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## Overview of one decade developments of an EVAR endograft

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# **Overview of one decade developments of an EVAR endograft**

**Steffan Gerhardus Johannes Rödel**

Steffan G.J. Rödel, MD, MSc

“Overview of one decade developments of an EVAR endograft”

PhD thesis, University Medical Center Groningen, with a summary in Dutch

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# Overview of one decade developments of an EVAR endograft

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# Chapter

# 1

General introduction and  
outline of this thesis

## General introduction and outline of this thesis

Abdominal aorta aneurysm (AAA) diameter growth is often asymptomatic until a sudden rupture of the aneurysm occurs, which then becomes a life-threatening medical emergency. This may result in a hypovolemic shock state due to ensanguining blood loss through the rupture outside the aorta and into the retroperitoneal space or free intra-abdominal cavity. As a result, hypoperfusion to the abdominal organs and lower extremities may also occur.

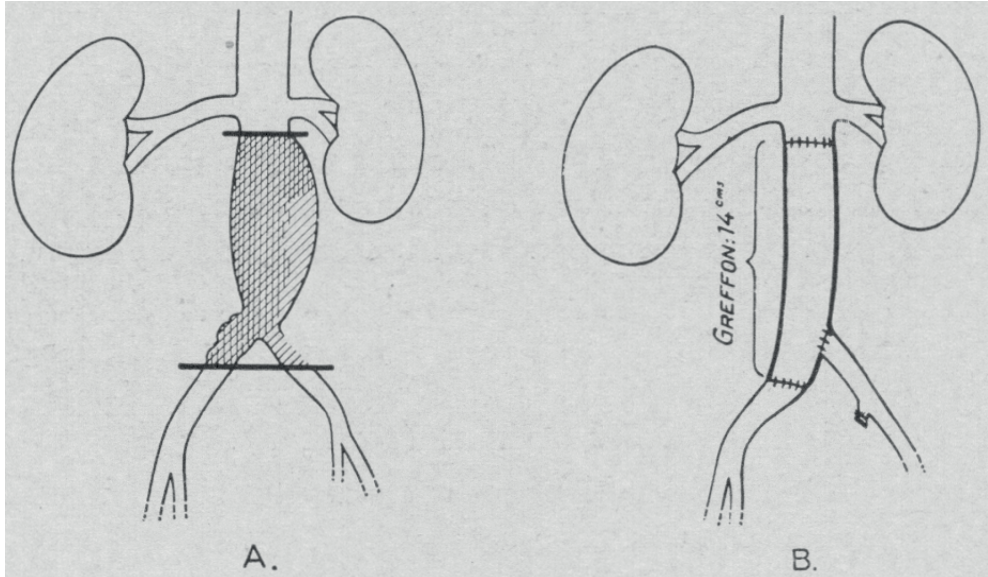
The most widespread definition of an AAA is an aortic diameter of 3.0 cm or more, although in women and Asian population this threshold may be set lower. The average growth rate of AAA between 3.0 and 5.5 cm is 0.2-0.3 cm per year and growth rate increases with increasing AAA diameter according to the law of Laplace in which spherical wall pressure increases with squared of the radius. AAA prevalence depends on screening study inclusion criteria and ranges between 1.3% and 5.1 % in the USA <sup>1,2</sup>.

In previous studies, increased rupture risk was related to current smoking, female sex, lower 1-second forced expiration volume (FEV<sub>1</sub>), higher mean blood pressure and larger initial AAA diameter. Elective AAA repair is considered when the aortic diameter reaches a minimum of 5.0 cm for females and 5.5 cm for men <sup>3,4</sup>.

When AAA diameter ranges between 4.0 and 5.0 cm the rupture risk is 1% per year, but there are circumstances in which this risk is higher, i.e. when growth rate is higher than 0.3 cm per year or when the aneurysm has a saccular instead of a fusiform appearance. Nevertheless, the mortality risk associated with intervention in this group is usually higher than the rupture risk so surveillance is the standard care. In order to prevent rupture, a preemptive lifesaving operation without significant comorbidity and with long-term survival is the ultimate goal of treatment.

The Greek verb "aneurynein" means to widen. In ancient publications aneurysms were already classified into two types; the first type was the post-traumatic or false aneurysm with blood confined in the local surrounding tissue around the vessel mimicking vascular dilatation and the second type was the true aneurysm in which widening of the entire involved aortic wall was the cause. Before the 1950s different approaches in the treatment of aneurysm disease were suggested such as aneurysm ligation, compression, extirpation and external wrapping<sup>5</sup>. Since then treatment modalities have clearly evolved. Currently, modes of repair include open surgical aneurysm repair (OSAR), endovascular aneurysm repair (EVAR) (including fenestrated endovascular aneurysm repair (FEVAR), branched endovascular aneurysm repair (BEVAR), chimney repair (ChEVAR), endovascular aneurysm sealing (EVAS) and laparoscopic surgical aneurysm repair (LSAR).

In 1948 the famous scientist Albert Einstein was operated. An AAA was discovered during explorative laparotomy. The aneurysm was wrapped in cellophane by Dr Nissen and Einstein recovered prosperously. He did not withdraw from his pipe smoking habits and lived until he suddenly died 7 years later in 1955. At autopsy a ruptured AAA was diagnosed<sup>6</sup>.



In February 1951 in the United States Dr Freeman performed the first successful OSAR of an AAA using an autogenous iliac vein as an aortic replacement. The anterior wall of the aneurysm was preserved and used as a bolster to prevent the blowout of the graft iliac vein. The patient was doing well one year thereafter<sup>5</sup>.

Simultaneously that year in Europe on March 29, Charles Dubost performed OSAR using a preserved homologous thoracic aortic graft of a 20-year-old female donor for replacement. The 50-year-old patient had an AAA with intermittent claudication with a walking distance of 100 meters due to left iliac occlusion. Only “wrapping” of the AAA would not be sufficient as this would leave occluded iliac artery untreated. Dubost hypothesized that removing the AAA, performing an endarterectomy of the iliac artery and restoring aorta-iliac continuity using a preserved aorta graft could be the solution. A left thoraco-abdominal extraperitoneal approach was performed clamping the infrarenal aorta just distal to the renal arteries and gaining control of the iliac arteries. The graft was sutured end-to-end with the right common iliac artery. The left common iliac artery, after removal of the obstruction, was anastomosed to the graft. The patient survived for eighth years<sup>5,7</sup>.

In March 1987 Nicolai Volodos and his team introduced the first endovascular aortic stent graft in the world. This thoracic aortic stent graft functioned for 18 years. His team introduced the first abdominal stent-graft as well in 1989, although in this patient the operation was converted to open surgery due to a twist of the contralateral limb.

Juan Parodi from Argentina worked on animal experiments and initial human cases exploring the feasibility of AAA exclusion by placement of an intraluminal stent-anchored Dacron prosthetic graft using retrograde cannulation of the common femoral artery under local or regional anesthesia. In 1991 both Volodos and Parodi published their results in two landmark publications which could be pointed as the start of the EVAR era worldwide<sup>8,9</sup>.

Over time, technological advances have improved the capacity of endografts to treat AAAs. Improved fabrics, better scaffolding designs and materials, low profile delivery systems, more precise deployment mechanisms, enhanced fixation, greater conformability, and diverse modular components were developed and applied to newer generation endografts. These technological improvements combined with increased experience and selection of patients within the specified instructions for use (IFU), led to higher reintervention-free survival and higher freedom from aneurysm-related death after EVAR. In the “standard AAA anatomy” without adverse features a broad range of CE marked endovascular stents can be selected in which the instructions for use are generally overlapping. Yin et al., examined the last decade outcomes of elective EVAR in a joined cohort of 30,076 AAA patients<sup>10</sup>. He reported an 1.2% perioperative mortality and a 30-day major complication rate of 4.5%. As a consequence, it looks like there is still work to be done to improve these results.

It is clear that with a short infrarenal aortic neck length (<15 mm), a neck angulation outside IFU (60-90 degrees or more), or a reversed conical neck, safe and durable infrarenal endograft placement is less likely. With FEVAR and BEVAR grafts, the clinical problem of inadequate neck length in the treatment of aortic aneurysm could be addressed. The fenestrated or branched segment of the stent are off-the shelf or custom made designed facilitating that the first sealing stent can be placed upstream inside a better portion of the aorta. With FEVAR and BEVAR devices aorta side branches such as the renal arteries, the superior mesenteric artery, the coeliac artery or the arch branches can be connected with the main device using small covered stents or fixed branches<sup>11</sup>. Nowadays, all kinds of fenestrated and branched endografts can be manufactured by which aneurysms from aortic arch down to the iliac arteries can be treated.

A so-called “chimney” endograft parallel to the main aorta endograft was used as a method to keep aorta side branches inside the circulation if overstenting (un)intentionally occurred. It can be used as a bailout technique in emergency surgery in which a tailor made fenestrated endograft cannot be

manufactured in time. With the ChEVAR technique an “off-the-shelf” endograft is placed simultaneously with smaller parallel covered endografts originating in the aortic side branches to maintain flow in these side branches. The smaller chimney graft does have a limiting diameter size due to the “gutter” it will produce beside the main endograft. Development of a proximal (Type 1a) endoleak is one of the main complications using this technique and long term results are lacking<sup>12,13</sup>.

With EVAS, a completely new concept to exclude AAAs had been introduced. The technique is based on aneurysm sac filling and the device commercially available is the Nellix endograft (Endologix Inc, Irvine, CA, USA). After placement of two covered balloon-expandable stents in the proximal aortic neck down to the iliac arteries, the entire aneurysm sac is sealed with two polymer-filled endobags surrounding the two tubes. The graft aims to minimize the risk of endoleaks and endograft migration. Unfortunately, studies with mid-term follow up have shown that complications occurred leading to explantation of the device in a substantial number of cases. Even after adapting the IFU, the EVAS technique has not yet developed as standard method of care, and has even been taken off the market recently<sup>14,15,16</sup>. Further translational research is essential for better understanding the mechanism behind this approach and further adaptations will clearly be necessary in the future before reintroduction of the system may be considered.

Laparoscopic surgery has also entered the vascular surgical area. LSAR can be divided into hand-assisted laparoscopic surgery, in which an incision is made to allow the surgeon’s hand to assist in the repair, total laparoscopic surgery, and robot assisted surgery<sup>17,18</sup>. Theoretically the laparoscopic method could be a possibility for the younger patient with vascular anatomy unsuitable for standard EVAR, not willing to undergo open surgery with higher 30-day mortality and not motivated for life-long follow-up after EVAR. However, laparoscopic and robotic AAA surgery never gained widespread adoption and is only offered in a few specialized vascular centers and could therefore be indicated in selected cases only. Cross-clamping of the aorta vessel is still mandatory in endoscopic surgery mimicking the technique of open aorta surgery as a possible disadvantage compared with EVAR.

One of the distinguishing marks between OSAR and EVAR is that the sealing and fixation of OSAR is created by suturing the prosthetic tube to the native aortic wall after aortic clamping, while with EVAR self-expandable stents create radial force for sealing and fixation and additional infrarenal or suprarenal hooks increase the migration resistance. In the 90’s commercial endografts entered the market and subsequently got their CE mark and FDA approval<sup>19</sup>. The very first endografts were flexible but without significant structural support which resulted in high rates of device migration and device occlusion. Many of these “early endografts” were taken off the market despite further modifications. The concept of EVAR however remained and significant improvements were made to the design, stent support and delivery system, thereby widening the range of possibilities to treat complex aneurysm anatomy as well.

Meanwhile it has become clear from randomized clinical trials that short and mid-term morbidity and mortality of EVAR are significantly less compared to OSAR in patients anatomically suitable for both techniques. EVAR using the common femoral artery as the access site for introduction of the endograft avoids surgical trauma related to laparotomy, blood-loss, and aortic clamping. These features, including the option of performing EVAR under local anesthesia are generally accepted as major improvements of EVAR over OSAR<sup>4</sup>.

At the longer term, however, specific EVAR related complications other than after OSAR may occur. These EVAR complications are related to the interaction between the endograft and the native aorta and the conceptual difference between the two methods in terms of sealing and fixation to the aortic wall. EVAR related complications such as different types of endoleaks, endotension, stent migration, stent failure, and the everlasting small chance of aneurysm rupture despite previous treatment warrants an intensive follow-up protocol of EVAR patients. After more than 30 years of EVAR experience we know that if the specific Instructions for Use (IFU) of the chosen endograft are followed, usually successful and durable proximal fixation and sealing of the endograft in the infrarenal aortic neck segment and proper distal fixation and sealing in the iliac arteries is feasible. Initially, nearly all AAA patients were treated strictly following IFU. However, improved experience of endovascular teams extended the use of endografts also outside the IFU. Various studies comparing results inside and outside IFU showed different results<sup>20,21,22</sup>.

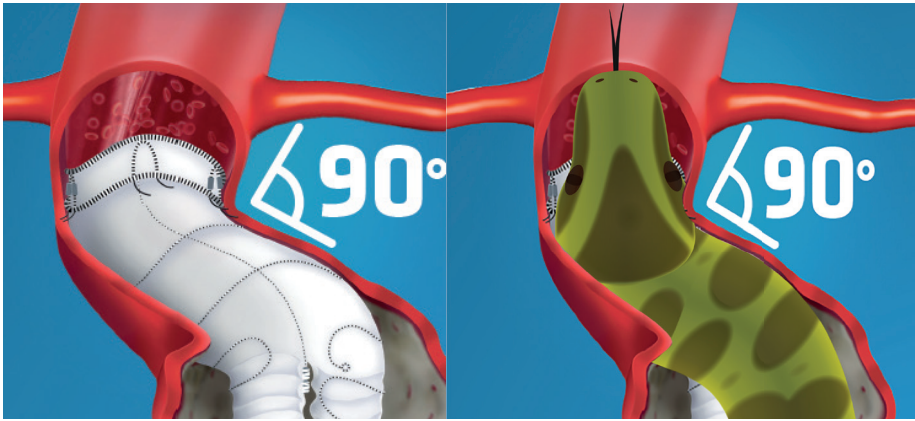
Nowadays in the Netherlands AAA treatment is monitored in the Dutch Surgical Aneurysm Audit (DSAA) registry as part of the Dutch Institute for Clinical Auditing (DICA). In this nationwide registry AAA treatment results are published every year.

