013 he is an Assistant Professor of Angiology and Vascular Surgery at the NOVA Medical School, in Lisbon.

He is the coordinator of the Vascular Biology Workgroup of the Portuguese Society of Angiology and Vascular Surgery since 2010, and an associate editor of the Portuguese Journal of Cardiothoracic and Vascular Surgery (Rev Port Cir Cardiotorac Vasc) since 2012. He is also a reviewer for the European Journal of Vascular and Endovascular Surgery, for the Journal of Vascular Surgery and for the Journal of Endovascular Therapy.