From 2013 until 2018 a total of 21950 patients were included, in which 20184 patients with AAA and 1110 patients with thoracic aorta aneurysm (registered since 2016). A total of 74 Dutch hospitals participated in this registry. In 2018 a total of 3728 patients were treated for AAA. A total of 76.9 % of treatments were elective, 7.6 % acute symptomatic non-ruptured and 15.5 % ruptured. A total of 76.6% of the patients in the elective AAA setting were treated using EVAR. In the ruptured AAA setting a total 40.1 % were treated using EVAR. The 30-day mortality was 1.7% in elective AAA repair, 5.3 % in symptomatic non-ruptured AAA repair and 28.2% in ruptured AAA repair. In all three categories in-hospital mortality and 30- day mortality was less in EVAR surgery compared with open surgery. The 30-day complication rate was 19.6 % in elective AAA repair, 31.4 % in symptomatic non-ruptured AAA repair and 64.8 % in ruptured AAA repair. Again, in all three categories 30-day complication rate was less in EVAR surgery compared with open surgery<sup>23</sup>.

# Outlines

In this thesis three aspects of AAA will be addressed.

In the first part pathogenesis and etiology of AAA are summarized. In the second part the possibility of inter-observer variability in AAA measurements and subsequent choice of endovascular device is discussed. The third part of this thesis focuses on the treatment of infrarenal AAA with a third generation endovascular endograft and highlights specific modifications to the device comparing different generation devices.



The proximal end of this endograft resembles the configuration of the head of an anaconda snake, which was the reason why the stent graft was called the “Anaconda™ AAA stent graft system”.

The etiology and pathogenesis of abdominal aortic aneurysm is complex and not yet fully understood. It is complex due to the fact that genetic, inflammatory, biomechanical and hemodynamic factors all play a role in the development and progression of the aneurysm.

Aneurysm growth and rupture is based on biomechanical principles in which aortic wall stress, aorta diameter growth, and tensile strength weakening could lead to aneurysm wall rupture. Basic physics of the law of Laplace  $H = P \cdot r / (2 \cdot T)$  in which (systolic) pressure  $P$ , vessel wall thickness ( $T$ ) inside an increased aorta vessel radius ( $r$ ) introduces an increase in wall tension ( $H$ ) cannot solely predict change of rupture and as a consequence, the preferred time of surgery. AAA diameter and shape are not the only determinants of the stresses acting on the wall<sup>24</sup>. Knowledge of both AAA wall stress and wall strength is necessary to assess rupture potential, knowing that approximately 80% of the large aneurysms will be stable in time and each year 2% of the small aneurysm rupture. New patient-specific indices

describing peak wall (shear) stress (PW(S)S), strain and peak wall rupture index (PWRI) have therefore been developed as tools to better estimate potential rupture<sup>25</sup>. Combining these biomechanical indices into a rupture risk equivalent diameter (RRED) could be promising for decision making in daily clinical practice.

In **chapter 2** a comprehensive overview on a variety of factors influencing AAA growth and rupture is provided. Results of basic research studies on pathophysiological processes in AAA thrombus and aortic wall are reported.

In clinical practice guidelines of AAA management little attention is given to vascular anatomy assessment. Several criteria that define the suitability for EVAR have to be considered before selection for EVAR can be made. The stent graft has to seal the sac from inside excluding the AAA from the circulation. Proper device designs and some degree of oversizing of the graft inside the aorta is mandatory to make this possible<sup>4</sup>.

Patient's individual anatomy, restrictions in IFU, and local experience with a particular type of EVAR device will decide if a specific EVAR device is possible or another type of EVAR device or open repair has to be considered. Regional EVAR collaborations with a broader range of experience using different brands on the market may optimize proper treatment selection. There are however no clear data that favor one particular EVAR device over another.

In **chapter 3** a group of five experienced EVAR clinicians assessed anatomical data of 202 patients for suitability for three different types of endografts. A total of 3030 assessments were made in which a quantification of the likelihood of effective and durable sealing and fixation had to be made. This chapter focusses on the interobserver variability in EVAR assessment.

The various modes of failure observed in proximal sealing and fixation using the first generation endografts emphasize the technical demands of the endograft design. One of the endografts commercially available and frequently used in our center is the Anaconda™ endograft. In the first-generation Anaconda European study a total of 54 patients were included. There were 15 cases of infrarenal neck dilatation and device migration and 3 cases of dilatation without device migration. One type-1 endoleak was presented combined with migration. The lack of proximal fixation without anchor hooks, although substantial radial force of the proximal saddle shaped ring stent, the continuation of body support and wire support in the legs without flexibility were the reasons for this withdrawal of this first generation and the endograft was redesigned<sup>26</sup>.

The second generation Anaconda™ endograft design, CE marked in 2005, has a more tapered proximal part of the endograft to the main body, combined with a dual ring stent and four pairs of nitinol hooks for better apposition and fixation of the stent to the wall. The wire support of the legs was removed in the second-generation device and the modular design was meant to optimize endograft choice and oversizing in reference to the patient individual anatomy.

In **chapter 4** we focus on the technical and the mid-term clinical success of the second-generation Anaconda™ AAA endograft. Results were summarized and discussed and compared with other available devices.

Using EVAR in clinical studies outside the IFU expanded the indications for endovascular treatment in more hostile anatomy in patients unfit for open repair. Endografts were redesigned and modified with specific attention to flexibility, proximal fit, and sealing which shifted the IFU towards cases with more neck angulation. With the latest generation endografts AAAs with a proximal infrarenal neck angulation of 60 degrees can be treated with a neck fixation length ranging from 10-15 mm. AAA with a neck angulation of 75 degrees can also be treated if the neck length is more than 15 mm. Other factors such as neck thrombus or calcification are also of importance and narrows the range for further use in hostile anatomy. In time more and more experience has been gained with EVAR in hostile angulated anatomy. In **chapter 5** we present the results of a Dutch prospective multicenter study in which 36 patients with a mean angulation of 82 degrees and a mean follow-up of 42 months treated with the Anaconda endograft were studied.

The 30-day mortality rate after ruptured AAA (rAAA) has decreased from more than 50% in earlier studies towards 28% in the Dutch Surgical Aneurysm Audit and 34 % in nationwide registries such as Medicare<sup>4,27</sup>. Endovascular suitability is an independent and strong positive predictor of survival in modern series of open rAAA repair. Patient comorbidity, intra-operative factors and post-operative complications such as multi-organ failure reduce the overall survival. In patients with ruptured AAA and suitable anatomy the most recent ESVS guideline recommends EVAR10.

In **chapter 6** the feasibility of endovascular repair of rAAA using the Anaconda™ endograft as first choice was studied. In a four-year period, all patients presented with rAAA were preferentially treated with the Anaconda™. Short-and long-term results are presented and treatment feasibility was discussed for patients with challenging anatomy as well as experience of treating centers.

Long term durability of EVAR without secondary reinterventions can be more demanding in comparison to open surgery. After OSAR para-anastomotic aneurysm formation, graft infection, symptomatic adhesions and incisional hernia are more common. Type-1 endoleak (flow between the graft and

native aorta) and type 2 endoleak (flow from collateral native branches into the aneurysm) are the most frequent EVAR related complications after 5 years. Another complication related to both open and EVAR procedures, which can result in acute or chronic limb ischemia, is limb occlusion which is discussed in **chapter 7**. In our single center study prospectively gathered data of 317 patients undergoing EVAR with the Anaconda device were retrospectively evaluated. We studied the incidence and treatment of limb occlusion in the second and third generation devices from 2003-2015 to reveal factors such as endograft design, patient characteristics and peri-operative factors predicting risk of limb occlusion.

In **chapter 8** we summarized the results of the studies and discuss future perspectives to gain more insight in the reasons for endograft dysfunction. Chapter 9 is the Dutch translation of the summary of this thesis.

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# Chapter

# 2

## Risk factors for AAA growth and rupture; more than diameter alone

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## Introduction

Knowledge of pathophysiological processes within the aortic wall is of eminent importance for accurate risk assessment in patients with an abdominal aortic aneurysm (AAA). The real cause of AAA development and growth, however, is not exactly known. Although repair is advocated in AAAs greater than 5.5 cm in men and 5.0 cm in women, ruptures do occur in considerably smaller aneurysms and on the other hand an asymptomatic aneurysm with a diameter above eight cm is not a rare event. Various factors such as age, gender, lifestyle characteristics, and co-morbidity have been studied for the effect on AAA development and growth. Also, genetic profile, and various phenotype processes such as inflammation, angiogenesis and apoptosis seem to play important roles. This chapter provides a comprehensive overview on a variety of factors influencing AAA growth and rupture. Results of basic research studies on pathophysiological processes in AAA thrombus and aortic wall are reported. Finally, the possible pharmacological treatment options in reducing AAA growth and rupture are summarized.

## AAA diameter and timing of intervention

There is strong evidence that elective open surgical repair of small symptomless (3.0-5.5 cm in diameter) AAA does not improve patient survival. The UK Small Aneurysm Trial- (UKSAT) randomised 1090 patients (83% men, age 60-76 years) between 1991 and 1995 to undergo early elective open surgical repair for small (4.0-5.5 cm) AAA or ultrasonographic surveillance until 5.5 cm. Patients were followed up for a mean of 4.6 years. The primary endpoint was mortality. The 30-day operative mortality in the early surgery group was 5.8%, indicating a 30-day survival disadvantage for operated patients in the trial. At the longer term mortality rates however did not differ significantly between the groups at two, four and six years follow-up. The results supported a policy not to operate patients with small aneurysms. In a 12-years follow-up report the authors did not observe any late survival benefit for early elective surgery and most deaths (59%) were attributed to cardiovascular disease. They concluded that the main target in patients detected with small AAAs should be cardiovascular risk reduction.<sup>1,2</sup>

In the United States the Veterans Affairs (VA) medical centers started recruitment of AAA patients in the Aneurysm Detection and Management (ADAM) study screening program. This randomised clinical trial included 1136 patients between 1992 and 1997, aged between 50 and 79 years and mostly men (99%), for immediate repair or ultrasonographic surveillance of AAAs in the range from 4.0 to 5.4 cm. They also concluded that survival was not improved by elective repair of AAAs smaller than 5.5 cm, despite a lower 30-day mortality rate (2.1 vs 5.8%) and in-hospital mortality (2.7 vs 5.8%) compared with UKSAT. Eleven patients in the surveillance group (0.6% per year) had experienced ruptured AAA.<sup>3</sup> As both studies showed that open repair provided no benefit in early elective surgery in small aneurysms the question

was raised whether endovascular aneurysm repair (EVAR) would show a difference in mortality rate between immediate repair or ultrasonographic surveillance of small AAAs.

The CAESAR (Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair) trial randomised between 2004 and 2008 a total of 360 patients in 20 centres. Originally, the trial aimed to include 740 patients, but due to a lower than planned enrolment recruitment the study stopped after futility analysis. A single device (Zenith AAA Endovascular Graft; William Cook Europe, Denmark) was allowed for EVAR to guarantee homogeneity of results. The peri-operative mortality risk with EVAR was 0.55%, which was significantly lower than in the UKSAT trial. However, after 54 months all-cause mortality, aneurysm-related mortality, and major adverse event rates did not differ between patients randomised to early EVAR and those randomised to surveillance of AAA.<sup>4</sup>

The PIVOTAL trial (Positive Impact of Endovascular Options for Treating Aneurysms Early) randomly assigned 728 patients with small (4 to 5 cm) AAAs between 2005 and 2008. Among patients randomised to treatment, 89% underwent aneurysm repair. Among patients randomised to surveillance, 31% underwent aneurysm repair during the course of the study. After a mean follow-up of  $20 \pm 12$  months (range, 0-41 months), 15 deaths had occurred in each group (4.1%). The authors concluded that early EVAR treatment and rigorous surveillance with selective aneurysm treatment when indicated both appear to be safe alternatives for patients with small AAAs. The observed risk of rupture in the surveillance group was significantly lower than predicted. For any statistically significant difference to be observed in this trial in favour of EVAR the rate of rupture in the surveillance group should have increased about eightfold. Again, the futility analysis triggered the decision to close patient enrolment before its planned enrolment of 1050 patients.<sup>5</sup>

The reason for the lower than expected rate of rupture in the surveillance group in both the CAESAR and PIVOTAL studies is unclear. First, patients enrolled were frequently treated with statins (47.7% and 78.4%, respectively) and  $\beta$ -blockers (24.8% and 51%, respectively). Second, the authors discussed the fact that in the surveillance group in CAESAR 47.8% of the patients received AAA repair within 54 months and in the PIVOTAL group 30.1% received AAA repair within 3 years after inclusion.

They suggested that the rigorous surveillance protocol would detect rapid expansion or expansion to more than 5.5 cm earlier in time thereby potentially lowering the rupture rate in the surveillance group.

Heterogeneity of the growth rates of small AAAs (3.0-5.5 cm in diameter) was demonstrated in a recent overview.<sup>6</sup> On average, a 3.5 cm aneurysm would take 6.2 years to reach 5.5 cm, whereas a 4.5-cm aneurysm would take 2.3 years and a 5.0 cm aneurysm would take 1.1 years to reach 5.5 cm. In the meta-regression analysis performed in this study the authors showed that a 10 mm larger aneurysm diameter was associated with a mean 1.62 mm/year increase in growth rate. This increase was age and gender independent. Early elective surgery conducted with AAA diameter between 4.0 and 5.5 cm is not recommended, although an enlargement rate of 1.0 cm/year or more or 0.7 cm/ 6 months is regarded as an indication for small aneurysm repair. The variability in growth rate of small aneurysms between individuals causes difficulties in determining a proper follow-up scheme for the whole group. In a proper scheme the probability of exceeding 5.5 cm and subsequent increased chance of rupture before the next follow-up visit should be below a specific threshold, for example 5% or less. Including the individual patient characteristics in these surveillance schemes could become more and more important for tailor made surveillance, and for further reducing the unsuspected rupture rate in small AAAs.<sup>1,3,6</sup>

## Pathophysiology and risk factors of AAA

The normal aortic wall consists of three morphologically distinct layers including intima, media and adventitia. The intima is bounded on the lumen by a continuous layer of endothelial cells. The media consists of smooth muscle cells oriented in a spiral fashion, surrounded by connective tissues, including collagen and glycosaminoglycan, as well as elastic fibres. The adventitia contains both smooth muscle cells and fibroblasts together with large amounts of collagen, glycosaminoglycan and elastic fibers.<sup>7</sup>

Elastic fibres and fibrillar collagen are the main determinants of the mechanical properties of the aorta. Elastin is stabilised by cross-links between the molecules and can be degraded by elastase active proteases. Elastic fibres interconnected with smooth muscle cells and fibrillar collagen (type 1 and 3) are most abundant in the media of the aortic wall and determine the visco-elastic properties of the aortic wall.<sup>8</sup>

Known risk factors for AAA development are age, male gender, smoking, hypertension and atherosclerotic disease.<sup>9</sup> In 1992, Reed et al. also described the association of AAA with the previously mentioned known risk factors but concluded that the baseline risk factors for AAA development were the same factors that predicted aortic atherosclerosis.<sup>10</sup> They suggested that atherosclerosis probably was a necessary element in the causal pathway to (the great majority) of AAA development. Currently, the conventional view of atherosclerosis damaging the aortic wall and subsequently resulting in AAA development is more and more challenged. In the Tromsø study, Johnson et al. reported a lack of consistent dose-response relation between atherosclerosis and abdominal aortic diameter. They suggested the opposite of Reed et al. and mentioned the possibility that atherosclerosis could be an event parallel with or secondary to aneurysmal dilatation.<sup>11,12</sup> (Fig.1)

### Smoking

The Whitehall study was set up in England in 1967 and followed 18403 male civil servants for 18 years. A total of 99 deaths were attributed to aortic aneurysm. Hypertension and smoking, particularly of hand-rolled cigarettes were confirmed as major and preventable risk factors for fatal aortic aneurysm.<sup>13</sup> Chang et al. included 514 patients in a study assessing the risk factors associated with rapid growth of small AAAs. A total of 461 patients had a history of active or past cigarette smoking. As a consequence, almost 90% of patients with faster growing aneurysms had a history of smoking.<sup>14</sup>

In the ADAM study group of all AAAs of 4.0 cm or greater, 75% was associated with smoking, supporting the hypothesis that AAA growth is a smoking-related disease.<sup>15</sup>

The UK Small aneurysm trial showed that AAA expansion was approximately 0.4 mm/year faster in current smokers than non-smokers. The authors showed that smoking increases AAA growth rates by 15-20%, although not sufficient enough to recommend different screening intervals for smokers.<sup>16</sup>

Similar results were reported in Sweden. In a screening cohort of 22,139 men, a total of 373 AAAs were detected (1.7%). In this observed low prevalence of AAA the value of a one-time ultrasound screening of the infrarenal aorta was questioned. The low prevalence found was attributed mainly to the decline of smoking habits in Sweden. Because of the almost fourfold additional risk observed for ever smokers, it was suggested to perform selective AAA screening among smokers.<sup>17</sup>

The mechanism linking smoking and aneurysm formation remains unclear. Buckley et al. used an aortic aneurysm mouse model, in which adult male mice were subjected to cigarette smoking for two or 12 weeks, combined with pancreatic elastase infusion after two weeks of smoking. Non-smoking mice undergoing elastase infusion were used as controls. After two weeks, aortic diameters were not significantly different. At 12 weeks (expressed as chronic cigarette smoking exposure), the aortic dilatation was substantially greater in the smoking group compared to the control group. This first published cigarette smoke-induced AAA mouse model indicated that the accelerated aneurysmal dilatation may be attributed to adverse effects of smoking on the mediating connective tissue repair within the aortic wall, rather than to the initial inflammatory response leading to AAAs.<sup>18</sup>

A second study of the same group showed that aneurysm development is dependent on the quantity of active elastase infused. After minor aortic elastase injury, tobacco smoke already induced increase in elastin degradation and AAA size without affecting aortic matrix metalloproteinase (MMP-9 and -12) expression.<sup>19</sup>

The strong association between smoking and aneurysm development is evident. Smoking is probably the single most important preventable risk factor for AAA development and growth. Pursue patients to stop smoking results in decline of thromboembolic events and in reduction of AAA growth rates.

## Diabetes mellitus

Shantikumar et al. identified 11 studies delineating the association between diabetes mellitus (DM) and AAA. The prevalence of DM in patients with AAA ranged from 6% to 14%. The prevalence of DM in control patients without AAA ranged from 17% to 36%. Nine studies found a lower prevalence of AAA in individuals with DM (three included data from the ADAM trial). Two studies found no difference between diabetes and non-diabetes patients. The meta-analysis excluded four out of eleven studies as there was

no or poor control group, or the studies were subgroup analyses. Pooled analysis demonstrated reduced odds of DM in patients with AAA (OR=0.65,  $p<0.000.1$ ). After excluding the results of the ADAM trial, the remaining data still suggested a reduced prevalence of DM in patients with AAA (OR=0.81,  $p=0.038$ ).<sup>20</sup> In a cohort of 39 diabetic patients, intima-media thickness (IMT) was measured in the abdominal aorta using B-mode ultrasound, and compared with 46 controls. The results showed a 22% ( $0.89 \pm 0.17$  mm vs  $0.73 \pm 0.11$ ) ( $p<0.001$ ) larger IMT in the abdominal aorta of diabetic patients. Aortic wall stress appeared to be 20% ( $p<0.001$ ) lower in the diabetic patient compared to non-diabetics.<sup>21</sup>

High glucose concentration in DM results in glycation of the extracellular matrix with formation of advanced glycation end products (AGEs). AGEs form protein cross-links, including vessel wall elastin and collagen and promote smooth muscle cell proliferation which may result in a stiffened aortic wall. In vitro studies indicate that AGE-mediated cross-links are resistant to proteolysis. High glucose concentrations result in increased collagen synthesis due to an increase in connective tissue growth factor (CTGF) and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1). AGEs also upregulate tissue inhibitors of metalloproteinase-1 (TIMP-1) using CTGF.

Increased activity of MMP-2 and MMP-9 has been found in the aneurysmatic aortic wall.<sup>22</sup> MMP-2 is capable of promoting elastolysis in a wide range of matrix proteins such as elastin. MMP-9 also is capable of degrading elastin and is found in increased amounts in the walls of AAAs. Hyperglycemia, upregulation of TIMP-1 and fibronolytic factors downregulate MMP-2 activation and expression, thereby reducing proteolysis, increasing matrix volume and increasing arterial wall stiffness resulting in less arterial expansion.<sup>20,23</sup> Plasminogen activator inhibitor-1 (PAI-1) inhibits plasminogen conversion to plasmin, thereby suppressing fibrinolysis, reducing clot degradation and renewal. The clot is thereby denser and more resistant to fibrinolysis.<sup>20,24</sup> (Fig 2)

In conclusion, there is a negative association with AAA development in patients with diabetes mellitus.<sup>9,20</sup>

## Interaction between intima and intraluminal thrombus in AAA

In most patients AAA is associated with intraluminal thrombus (ILT). Understanding the role of ILT as a possible factor promoting decrease of mechanical strength of the aneurysmal wall is important and may lead to new treatment modalities reversing the weakening proces and eventually rupture.<sup>25</sup>

Adolph et al. analysed 24 intraluminal thrombi from patients who underwent elective open aortic repair for AAA. AAAs were typically  $> 5$  cm, predominantly from male patients (3:1) and current or past smokers. Histological slices and electronic microscopic evaluation were conducted to examine the fine structure

and cellular composition of aneurysm thrombus. The study demonstrated a system of reticular canaliculi that may act as an alternative delivery system for cells and macromolecules to the aortic wall due to the fluid permeability of the thrombus. No cells were detected towards the abluminal surface of clots thicker than 1 cm which suggests that the majority of cells enter from the luminal surface. Fibrin deposition occurred throughout the thrombus, whereas fibrin degradation occurred principally at the abluminal surface. The viable macrophages within the thrombus may contribute to the pathologic mechanism of AAA by chronic cytokine production.<sup>26</sup>

Vorp et al. studied aortic wall hypoxia after computer modelling suggesting that ILT reduced oxygen flow from the lumen to the aortic wall. Intra-operative  $pO_2$  measurements were done in eleven patients. The resected aortic specimens were also subjected to histological, immunohistochemical and tensile strength analyses. AAA regions with thick ( $> 4$  mm) ILT exhibited more aortic wall hypoxia than regions with thin ( $< 4$  mm) ILT according to intra-operative aortic wall  $pO_2$  measurements (18% vs 60%  $pO_2$ ,  $p < 0.01$ ). Furthermore, the thick ILT specimens showed greater inflammation, more neovascularisation and less tensile strength compared to thin or no ILT.<sup>27</sup>

AAA wall segments covered with thrombus were compared with wall segments without thrombus and thereby well exposed to blood flow. Kazi et al. discovered that the aneurysm wall covered with thrombus was thinner, contained fewer elastin fibres and that the fibres were fragmented. Segments from thrombus covered aneurysm walls were more heterogeneous, with fewer smooth muscle cells in the intima and media, more inflammatory T- and B-cells, more signs of apoptosis and more degraded extracellular matrix compared with thrombus free wall. In this study no difference was seen between macrophages infiltration in aneurysm wall segments or atherosclerotic wall segments. The cellular and structural pattern of the aneurysm wall differed between thrombus and non-thrombus covered wall segments. These results suggested that wall segments covered with thrombus had less structural integrity and were more predisposed to rupture.<sup>28</sup>

Fontaine et al. explored the involvement of the thrombus in storage and release of leucocyte and plasma proteinases, involving aneurysmal evolution. The metalloproteinase (MMP) and fibrinolytic system were both explored. Thirty-five patients operated for AAA and eight healthy volunteers were included. In 15 out of 35 operated patients a liquid phase was present at the interface between thrombus and aortic wall, suggesting fibrinolysis at the abluminal pole of the thrombus. Circulating plasminogen binds to fibrin and is absorbed from the plasma onto the ILT, serving as a substrate for plasmin generation. Amounts of circulating plasmin, a possible activator of MMPs and its precursor plasminogen were significantly higher in the ILT and not detected in the wall or liquid interface, probably because of inhibitors such as Plasmin- $\alpha_2$ -anti-Plasmin complexes (PAPs) detected in the liquid interface, thrombus and aortic wall. PAPs reflect plasmin generation from plasminogen activators. Free t-PA (tissue type

plasminogen activator) and u-PA (urokinase type plasminogen activator) activities were present only in the aneurysmal wall and (u-PA) mainly produced by inflammatory cells in the aortic wall. Histological examination showed a marked enrichment of polymorphonuclear cells (PMN) and MMP-9 in the most inner layer of the ILT, whereas the abluminal thrombus was devoid of cells. The data suggested that MMPs could be stored and released by PMNs entrapped in the thrombus on the luminal side. Fontaine suggested that ILT and its platelets, cells and absorbed plasmaprocomponents could act as a source of secreted proteases within the aneurysm. The aneurysm wall contains tissue proteases (MMPs and Pg-activators of mesenchymal cell origin) and linking these with the plasminogen in the thrombus could create a liquid fibrinolytic interface. This fibrinolytic interface activity could be a critical factor in further AAA enlargement and rupture.<sup>29</sup>

The more active role of ILT was further investigated by Houard. Plasma samples (24 AAA patients and 18 matched healthy individuals) and eight surgical resected AAA thrombus and aortic wall samples were analysed. D-dimer and PAPs (both evidence of plasmin proteolytic activity), t-PA and u-PA and plasminogen activator inhibitor-1 (PAI-1) were further analysed in AAA patients. Elevated PAPs and D-dimer plasma concentrations were found in AAA patients compared with healthy controls. In the thrombus, D-dimer and PAPs were mostly released by the luminal layer of the thrombus, although both substances were detected (in negative gradient) in all thrombus layers (luminal, intermediate and abluminal) and aortic wall layers (media and adventitia). Stored t-PA was detected in the inner part of the media and associated with the vasa vasorum of the adventitia. u-PA and PAI-1 were found in inflammatory areas of the media and adventitia. Houard et al. indicated that the release of products of fibrinolysis predominates at the luminal side of the thrombus, which maintains an interface with the circulating blood. Despite PA synthesis and retention within the aneurysmal wall, PAs are also dominantly stored within the luminal side of the thrombus. Using the ligand <sup>99m</sup>Tc-aprotinin (in vivo used for amyloidosis and renal morphology) Houard et al. concluded that retention of fibrinolytic system components within ILT in the future may be exploited in functional imaging for diagnostic purposes.<sup>30</sup>

Elastase release from neutrophils and macrophages stimulated by elastin-derived peptides is an essential event in aortic wall elastin loss and AAA formation. Neutrophils may also be a source of MMP-9 and MMP-8 (neutrophil collagenase) further degrading collagen in AAA. Wiernicki et al. postulated that the optimum intramural alkaline pH for elastase in the aneurysm wall is situated adjacent to the thin part ( $\leq 10$  mm) of the ILT. This suggests more enhanced matrix-degrading proteolytic activity in thin thrombus-covered wall. Influence of tissue inhibitors of MMPs (TIMP-1) was also discussed. A total of 40 AAA mural thrombus samples were used. The study showed that the activity of elastase ( $p < 0.0001$ ), concentrations of active MMP-9 ( $p = 0.001$ ), total MMP-8 ( $p < 0.0001$ ) and active MMP-9/total TIMP-1 ratio ( $p = 0.002$ ) were significantly higher in the thin thrombus-covered wall in comparison with the thick thrombus-covered wall. Furthermore the active MMP-9 / total TIMP-1 ratio (a relative index of proteolytic state) was raised

(more proteolysis) in the thin thrombus-covered in comparison with the thick thrombus-covered wall ( $p=0.003$ ). They argued that high protease activity in thin thrombus covered wall may explain why some small aneurysms rupture and large ones do not.<sup>31</sup> Folkesson et al. studied the protease activity in thick ILT. A total of 32 AAA mural thrombus patient samples were used. Mean thickness of the ILT was  $27 \pm 10.8$  mm. The ILT was divided in a luminal, intermediate and abluminal layer. Neutrophils (NE) and MMP-1,2,9,13 proteases, inhibitors (TIMP-1, PAI-1,  $\alpha$ 1-antitrypsin) and protease activity of MMP-9 and NE were measured. In ILT smaller than 1 cm thick, they demonstrated presence of only one single layer containing numerous neutrophil leucocytes. In thicker ILT the abluminal layer is almost devoid of cells. Neutrophil leukocytes and platelets were mostly detected in the luminal layer. MMP-9 and neutrophil elastase were also abundant in this layer, although with low activity. The molar concentration of TIMP-1 in the abluminal layer was 13 times higher than MMP-9 suggesting effective inhibition of MMP-9. The neutrophilic inhibitor  $\alpha$ 1-antitrypsin showed the same pattern as NE with highest concentration in the luminal layer. They concluded that in thick multi-layered ILTs in AAA proteases in the abluminal layer are mostly inactive, likely due to excess of inhibitors. Direct influence of proteases from thick ILT through canaliculi is also restricted to 1 cm.<sup>27</sup> In AAA thick ILTs with multiple layers contain substantial amounts of proteases, but their activity is limited to the luminal layer. Proteases in the abluminal layer are mostly inactive, probably due to excess amounts of inhibitors and are consequently unable to directly participate in the pathogenesis of AAA. Sakalihasan et al. measured activity of MMP-9 in the abluminal ILT layers, which could be originating from the vessel wall itself or from the liquid interface between thrombus and ILT.<sup>22</sup> Rupture often occurs through the aortic wall covered with ILT after bleeding in the thrombus. Folkesson et al. suggested that possibly the neutrophilic effect on the luminal layer of the ILT degrades the ILT, causing proteases, blood and neutrophils to enter the thrombus and reach the underlying wall causing rupture. Secondary mechanisms, such as hypoxia and neovascularisation in the aortic media further may contribute to AAA wall degradation by allowing neovascular entrance of inflammatory cells from media and vasa vasorum to the already degraded wall.<sup>27,32</sup> In conclusion, the influence of the intima and intraluminal thrombus characteristics on AAA growth and rupture is ambiguous.

## Aortic wall pathophysiology in AAA

More and more research is done to study the influence of inflammation, neovascularisation, immune response and oxidative stress on the extra cellular matrix (ECM).

The ECM is responsible for the resistance to aortic arterial flow and pressure. Although intimal atherosclerosis often accompanies AAA, degradation and failure of the elastic media is responsible for aneurysm development.

Dobrin et al. described in their experiments in rats the contribution of the fibrous connective tissues elastin and collagen on aneurysm formation and rupture. The proteases elastase and collagenase were infused in arteries, triggering vessel dilatation, elongation and rupture. Elastin and collagen degradation and failure are critical in AAA growth and rupture.<sup>33</sup> Anidjar et al. induced in an in vivo rat model aneurysmal dilatation using pancreatic elastase and showed total loss of elastic tissue in perfused areas of the wall media. They also used thioglycolate to provoke macrophage activation and elastase secretion. They showed that passive transfer of activated macrophages (from adventitia to media) or direct activation of macrophages within the aortic wall by thioglycolate can induce "in situ" elastolytic activity. Plasmin may enhance the macrophage elastolytic activity in vivo and cooperates with elastolytic activity.<sup>34</sup>

Using the same Anidjar/Dobrin rat aneurysm model Nackman et al. showed in their experiment that using elastin degradation products (EDPs) (products of elastine degradation) a remarkable adventitial angiogenesis occurred and prominent vasa vasorum developed, promoting neovascularisation and increasing the collagenase contents in the aneurysmatic aortic wall.<sup>35</sup>

The role of cellular immunity in AAAs was analysed in the study of Koch et al. Using inflammatory cell-specific monoclonal antibodies against B-lymphocytes, macrophages and T-lymphocytes, Koch compared normal, occlusive and aneurysmal aortic tissue. Five out of 23 aortic aneurysms were classified as inflammatory. Normal aortic tissue contains only a few, if any inflammatory cells. There were mild inflammatory changes in occlusive aortas, but severe in AAA, most prominent in inflammatory samples. Many CD3+ T-lymphocytes were seen in all the diseased (occlusive and aneurysmal) aortas. One out of four lymphocytes in aneurysmal aortas were CD19+ B-lymphocytes, mostly found in the adventitia. B-lymphocytes were rarely found in occlusive aortas. Between 67-80% of the inflammatory cells in the diseased groups were CD3+ T-lymphocytes present in the media and adventitia. Macrophages were found in each type of diseased aortic tissue, most often within lymphoid aggregates.<sup>36</sup>

Normally the vascular smooth muscle cells (VSMCs) are the predominant cell type in the media. Cohen et al. showed that neutrophils and VSMCs are responsible for the increased levels of elastase in AAA, in response to EDP. They postulated that the response of VSMC in AAA is abnormal, compared with aortic occlusive disease and that VSMC deliver more proteolytic enzymes in AAA, resulting in further aneurysmal degeneration.<sup>37</sup>

Lopez-Candales et al. showed that VSMC density was significantly decreased in human AAA associated with evidence of apoptosis or physiological cell death and increased production of p53 which is a mediator of cell cycle arrest and programmed cell death. The loss of this cell population due to apoptosis results in further deterioration of the aneurysmal aorta. A number of mechanisms were given to explain

the SMC apoptosis and cell death in the media of AAA. The cytotoxic effects of high local oxidants such as nitric oxide, oxygen free radicals and oxidized LDL could induce VSMC apoptosis. Secondly, VSMC are totally dependent on nutrient diffusion from the lumen, because of the sparse vasa vasorum in the abdominal aorta. Atherosclerotic plaques and a thick ILT could result in chronic medial ischemia. High local concentrations of cytokines such as interleukin, tumour necrosis factor- $\alpha$ , interferon, produced as a product of macrophages and T- lymphocytes could also influence VSMC apoptosis.<sup>38</sup>

In atherosclerosis, restenosis and response to injury, VSMC are one of the main cellular components of arterial healing. Using an already developed aneurysm expanding model, Allaire et al. provided evidence that endovascular VSMC seeding could stabilise AAA diameter, block the ECM degradation and regenerate the diseased wall. There was a dramatic decrease in MMP expression, an increase in tissue inhibitors of MMPs (TIMP) and an increase in collagen accumulation at histology.<sup>39</sup>

Inflammation and neovascularisation are prominent in AAA growth and the AAA rupture site. MMPs are observed in AAA rupture site and in the diseased aneurysm wall.<sup>40</sup>

Reeps et al. showed that invading neovessels and inflammatory infiltrates were relevant sources of MMPs and may substantially contribute to aneurysm wall instability. Neovascularisation was seen in the medial and intimal layer of AAAs. Small vessels of the vasa vasorum were only seen between the border of the media and adventitia. They also suggested that MMP activity is associated with T-lymphocytes and plasma cells. In this way inflammatory cells contribute to proteolytic matrix destabilisation.<sup>41</sup>

Investigation regarding kinase inhibitors such as c-Jun N-Terminal kinase (JNK) or amino oxidase such as lysyl oxidase (LOX) both enhancing extracellular matrix degradation are promising. c-Jun N-Terminal kinase or JNK inhibition in vivo in mouse models showed that inhibition largely prevented thinning of the media or disruption of the elastic lamellae. The macrophage infiltration in the periaortic tissue also was reduced, suggesting that inhibition of JNK also reduced proinflammatory signaling.<sup>42</sup>

LOX activity is essential to maintain the tensile and elastic features of connective tissue. In the vascular wall, LOX is expressed in fibroblasts, endothelial cells and VSMC. LOX inhibition in animal models causes elastase-induced AAAs. Using JNK or LOX targeted therapy could provide nonsurgical therapeutic options in the future.<sup>43</sup>

The role of mast cells was recently reviewed as cells involved in the inflammatory response in AAA. Mast cells contain a variety of factors such as chymase, carboxypeptidase A and cathepsinG, but also histamine, tumour necrosis factor- $\alpha$ , transforming growth factor- $\beta$ , vascular endothelial growth factor (VEGF) and chemokines. Activated mast cells influence angiotensin conversion, angiogenesis, VSMC

apoptosis and macrophage activation, but also activate MMPs, all pathways in further degradation of the ECM. Mast cells stabilizing factors, histamine blockers and leukotriene receptor antagonists could be used as a possible targeted therapy in preventing AAA.<sup>44</sup>

The basement membrane (BM) is a highly specialised component of ECM, separating endothelium and stroma in all tissues and is detected using electronic microscopy. It regulates cell behaviour, provides structural support and divides tissues in compartments. Collagen IV, XV, XVIII and laminin are component of the BM and the role of the BM in tumour angiogenesis is evolving. MMP's, growth factors such as VEGF and other components are key factors in neoangiogenesis using MMP-2 and -9 as collagen degraders.<sup>45</sup>

Ramazani et al. studied the circulating plasma levels of BM fragments in patients with AAA, using the BM components collagen type IV and XVIII in plasma. In a small group of ten AAA patients, ten healthy controls and nine patients with peripheral artery disease (PAD) he concluded that circulating levels of type XVIII collagen was significantly increased in AAA patients compared with the two other groups. Type IV collagen was significantly increased between AAA patients and healthy controls but not significant different between AAA patients and PAD patients. As a key component of the BM collagen IV and XVIII could be potentially serve as a marker of vascular remodelling in AAAs, but larger cohort studies are necessary.<sup>46</sup>

In conclusion, ECM characterisation could become important in predicting AAA behaviour but the exact influence of the distinguished components has to be elucidated before clinical applicability is achieved.

## Pharmacological pathways and possible treatment options

Medical intervention in decreasing growth rate or ultimately decreasing aneurysm size are focus of this chapter. Recent reviews summarised the evidence of medical interventions in randomised clinical trials and cohort studies. Although further properly designed randomised clinical trials (RCT) are needed, some medical interventions could be promising.<sup>12,47,48</sup>

### Statins

Statins are used to decrease the low density lipoprotein (LDL) cholesterol concentration. Statin therapy can safely reduce the 5-years incidence of major coronary events and stroke.<sup>49</sup> There is also strong evidence that perioperative statin use in high-risk patients undergoing elective or emergency surgery is recommended.<sup>50</sup> The presumed mechanism of statins in reducing AAA growth is the so called “pleiotropic effects”; altering the inflammatory status and MMP activity of the aortic wall.<sup>51-53</sup> There are however no randomised clinical trials comparing reduction of AAA expansion rate between patients taking statins versus those not taking statins. Twine et al. included 12 cohort studies including 11.933 individuals in the systematic review and meta-analysis. Expansion rate, 30-day mortality and long term all-cause mortality outcome parameters were selected for inclusion in the meta-analysis. There was a significant reduction in AAA expansion rate including all seven studies. Including only the four high-quality studies showed however no significant difference in AAA growth between the two groups. The 30-day mortality rates were not significantly different in meta-analysis including two studies. The 1-, 2-, and 5-years mortality in meta-analysis after AAA repair in patients taking statins was significantly lower. They concluded that reduction in AAA expansion rate with statin therapy was not significant on meta-analyses, but mortality rates are significantly lower.<sup>54</sup> McNally et al. initiated statin treatment in the preoperative optimization in the care process for AAA regardless of preoperative lipid profile.<sup>55</sup>

Referring to the overall benefits, statins are recommended in AAA patients undergoing elective AAA repair.

### Antibiotics

Doxycycline, a tetracycline based antibiotic, has shown to prevent AAA formation in animal models.<sup>8,48</sup> The effect of doxycycline was related to effects on MMP-9 activity and its effect in treatment of Chlamydia pneumonia infection, possibly involved in formation and expansion of AAAs. The mode of action in humans however is still unclear. A recent study suggested that doxycycline has a selective effect on the

proteolytic balance in the AAA, indicated by reduced MMP-8 and -9, TIMP-1 and cystatin C levels but also on neutrophil influx in the aortic wall.<sup>56</sup>

A small randomised trial with a total of 32 patients suggested that doxycycline resulted in a lower aneurysm expansion rate during the 6 to 12-months and 12 to 18- months periods, but overall results were not significant.<sup>57</sup> In 2012 the results of the FAST study, a placebo controlled randomised clinical trial, are awaited. The power analyses of this study including nearly 300 AAA patients was based on the presumption that the AAA growth was halved (unpublished data). Results of other two larger randomised trials are expected to be reported in 2014.<sup>48</sup>

Roxithromycin, a macrolide antibiotic, was studied in two randomised clinical trials. The association between *Chlamydia pneumoniae* in atherosclerotic lesions, the inflammatory process in the AAA in general, provided the rationale for effect of antichlamydial treatment on the expansion rate of AAAs. One randomised clinical trial, first published in 2001, including 92 patients, concluded that roxithromycin used for 28 days (annually) reduced the mean expansion rate of AAAs by 43% in the first year. The second year the reduction was only 5% in the intervention group. The study was prolonged with a total of 84 patients and followed for 5.27 years. The long term result was a 36% reduced mean annual growth rate in the roxithromycin group. The author stated that beside statins and ACE inhibitors, macrolide treatment could be considered in patients unfit for surgery. Larger trials are needed.<sup>58,59</sup>

## Betablockers

The potential effect of betablockers was demonstrated in an aortic dissection animal model. Propranolol lowers the heart rate and blood pressure and increases the aortic wall tensile strength.<sup>60</sup> Two large and one small randomised clinical trial included a total of 1078 patients. The final results showed no significant reduction in the mean annual growth rate between the intervention and the control group. In the Propranolol Aneurysm Trial a total of 548 patients were included. 26.8% of the patients in the control group stopped their medication and 42.4% in the propranolol group, because of fatigue, shortness of breath, heart failure and bradycardia and a poorer quality of life on all eight items of the SF-36 item list. They showed that propranolol was poorly tolerated by many patients. Because of the consistent lack of an overall effect on growth and the significant intolerance on propranolol medication the betablocker propranolol was not recommended for AAA treatment in these trials.<sup>48,61</sup>

## Angiotensin converting enzyme inhibition

Infusion of angiotensin II into animals promotes aortic aneurysm formation. Stimulating the aortic inflammatory response and aortic wall proteolysis could be the aneurysm promoting effect. The effectiveness of angiotensin converting enzyme (ACE) inhibitors in rodents is not always reducing AAA growth. There are no randomised clinical trials on this subject.<sup>48</sup>

Hackam et al. conducted a population-based case control study, including 15326 patients who were admitted to the hospital for AAAs. Overall 3426 patients (22%) already used ACE inhibitors therapy before admission to the hospital including 665 / 3426 (20%) of the ruptured AAA cases and 2761/11900 (23%) of the controls with non-ruptured AAAs. He concluded that ACE inhibitors were associated with reduced risk for AAA rupture. Patients receiving ACE inhibitors did have 18% lower odds of aortic rupture compared with patients who did not receive ACE inhibitors.<sup>62</sup>

The UK Small Aneurysm trial surprisingly showed, in contrary to Hackams decreasing rupture rate, that aneurysm patients taking ACE inhibitors had on average a 0.63 mm/yr increased growth rate compared with individuals who were not on ACE inhibitors (growth rates 3.37 and 2.74/year).<sup>63</sup>

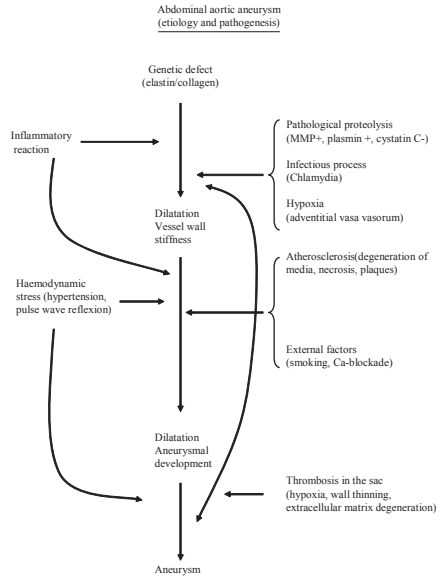
Thompson et al. performed a retrospective analysis of growth rates of prospectively collected AAA screening data. Thompson included data of 1231 subjects. AAA growth showed a bimodal pattern, growth rate differences were not associated with ACE inhibition or statin use and growth rates were associated with smoking. There was a negative association between growth rate and diabetes.<sup>64</sup>

The exact place of ACE inhibitors in preventing AAA growth is not clear yet.

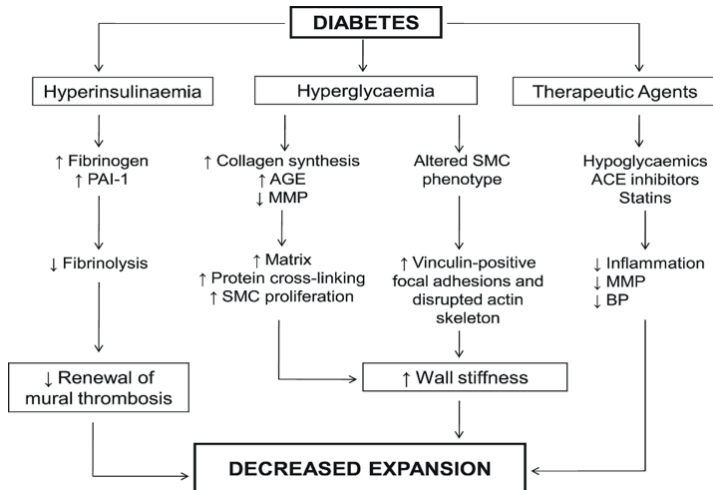
## Conclusions and future directions

In the latest randomised control trial using EVAR in treatment of small AAAs, the rupture rate was lower than expected. Rigorous surveillance in the small AAA group, beneficial effects of statin medication and smoking cessation probably reduced unexpected AAA rupture in this group, but asymptomatic AAA more than 8 cm do occur outside RCTs and screening protocols. Studying the pathophysiology of smoking, diabetes and atherosclerosis in AAA, more and more essential factors about AAA growth or growth stagnation become clear. Using fundamental research in aortic wall, thrombus and luminal blood flow interactions more of the intricating fundamentals of AAA development, growth and ultimately rupture is known.

The tailor-made individual approach, more advent in medicine due to genome-mapping, hormone receptor treatment, and gene-amplification could become more important in AAA medicine. In the future sampling of tissue-factors in plasma could possibly predict eminent rupture signs of AAA. Tailor-made treatment using pharmacological pathways to stop or reverse aortic wall degradation, promoting aortic wall tissue regeneration and stabilisation could reduce the operative treatment of AAAs. However, until now AAA diameter remained the main clinical tool to decide whether to exclude the AAA or not.



**Figure 1.** Aetioliology and pathogenesis model of abdominal aortic aneurysm development as previously suggested by Bergqvist<sup>12</sup>. (Reprinted with permission by Elsevier Ltd, Oxford, UK)



**Figure 2.** Pathophysiological model of AAA and diabetes mellitus<sup>20</sup>. (Reprinted with permission by Elsevier Ltd, Oxford, UK)

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# Chapter

# 3

## Consistency in endovascular aneurysm repair suitability assessment requires group decision audit

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**Introduction:** Proper selection of patient and stent-graft combinations in endovascular aneurysm repair (EVAR) depends on knowledge and experience with the different types of stents that have to be adapted to the patient's unique abdominal aortoiliac anatomy. The aim of this study was to analyze the consistency and variance in EVAR suitability assessment between clinicians.

**Methods:** Worksheets that contained anatomic data derived from computed tomography scans and angiography were compiled for 202 patients. Five clinicians, all experienced in EVAR surgery, assessed the anatomic data on the worksheets for suitability for three types of stent-grafts. The obtained 3030 assessments represented a quantification of the likelihood of success the clinician expected for effective and durable sealing and fixation of the stent-graft in EVAR. The Delphi method was used to determine consensus in the thinking process among clinicians, and analysis was used to determine the proportion of variances in the assessment result between clinicians.

**Results:** With the Delphi method, Cronbach  $\alpha$  values of 0.87, 0.87, and 0.90 were reached for the three types of stent-grafts in the second assessment round. The individual clinician-group correlation in round two was between 0.69 and 0.86 for clinicians 1, 2, 3, and 4. Between clinician 5 and the others, correlation varied between 0.43 and 0.64. The  $\kappa$  values ranged between 0.32 and 0.51 among clinicians 1, 2, and 3. Between clinician 5 and the others,  $\kappa$  values between 0.08 and 0.29 were reached.

**Conclusion:** EVAR suitability estimation in a cohort of patients is highly consistent in a group of experienced clinicians. The EVAR suitability estimation at the individual patient level varies substantially between clinicians, however. Aggregating expert opinions in abdominal aortic aneurysm anatomic suitability assessment for EVAR had the opportunity to replace individual clinician decision diversification in a more solid and consistent group decision process. (J Vasc Surg 2006;43:671-6.)

Endovascular aneurysm repair (EVAR) requires preoperative measurement to precisely define the aneurysm morphology and subsequently select the appropriate type of stent-graft. EVAR suitability or “likelihood of success” is a result of the combination of aneurysm morphology and thorough knowledge and experience with different types of stent-grafts. Preoperative EVAR suitability assessment is an important factor in determining successful aneurysm exclusion, minimizing intraoperative difficulties, and endeavoring the likelihood of attaining EVAR durability.<sup>1-9</sup>

Extracting EVAR decision algorithms to quantify the likelihood of success from a large panel of experienced clinicians has the potential to become an EVAR suitability reference guide, thereby protecting patients against an individual clinician’s uncertainty. A condition for developing applicable EVAR suitability algorithms is a high consistency in decision-making strategy between individual clinicians for each type of stent-graft.

The aim of the present study was to determine consistency and variance in the preoperative assessment of EVAR suitability between experienced clinicians.

## Methods

Anatomic data from 202 abdominal aortoiliac aneurysm (AAA) patients from two high-volume teaching hospitals were included in this study. All 202 patients were presented for EVAR assessment in the period 1999 to 2001 (Table I). For all patients, data from plain and contrast-enhanced computed tomography (CT), or calibrated intraarterial digital subtraction angiography (iaDSA), or both, were always available.

In both clinics, a minimum of at least three clinicians performed the standardized measurement procedure of all 202 AAAs. In three cases of neck configuration discrepancy, two more clinicians were involved in the measurement procedure until consensus was reached.<sup>10</sup> A standardized worksheet was used to divide each AAA into 10 segments: suprarenal aorta, infrarenal aortic neck, aneurysm, aortic bifurcation, right and left common iliac artery, right and left external iliac artery, and right and left common femoral artery (Fig 1). Six characteristics were recorded for each segment: diameter, length, percentage of thrombus, percentage of calcification, angulation, and shape (Table II).

When both were available, we preferred images of CT scans for diameter measurement and iaDSA for length measurement. Diameter was measured from intima to intima. The percentage of thrombus and percentage of calcification were defined as the percentage of the circumference of the total segment assessed from plain CT scans and contrast-enhanced CT-scans, respectively; angulation was defined as the sharpest central lumen line angulation in one or between two segments.

A total of 72 different criteria were used to describe the full anatomic characteristics of each individual AAA. The outcomes of all these measurements were tabulated on an AAA stent-grafting assessment worksheet (Table II). According to the aim of this study, we removed other patient characteristics such as age and comorbidity from the worksheet, providing the experts with only the numeric anatomic AAA data to assess the anatomic suitability for EVAR.

**Suitability assessment.** One interventional radiologist and two vascular surgeons from one hospital and one vascular surgeon and one radiologist from two other hospitals were part of this study. Each clinician had an individual EVAR experience of at least 100 procedures. The five clinician independently assessed EVAR suitability by using the numeric anatomic data of these 202 AAA worksheets.

All of the commercially available configurations of three stent-grafts—the Talent standard, the Talent custom-made, and the AneuRx (Medtronic AVE, Santa Rosa, Calif)—were available for selection.

*EVAR suitability* was defined as the clinician's expectation for the likelihood of an effective and durable sealing and fixation preventing proximal or distal leakage (type I endoleak) or stent-graft disconnection (type III endoleak). Because each AAA consisted of 10 segments, the overall suitability score for EVAR consisted of the aggregation of the score of these 10 segments by the individual clinician. We did not analyze the segmental information in this study.

The suitability for EVAR expressed by each clinician had to be rated on a 0 to 100 scale, between very suitable (0 to 49) and not suitable (100). To categorize the suitability, five clinically relevant asymmetrical groups (Fig 2) were defined for this study in dialogue with three other EVAR specialists not related to the assessments. The more difficult cases were rated in three of the five categories, ranging from 50 to 99, rendering the clinical relevancy. For intermediate or highly suitable cases, no subcategorization was made, thereby reducing the total number of categories needed in five. Based on the criteria and the available stent-grafts, the clinicians used the data from 202 patients to make a total of 3030 EVAR suitability assessments in the first round.

**Statistical analyses.** The Delphi method<sup>11,12</sup> was used to measure the consensus in EVAR suitability estimation for the 202 different AAA cases. Each worksheet was seen as an item of an "assessment questionnaire." The five clinicians evaluated each item with a suitability score for EVAR for each of the three stent-grafts separately. Applying the Delphi method, we created five clinician-ranking scores expressing the likelihood of success on a scale from 0 to 100 for each item for each type of stent-graft (Fig 3). We used Cronbach's  $\alpha$  as a coefficient for internal consistency between the five clinician ranking scores. The more the five clinicians were equal in their way of ranking EVAR suitability for the 202 worksheet cases, the closer the Cronbach  $\alpha$  value was to 1.0. A Cronbach  $\alpha$  value of 0.7 to 0.8 is regarded as satisfactory

consistency between clinicians. For clinical application, values near 0.90 are recommended.<sup>11,12</sup> To determine individual clinician-group correlation, we used the inter-item correlation matrix.<sup>11</sup>

Two Delphi assessment rounds were conducted for each clinician. In the first round, all 202 assessments had to be made. In the second round, the clinicians had to reassess their outliers, which were defined as EVAR suitability assessments that deviated more than one EVAR suitability category (Fig 2) of the clinician's mean EVAR suitability score. In this second round, clinicians were blinded for the outcome of their assessments in the first assessment round. They knew, however, that the assessment they made was different from the group assessment and reassessment was asked. If an individual assessment after the second round persistently deviated more than twice the standard error of the mean, the chief author discussed the case with the clinician, using the segmental scoring information as a check for misinterpretation of numeric anatomic data. If a misinterpretation was excluded, the suitability assessment of a case was considered as a consistent outlier. After the second round, the Delphi process was terminated because clinically applicable Cronbach  $\alpha$  values were reached.

With the  $\kappa$  method, clinical relevant variances in the outcome of suitability assessment between clinicians for individual patient and stent-graft combinations were determined. The following nomenclature of Landis and Koch,<sup>13</sup> was used: poor ( $\kappa$ , 0), slight ( $\kappa$ , 0 to 0.20), fair ( $\kappa$ , 0.21 to 0.40), moderate ( $\kappa$ , 0.41 to 0.60), substantial ( $\kappa$ , 0.61 to 0.80), and almost perfect ( $\kappa$ , 0.80 to 1.00) agreement. Four categories of overall EVAR suitability assessments were defined to calculate  $\kappa$  values: group 1, <50; group 2, 50 to 94; group 3, 95 to 99; group 4, 100. This redefinition was necessary because our original categorization in five groups (Fig 2) did not have any assessment scores in the 99 groups for some clinicians, so  $\kappa$  could not be calculated.

The statistical analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, Ill) for Windows (Microsoft, Redmond, Wash).

## Results

In round one for the Talent standard, Talent custom made, and AneuRx stent-graft assessments, Cronbach  $\alpha$  values of 0.79, 0.81, and 0.85, respectively, were found. The second round increased the Cronbach  $\alpha$  values to 0.87, 0.87, and 0.90, respectively.

The individual clinician group correlation over two Delphi iterations is presented in Table III. In all three stent-graft assessments, the individual clinician-group correlation in round two was between 0.69 and 0.86 for clinicians 1, 2, 3, and 4. Compared with clinician 5, a persisting clinician-group correlation of < 0.64 was seen.

The  $\kappa$  values (Table IV) ranged between 0.32 and 0.51 among clinicians 1, 2, and 3. Between clinician 5 and the others,  $\kappa$  values between 0.08 and 0.29 were reached.

For eight of 30 clinician-clinician comparisons, the  $\kappa$  value was moderate, for only one of 30 was the  $\kappa$  value substantial at 0.62, which indicates an agreement tendency.

## Discussion

This study clearly demonstrated that aggregating expert opinions in AAA anatomic suitability assessment for EVAR had the opportunity to replace individual clinician decision diversification with a more solid and consistent group decision process.

The decision-making strategy for EVAR suitability estimation in a group of AAAs was satisfyingly consistent between experienced clinicians. The high Cronbach  $\alpha$  values indicated a clinically applicable equivalent thinking process or group consensus. Only for clinician 5 was the clinician-group correlation low. This indicated that the decision-making strategy of clinician 5 was a consistent outlier compared with the other four clinicians. Clinician 5 had a tendency to rank EVAR suitability in extreme categories. The other four clinicians had a more deliberate assessment of the AAA data for EVAR.

The  $\kappa$  analysis demonstrated that the estimation on the level of each individual patient frequently varies one, or even more, categories between clinicians. Clearly, estimating the level of EVAR suitability for an individual AAA anatomy dataset is mostly an expression of objective clinical knowledge, intuition, and the clinician's past experience. From a patient perspective, this indicates that estimating the chance of effective and durable sealing and fixation of the stent-graft depends not only on the unique morphology of the patient but, importantly for a significant part, also on the risk assessment of each individual clinician.

The clinicians were selected because of their educational expertise as proctors and they were familiar with assessing numeric anatomic AAA data for EVAR as used in this study. Also, the clinicians had different backgrounds in their original vascular traineeship. These facts contributed to minimize biasing

of the Delphi method. As mentioned before, the clinicians were only aware of the numeric anatomic AAA data, although of course in practice, the definitive decision for or against EVAR application is only possible by balancing not only the anatomic characteristics but also the many other relevant patient characteristics. According to the aim of this study, acquaintance with other patient data or reviewing the original CT or iaDSA images was not allowed, thereby excluding, among other things, the influence of the interobserver variation of AAA measurement.<sup>10</sup>

Even high-volume AAA-EVAR teams will not develop enough experience to offer the individual patient comprehensive and balanced advice on EVAR suitability for all of the different commercially available stent-grafts. Moreover, EVAR is a rapidly evolving technology. The frequent introduction of new types of stent-grafts with their own unique characteristics results in more intuitive rather than knowledgebased decision-making in daily practice.<sup>14,15</sup>

## Conclusion

Extracting EVAR suitability decision algorithms from a large panel of experienced clinicians has the potential to become a gold standard if the algorithms are validated, easily accessible, and continuously updated with the latest peer-reviewed knowledge on the outcome of EVAR. The validation process of these algorithms should include future studies comparing the ultimate clinical outcome of individual patients with the initial suitability assessment, supporting the hypothesis that differences in preoperative suitability assessment predicted the ultimate results. Developing such a gold standard protects patients against individual clinician misinterpretation and against delay in the introduction of new EVAR knowledge in the medical community.<sup>14,15</sup>

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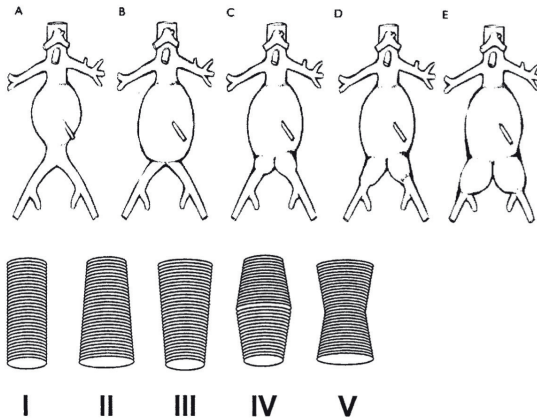
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**Table I.** Patient demographics

	Hospital I	Hospital II	Total	P
Patients (n)	100	102	202	NS
Mean age (years) (range)	71 (51-92)	71 (48-89)	71	NS
Male gender (%)	94	94	94	NS
Mean average sac diameter (mm) (range)	56 (18-90)	58 (35-90)	57 (18-90)	NS
EVAR yes/no (%)	70/30	102/0	172/30	<.05

**Table II.** AAA–EVAR assessment worksheet. **A,** Aneurysm classification (Eurostar) **B,** Neckshape<sup>16</sup> **C,** Measurements (mm)



Diameter	CT MRA	DSA	Tromb. % Ø	Calc. % Ø	Height	CT MRA	DSA
D1					H1		
D 2a					H2		
D 2b					H3		
D 2c					H4a		
D 3					H4b		
D 3a							
D 4					Abgulation	Angle °	Angle °
D 5a					Aortic neck		
D 5b					Aneurysm		
D 6a					Right com illiac		
D 6b					Left com illiac		
D 7a					Right ext illiac		
D 7b					Left ext illiac		

CT, computed tomography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography.

**Table III.** Individual clinician-group correlation over two Delphi iterations

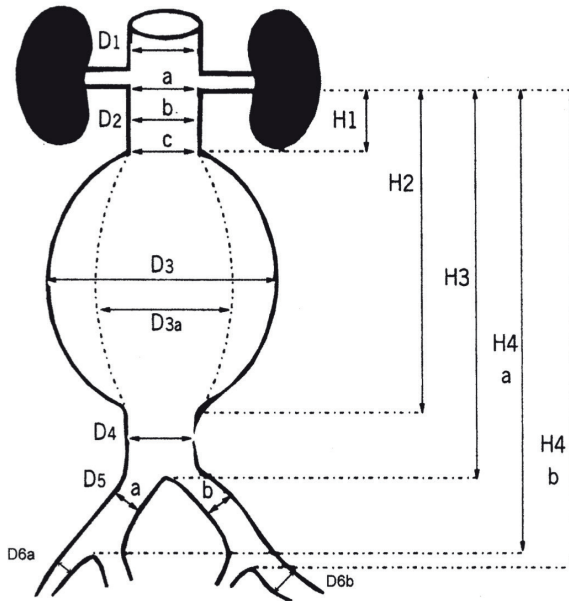
	Talent standard		Talent custom made		AneuRx	
	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Clinician 1	0.74	0.83	0.78	0.84	0.82	0.86
Clinician 2	0.69	0.79	0.71	0.80	0.75	0.83
Clinician 3	0.48	0.70	0.51	0.69	0.64	0.71
Clinician 4	0.61	0.72	0.64	0.75	0.64	0.74
Clinician 5	0.34	0.43	0.34	0.43	0.50	0.64

**Table IV.** Accordance after EVAR suitability assessment (round two) between clinicians expressed in with Talent standard, Talent custom, and AneuRx stent-grafts

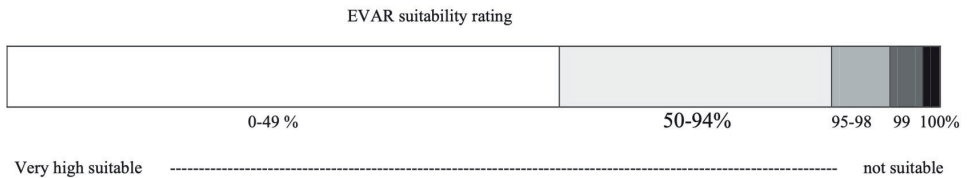
	Clinician 1	Clinician 2	Clinician 3	Clinician 4
Clinician 1	X	X	X	X
Clinician 2	0.48/0.51/0.62	X	X	X
Clinician 3	0.40/0.33/0.49	0.33/0.32/0.48	X	X
Clinician 4	0.47/0.44/0.50	0.37/0.34/0.47	0.23/0.19/0.31	X
Clinician 5	0.11/0.09/0.29	0.09/0.08/0.27	0.14/0.11/0.23	0.09/0.08/0.18

Data correspond with Talent standard, Talent custom, and AneuRx stent-grafts, respectively.

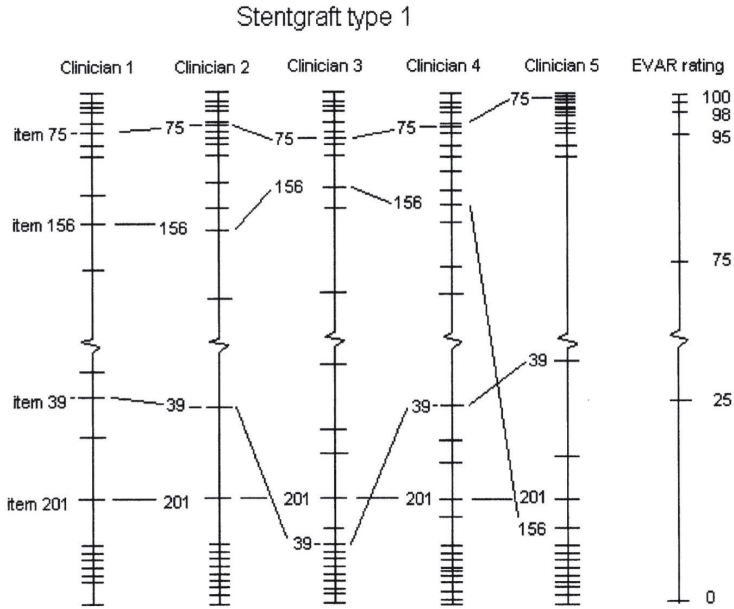
**Fig 1.** Infrarenal abdominal aortic aneurysm segments (Eurostar worksheet).



**Fig 2.** The suitability for endovascular aneurysm repair is divided in five categories: 0 to 49 (high to intermediate suitable); 50 to 94 (intermediate to low suitable); 95 to 98 (very low suitable), 99 (practically not suitable), 100 (not suitable).



**Fig 3.** Consistency and variance of assessments between individual clinicians. Example of a high consistency in decision making but also and high variance in suitability estimation per assessment between A, B, C, D, and E.





# Chapter

# 4

## The Anaconda™ AAA Stent Graft System: 2 year clinical and technical results of a multicentre clinical evaluation

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**Introduction:** This study reports the technical and mid-term clinical results of the second-generation Anaconda™ AAA Stent Graft System endovascular device for treatment of abdominal aortic aneurysm (AAA). The design of the Anaconda™ AAA Stent Graft System is characterised by a three-piece system consisting of two proximal independent saddle-shaped nitinol self-expandable rings with hooks fixation, zero body support and vacuum-cleaner tubeleg design.

**Methods:** From July 2002 to April 2005, a total of 61 patients with AAA were enrolled in a multicentre, prospective, non-randomised controlled design study. All patients received a second-generation Anaconda™ AAA Stent Graft System. They entered a standard follow-up protocol at discharge for 3, 6, 12 and 24 months. Follow-up data included survival; rupture-free survival; incidence of aneurysm rupture, death from aneurysm rupture, aneurysm-related death; freedom from aneurysm expansion; freedom from Types I and III endoleaks; endograft patency and technical and clinical success rates.

**Results:** Successful access to the arterial system was achieved in all patients. The primary technical success was 59 out of 61 and the primary assisted technical success was 60 out of 61. All endovascular grafts were patent without significant twists, kinks or obstructions. Migration was not observed in any of the grafts. During the first 30-day period, two serious adverse events (3%), both not related to the procedure, were observed. Nine patients (15%) needed a secondary intervention; two of these interventions were related to stent graft (3%). The mean aneurysm sac diameter decreased significantly from 57 mm pre-operative to 45 mm after 24 months, without aneurysm growth. There was one Type I endoleak at initial implantation, which was corrected using a proximal extension cuff. In total, three Type II endoleaks were still present after 24 months without any signs of aneurysm growth.

**Conclusion:** The design features of the second-generation Anaconda™ AAA Stent Graft System are effective in the treatment of AAAs on mid-term evaluation.

## Introduction

With the primary objective to exclude the abdominal aorta aneurysm (AAA) sac from the arterial circulation and to consequently eliminate the risk of aneurysm rupture, several endovascular graft devices were developed during the past 2 decades. The basic concept of endoluminal AAA exclusion has not changed during this period but the failure modes observed during this era inspired companies and clinicians to reappraise the endograft design configurations.

First-generation homemade devices were custom-made endografts using off-the-shelf stents combined with various graft materials used for conventional vascular procedures.<sup>1</sup> Clinical experiences were rapidly gained with second-generation, commercially available endoprotheses in the 1990s, which were used in the USA and Europe depending upon regulatory approval status.<sup>2,3</sup> Various failure modes of these stent grafts were identified. The two most clinically significant failures are endoleak (particularly Types I and III) and migration,<sup>4-6</sup> ranging between 10% and 30% 1 year after graft placement depending on endograft type. The first-generation Anaconda™ AAA Stent Graft System was developed without hooks and completely relied on friction sealing for proximal fixation. The second-generation Anaconda™ AAA Stent Graft System has been redesigned with the intention of addressing the failure modes observed in the earlier generations of stentgrafts, including the first-generation Anaconda.<sup>6-9</sup> The two major modifications were the introduction of proximal hooks connected to the proximal two-ring stents and the introduction of the zero body support of the graft, both with the intention to decrease the chance of migration. The name Anaconda™ was chosen because of the similarity between the shape of the proximal ring stent and a snake's mouth. The second-generation Anaconda™ AAA Stent Graft System was CE marked in April 2005. This study reports on the technical and the mid-term clinical results of the second-generation Anaconda™ AAA Stent Graft System for the treatment of AAA.

## Materials and methods

### Study design

From July 2002 to April 2005, a total of 61 patients with AAA were enrolled in a multicentre, prospective, non-randomised controlled study (Anaconda 004 study). Each patient underwent a detailed pre-operative screening to ensure that the general medical condition was satisfactory for conversion from endovascular aneurysm repair (EVAR) to conventional repair, if necessary. The information collected consisted of a general health analysis including the Society of Vascular Surgery-International Society of Cardiovascular Surgeons (SVS-ISCVS)<sup>10</sup> risk scores for diabetes, smoking, hypertension, hyperlipidaemia, cardiac status, carotid disease, renal status, pulmonary status and American Society of Anesthesiologists (ASA) classification. pre-operative AAA assessment included detailed spiral computed tomography (CT) scanning and standard contrast arteriography as detailed in the Core Laboratory Protocol. The selected medical and anatomical inclusion and exclusion criteria are listed in Table 1.

### Study hypothesis and definitions.

The primary objectives of this study were to examine the technical and clinical success of the Anaconda™ AAA Stent Graft System for the treatment of AAA. The following definitions, in line with the suggestions of Chaikof et al., were used.<sup>11</sup>

**Technical success** was defined as successful access to the arterial system using a remote site, successful deployment of the stent graft with secure proximal and distal sealing and fixation of the attachment devices, demonstrating safe and effective exclusion of the AAA without Type I or III endoleak and patent endoluminal graft without significant twists, kinks or obstruction by intra-operative angiography measurements periprocedural and in the first 24-h period. In case of unplanned endovascular or surgical procedures, it was defined as assisted primary or secondary technical success.

**Clinical success** was defined as successful deployment of the endovascular device at the intended location without death as a result of aneurysm-related treatment, Types I and III endoleak, graft infection or thrombosis, aneurysm expansion (diameter  $\geq$  5 mm, or volume  $\geq$  5%), aneurysm rupture or conversion to open repair. In cases with Type II endoleak, clinical success was only claimed in the absence of aneurysm expansion. **Primary clinical success** is clinical success without the need for an additional or secondary surgical or endovascular procedure. **Secondary clinical success** is clinical success obtained with the use of an additional or secondary surgical procedure.

**Clinical failure** includes a failure to deploy the endovascular device at the intended location, the presence of a Type I or III endoleak, graft thrombosis or infection, graft dilatation of 20% or more by diameter, graft migration, failure of device integrity, aneurysm expansion or rupture, conversion to open repair or death.

A **serious adverse event** was defined as any clinical event which results in death, or is life threatening, produced permanent or significant disability / incapacity, results in-patient hospitalisation or prolongation of existing in-patient hospitalisation, is a cancer or requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure.

Clinical success is reported as short term clinical success (30 days) and mid-term clinical success (2 years follow up).

### Device description

The Anaconda™ AAA Stent Graft System (Vascutek, Terumo, Inchinnan, Scotland) (fig1a,b) is a three pieces endovascular device made of multiple element nitinol stents combined with woven polyester graft material. At the top of the graft there is a dual-ring stent design which provides a haemostatic sealing against the vessel wall. The proximal ring stent is anchored in an infrarenal position by four pairs of nitinol hooks which preventing device migration (fig 1b). The body is unstented, resulting in zero column strength which is comparable to conventional bifurcated prosthesis design. The iliac legs are fully supported with independent nitinol ring stents which provides flexibility and prevents kinking in tortuous anatomy. The cannulation of the contralateral gate of the body is facilitated with a magnet system. The delivery device system of the body is flexible, kink resistant and allows multiple rotational, proximal and distal repositioning (fig 2). The delivery system of the main body has an outer diameter from 20.4 or 22.5 French (6.8 or 7.5 mm), depending of the stent graft neck diameter used. The delivery system for the iliac legs has an outer diameter of 18.3 French (6.1 mm).

AAA sizing and stentgraft selection was in line with the recommendations of the Anaconda™ AAA stentgraft system and sizing referenced chart. The oversizing at the level of the infrarenal neck was between minimal 7.3% and maximum 21.8% and at the level of the common iliac artery between 5% and 28.5% respectively.

### Operative procedure

The operation was performed under local, epidural or general anaesthetic in the operating room with a radiolucent table under fluoroscopic guidance. The procedure required surgical exposure of the femoral arteries or common iliac arteries and was performed by surgical cut down and formation of an arteriotomy. During the procedure intravenous Heparin 5,000 IU or 100 IU heparin/kg bodyweight was required in accordance with standard endovascular procedures. The surgical technique was carried out in accordance with the Vascutek Limited Instructions for Use (see [www.vascutek.com](http://www.vascutek.com)). All necessary operative details, overall outcome of the procedure as well as any adverse events during the operation were recorded using the case report form.

### **Follow-up protocol**

All patients were entered in a standard follow-up protocol at discharge and at 3, 6, 12 and 24 months follow-up. Each patient underwent a postoperative contrast enhanced CT-scan and plain abdominal x-ray. All radiological data were independently reviewed by a core lab (Cleveland Clinic, Cleveland, Ohio). Recorded follow-up data included survival; rupture-free survival; incidence of aneurysm rupture, death from aneurysm rupture, aneurysm-related death; freedom from aneurysm expansion; freedom from Type I and III endoleaks; endograft patency; an

d technical and clinical success rates.

### **Statistical analysis**

Results are reported as mean  $\pm$  SD (range) or with a 95% confidence interval where appropriate. Student t-test was used to compare continuous variables. Significance was assumed at a P value of less than 0.05. Kaplan-Meier curves and log-rank tests were used to plot survival over time. The statistical analyses of this study were carried out by an independent statistician.

## Results

### Demographics

Relevant patient characteristics were reflected in table 2. The patients' age ranged between 51 and 87 years with a mean of 71 years. The average aneurysm sac diameter was 57 mm (range 50–83).

### Technical success

The technical results were summarized in table 3a. In all patients successful access to the arterial system was achieved. In all cases the body of the Anaconda™ could be precisely positioned and if necessary repositioned due to the delivery device. One implantation could not be completed due to accidental loss of the guide wire of the main body during operation. The local physician decided to convert to conventional open repair. Access to the contralateral gate was quick and easy. Intra-operatively there was one Type I endoleak which was treated successfully with a proximal extension cuff. There were no Type III endoleaks. All endoluminal grafts were patent without significant twist, kinks, or obstruction.

### Short term clinical success

The short term clinical outcome was summarized in table 3a.

During the first 30-day there were two serious adverse events resulting in death; one patient died due to a cardiac arrest eight days after EVAR and another patient died as a result of a severe lung bleeding twelve hours after an uncomplicated EVAR. The cause of death in the second patient was a ruptured bronchial artery in a necrotic lung segment due to radiotherapy for bronchial carcinoma two years before, which could not be foreseen at forehand. At autopsy it was confirmed that the AAA exclusion with the Anaconda™ stentgraft was uncomplicated in both cases. Other early serious adverse events were not experienced.

### Mid term clinical results

The mid term clinical outcome was summarized in table 3b and 4.

The 2-year loss to follow-up was zero. There were seven serious events including four additional deaths after 30 days (heart failure (2), carcinoma and CVA) and one patient with occlusion of an iliac device leg, treated successfully with a PTA procedure. There were no aneurysm-related deaths. There were no device fixation failures at the proximal neck, specifically no wire or hook fractures or migrations at 2 years. Nine patients needed a secondary intervention; two of these interventions were related to graft. The mean aneurysm sac diameter decreased significantly from 57 mm ( $\pm 7$ mm) pre-operative to 45 mm ( $\pm 11$ mm) after 24 months evaluation ( $p < 0.0001$ ). At 24 months no patient had an increase of the aneurysm sac diameter, eight patients remained stable and 39 patients had a decrease of the aneurysm sac of 5 mm or more. Eight patients were not evaluated at 24 months, but all these patients showed no increase at 18 months' follow-up.

## Endoleak

Neither Type III nor Type IV endoleaks were observed during the 2-years' follow-up. One Type I endoleak occurred during operation, which was corrected intra-operatively using a proximal extension cuff and Palmaz balloon-expandable stent. Retrospectively, less than 6% oversizing of the Anaconda stent caused this problem. Eight Type II endoleaks, seven lumbar artery and one inferior mesenteric artery were observed intra-operatively. One patient with a Type II endoleak died 8 days after discharge due to cardiac arrest. In two other patients with stable aneurysm diameter, coiling of a Type II endoleak was performed at 3 months. One Type II endoleak disappeared spontaneously after 18 months and another after 24 months. A new Type II endoleak was discovered at 12 months follow-up and disappeared spontaneously at 18 months follow-up. In total, three Type II endoleaks were still present after 24 months without any signs of aneurysm growth.

## Discussion

The second-generation Anaconda™ AAA Stent Graft System was introduced in the clinic 6 years ago. The present report focusses on the technical and the mid-term clinical success of this new device. Including the 61 patients in this present study, until now technical success has been reported in 173 out of 175 patients (99%) receiving an Anaconda™ stent graft.<sup>12-14</sup> These results are comparable with the Zenith and Excluder trials recently published.<sup>6,15</sup> The only conversion in the present series was due to loss of guide-wire access while no additional endovascular equipment, such as long wires for a brachial approach, a goose neck or a shepherd's hook catheter, was available at the local site to resolve the problem. In our opinion, lack of technical success in this case was not related to any failure of the Anaconda™ system. The present multicentre prospective, core labcontrolled study determined the mid-term clinical outcome of AAA patients treated with the Anaconda™ AAA Stent Graft System. In line with the in- and exclusion criteria, selecting anatomically and physically favourable patients, excellent outcomes should be feasible. The 2-year overall mortality rate of 10%, non-related to aneurysm, was comparable with the DREAM trial,<sup>16</sup> although 30-day mortality in our group was slightly higher (3.2% vs. 1.1%). In particular, the low incidence of Types I and III endoleaks, the absence of migration, the absence of increase of aneurysm diameter and the 100% rupture-free survival were considered to be excellent and comparable with the Zenith and Excluder trials.<sup>6,15</sup> experience and on short term the docking zone diameter of the small bodies will be enlarged.

One special feature of the Anaconda™ AAA Stent Graft System is the possibility of using the magnetic docking system for cannulation of the contralateral gate. Although time to access to the contralateral gate was not part of the study protocol, the personal experience of the participants was that the magnetic

system significantly reduced the cannulation time of the contralateral side compared with standard cannulation techniques. Other single-centre studies reported a mean contralateral cannulation time of 4 min (range: 3-22 min) with a magnetic coupling success rate of 94-100%.<sup>12-14</sup> After modification with stronger magnets in the year 2005, a further reduction of the cannulation time of the contralateral body was achieved according to Stehr.<sup>13</sup> Another special feature of the Anaconda™ AAA StentGraft System is the possibility of repositioning the two proximal sealing and fixation stent rings. This feature allowed accurate infrarenal placement in angulated necks as well. Repositioning rates reported in the literature varied between 38% and 10% to achieve more satisfactory stent-graft positions.<sup>12-14</sup> The Anaconda™ AAA Stent Graft System is not more difficult in stent placement than are other systems, and getting the most optimal result using a repositional system during the intervention is attractive and forgiving in first-time suboptimal stent placement. Most stents do not have this feature and stent replacement could be difficult to achieve. The saddle-shaped proximal ring design facilitates adaptation to local anatomy, also during the first few days after implantation. If this occurs, the valley of the proximal stent ring could migrate a few millimetres upstream. If the Anaconda is placed juxtarenal with the valleys functioning as scallops around the renal orifices, we advise placement of short balloon-expandable stents in these orifices to prevent renal artery stenoses or occlusion.

It is noted that although the number of leg occlusions observed was reasonably low and comparable to other devices, the majority of occlusions in the current worldwide Anaconda™ experience is observed in the combination of small body diameter (<25 mm) and relatively large diameter legs. Consequently, the sizing and reference chart concerning the body leg combination was recently adjusted to this latest worldwide experience and, on short notice, the docking zone diameter of the small bodies will be enlarged. The secondary intervention rate of 15%, including coil embolisation of a Type II endoleak in two patients with stable aneurysm diameter, was comparable with other prospective studies and represents the known difference between conventional surgical repair, with a low incidence of secondary interventions, and EVAR.<sup>17</sup> Most vascular centres do not advise coil embolisation in asymptomatic patients with a Type II endoleak in case of stable aneurysm diameter. We conclude that the design features of the second-generation Anaconda™ Stent Graft System allow easy placement of the stent and are effective in the mid-term in the treatment of AAAs in patients with straightforward anatomy. Studies focussing on patients with challenging AAA anatomy and patients with rupture AAA will shed further light on the additional clinical value of the Anaconda™ AAA Stent Graft System design.

## Acknowledgements and disclosure

### *Participants in ANA 004 study and number of patient included*

Participant	Clinic	Number of patients included
Wolff W. Stelter, MD, PhD	<i>Department of Surgery, Städtische Kliniken; Germany</i>	4
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Jan Brunkwall, MD, PhD	<i>Department of Vascular Surgery, Klinikum der Universität Köln</i>	7
Klaus Balzer, MD, PhD	<i>Department of Vascular Surgery, Evangelisches Krankenhaus</i>	3
Gernot Wozniak, MD, PhD	<i>Department of Surgery, Krankenhaus Knappschafts</i>	3
Peter Kasprzak, MD, PhD	<i>Department of Surgery, Klinikum de Universität Regensburg</i>	8
Ingo Flessenkämper, MD, PhD	<i>Department of Vascular Surgery, DRK-Kliniken Mark</i>	5
Peter Taylor, MD, PhD	<i>Department of Surgery, London Health Science Centre</i>	4
Robert H. Geelkerken, MD, PhD, Rob J.Det, MD, Pieter de Smit, MD, PhD, D.G. Gerrits, MD, Ad.B. Huisman, MD, PhD	<i>Department of Vascular surgery and interventional radiology Medical Spectrum Twente; Enschede, The Netherlands</i>	18

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**Table 1** Anaconda 004 AAA stentgraft study

**Inclusion criteria**

▪ Patients aged 18 years – 85 Years
▪ Patient willing and available to comply with follow up requirements
▪ Patient can comply with instructions and give informed consent
▪ Life Expectancy > 2 Years
▪ Patient is a candidate for open surgical repair
▪ AAA > 50 mm in diameter
▪ Infrarenal proximal neck diameter 18 – 31.5 mm
▪ Infrarenal proximal neck length >15 mm
▪ Distal Iliac fixation site diameter < 16 mm and > 30 mm in length
▪ Access vessels > 7.5 mm in diameter

**Exclusion criteria**

▪ Ruptured AAA
▪ Symptomatic AAA
▪ Juxta or suprarenal extension of aneurysm
▪ Presence of serious concomitant medical disease or infection
▪ Known allergy to contrast medium, nitinol or polyester
▪ Inability to preserve at least one hypogastric artery
▪ Connective tissue disease
▪ ASA Grade IV or V
▪ Need for surgical reconstruction of other visceral arteries
▪ Infra renal aortic angulation > 45°
▪ Presence of > 50% continuous calcification of proximal neck
▪ Presence of > 50% thrombus in proximal neck
▪ Presence of conical infrarenal neck
▪ Other unsuitable anatomy

**Table 2** Anaconda 004 AAA stentgraft study; Patient characteristics

Demographic		Present study number of patients
		<i>(range or %)</i>
<b>Age (years)</b>	Mean (Range)	71.2 (51-87)
<b>Gender</b>	Male	60 (98.4)
	Female	1 (1.6)
<b>ASA grade</b>	I	3 (4.9)
	II	38 (62.3)
	III	19 (31.1)
	Unknown	1 (1.6)
<b>Diabetics</b>	Only diet controlled	9 (14.8)
<b>Hypertension</b>	None	16 (26.2)
	Drug controlled	43 (70.5)
	Uncontrolled	2 (3.3)
<b>Hyperlipidaemia</b>	Normal	26 (42.6)
	Mild	20 (32.8)
	Diet and or drugs	14 (23)
	Not recorded	1 (1.6)
<b>Cardiac status</b>	Normal	30 (49.2)
	Asymptomatic - MI	18 (29.5)
	Angina etc.	13 (21.3)
<b>Renal disease</b>	Normal	57 (93.4)
	Increased	4 (6.6)
<b>Pulmonary disease</b>	Normal	48 (78.7)
	Mild	9 (14.8)
	Moderate / severe	1 (1.6)

**Table 3a** Anaconda 004 AAA stentgraft study; Technical success and short term clinical success

	Present study	
Primary technical success <sup>&amp;,&amp;#</sup>	96.7 %	(59 / 61)
Primary assisted and secondary technically succes <sup>90</sup>	98 %	(60 / 61)
Primary clinical success <sup>&amp;,&amp;#,&amp;#</sup>	93 %	(57 / 61)
Secondary clinical success <sup>&amp;</sup>	95 %	(58 / 61)
Adverse events <sup>*,#,&amp;</sup>	3.2 %	(2 / 61)
Clinical failure <sup>*,#,&amp;</sup>	4.9 %	(3 / 61)

<sup>90</sup> One conversion due to loss of guide wire.

<sup>&</sup> One type 1 endoleak. Proximal extension cuff resolved endoleak.

<sup>&#</sup> Type 1 endoleak during operation, proximal extension cuff needed.

<sup>\*</sup> One conversion due to loss of guide wire. Clinical failure.

<sup>#</sup> Death due to cardiac arrest. Not device related. Clinical failure.

<sup>&</sup> Severe long bleeding. Not device related. Clinical failure.

**Table 3b** Anaconda 004 AAA stentgraft study; Mid term clinical success (2 years)

	Present study (Overall)	
Primary clinical succes <sup>1</sup>	72.1 %	(44 / 61)
Secondary clinical succes <sup>2</sup>	88.5 %	(54 / 61)
Clinical failure <sup>3</sup>	11.4 %	(7 / 61)
Serious adverse events <sup>4</sup>	11.4 %	(7 / 61)
All cause mortality	9.8 %	(6 / 61)
Aneurysm related mortality	0 %	(0 / 61)
Freedom from reintervention <sup>5</sup>	85.2 %	(52/61)
Freedom from migration <sup>6</sup>	100 %	(60/60)

<sup>1</sup> Primary after 24 months. (61-1 conversion- 1 prox cuff - 6 deaths during follow-up- 9 interventions)

<sup>2</sup> 61-6 deceased – 1 conversion

<sup>3</sup> Clinical failures. (6 deaths (not as a result of aneurysm-related or procedure related death), 1 conversion)

<sup>4</sup> Serious. (6 deaths (not as a result of aneurysm-related or procedure related death), 1 conversion)

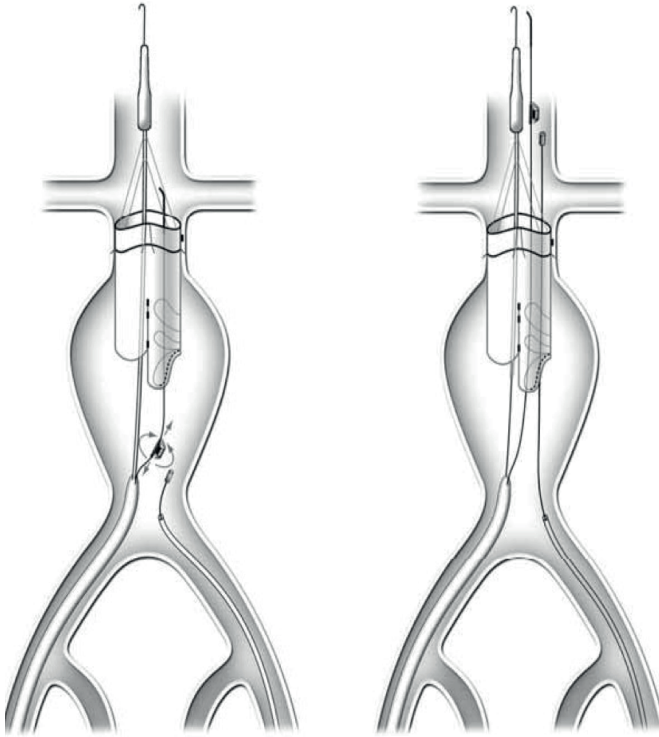
<sup>5</sup>-9 interventions

<sup>6</sup>- 1 conversion, 60/60 without any migration.

**Table 4** Anaconda 004 AAA stentgraft study; Re-interventions

Patient	Re-Intervention	Details	Follow Up
25	Coiling	Patient had persistent Type II lumbar endoleak. Elective angiography with attempt to coil.	3 m
23	Coiling	Patient has a new Type II collateral vessel endoleak. Collateral vessels coiled.	3 m
1	Iliac extension to treat aneurysm.	Patient had distal iliac aneurysm successfully treated with an Anaconda iliac extension.	10 m
47	Iliac extension to treat dilatation.	Increased diameter of left CIA.	12 m
5	Fem Fem cross-over	Right iliac obstruction with stenosis in external iliac artery.	3 m
33	Thrombendarterectomy & SFA Proximal Vein Patch Plasty	Occlusion of artery access.	15 m
3	PTA	Femoral artery occlusion. High grade stenosis of common femoral artery.	12 m
58	PTA	Internal iliac occlusion.	12 m
27	Thrombectomy & Stent	Right iliac device obstruction	16 m

**Figure 1a** The Anaconda™ AAA Stent Graft System (Vascutek, Terumo, Inchinnan, Scotland) is a three pieces endovascular device made of multiwire twisted nitinol stents combined with woven graft material. The cannulation of the contralateral gate of the body is facilitated by a unique magnet system.



**Figure 1b** The proximal ring stent is anchored in an infrarenal position by four pairs of nitinol hooks which preventing device migration.



**Figure 2** Repositionable proximal neck

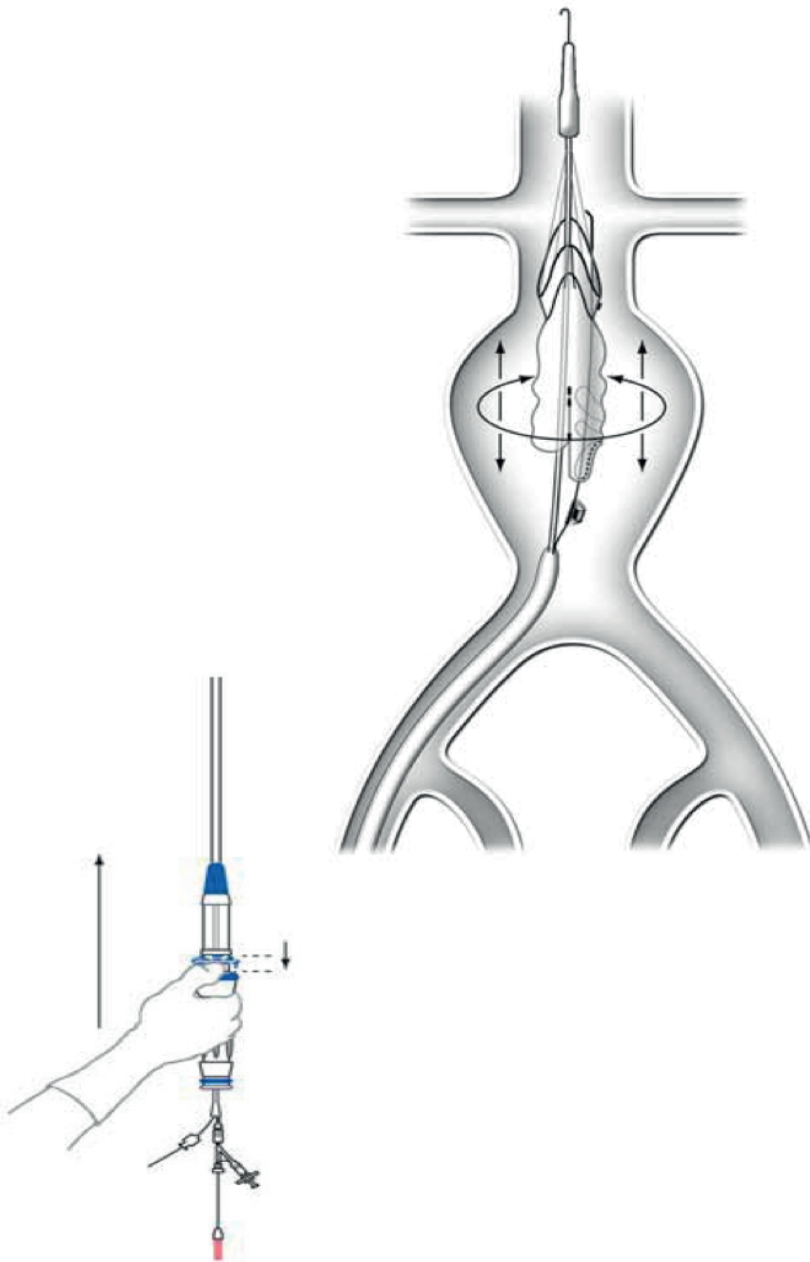
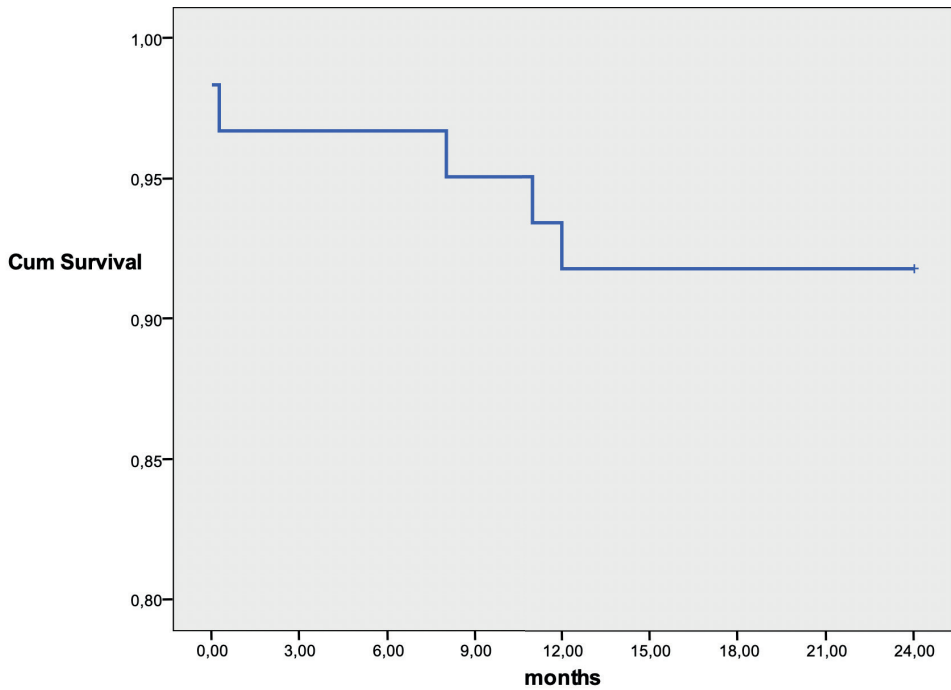


Figure 3 Kaplan-Meier survival curve survival.



Months	N=0	3	6	9	12	15	18	21	24
Patient at risk	60	58	58	57	56	55	55	55	54
No Deaths	2	0	0	1	1	1	0	0	1
Cumulative survival	96.7%	96.7%	95%	95%	93.3%	91.7%	91.7%	91.7%	90%
Cumulative mortality	3.3%	3.3%	5%	5%	6.7%	8.3%	8.3%	8.3%	10%



# Chapter

# 5

## Results of the Anaconda endovascular graft in abdominal aortic aneurysm with a severe angulated infrarenal neck.

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**Introduction:** Proximal neck anatomy of an abdominal aortic aneurysm (AAA), especially a severe angulated neck of more than 60 degrees, predicts adverse outcome in endovascular aneurysm repair. In the present study, we evaluate the feasibility of the use of the Anaconda™ endovascular graft (Vascutec, Terumo, Inchinnan, Scotland) for treating infrarenal AAA with a severe angulated neck (>60 degrees) and report the midterm outcomes.

**Methods:** In total, nine Dutch hospitals participated in this prospective cohort study. From December 2005 to January 2011, a total of 36 AAA patients, 30 men and six women, were included. Mean and median follow-up were both 40 months.

**Results:** Mean infrarenal neck angulation was 82 degrees. Successful deployment was reached in 34 of 36 patients. Primary technical success was achieved in 30 of 36 patients (83%). There was no aneurysm-related death. Four-year primary clinical success was 69%. In the first year, eight clinical failures were reported including four leg occlusions which could be solved using standard procedures. After the first year, three patients with additional failures occurred; two of them were leg occlusions. Four patients needed conversion to open AAA exclusion. In six of 36 patients, one or more reinterventions were necessary. Three of them were performed for occlusion of one Anaconda leg and two were for occlusion of the body.

**Conclusion:** The use of the Anaconda endovascular graft in AAA with a severe angulated infrarenal neck is feasible but has its side effects. Most clinical failures occur in the first year. Thereafter, few problems occur, and midterm results are acceptable. Summarizing the present experiences, we conclude that open AAA repair is still a preferable option in patients.

## Introduction

Since its introduction endovascular aneurysm repair (EVAR) has gained widespread adoption as a routine treatment alternative for patients with abdominal aortic aneurysm (AAA). However, meanwhile it has become clear that failure of EVAR depends both on features of AAA anatomy and endovascular graft characteristics. The proximal AAA neck anatomy, especially a severe angulated neck of more than 60 degrees predicts adverse outcome in EVAR.<sup>1-5</sup> However, this opinion has been challenged recently.<sup>6</sup>

Learning from the experience with first generation endovascular grafts and due to technological advances, the latest generations of commercially available endovascular grafts have been clearly improved. Modification and redesigning of the endovascular graft with specific attention to flexibility, proximal fit and sealing intended to decrease the chance of type 1 endoleak and endovascular graft migration.<sup>7-9</sup> As a consequence, indications outside instruction for use (IFU) were sought in patients with hostile neck anatomy unfit for open repair.<sup>10-16</sup>

The Anaconda endovascular graft (Vascutec, Terumo, Inchinnan, Scotland) was designed with the intention of addressing some of the failure modes observed in the 1990s. Hypothetically, because of the zero body columnar strength design and the high flexibility of the system during placement, it should be feasible to utilize the Anaconda in AAAs with severe infrarenal angulations.<sup>17</sup>

In the present study we evaluated the feasibility and mid-term outcome of the Anaconda™ endovascular graft for treating infra-renal AAA with a severe angulated neck.

## Methods

In total, nine Dutch hospitals participated in this prospective cohort study. From December 2005 to January 2011, a total of 36 AAA patients, 30 men and six women, were included. Mean and median follow-up were both 40 months (range, 0-69 months).

### Study design

Patients with an AAA and an infrarenal neck angulation of 60 degrees or more were eligible for inclusion in the Multicenter Angulated Neck Study with the Anaconda endovascular graft (MANSA).

Table I presents an enumerative description of all the inclusion and exclusion criteria for the MANSA study. The study protocol was approved by the institutional review board. Aneurysm anatomy was defined through the use of Eurostar criteria.<sup>18</sup>

Each patient underwent a detailed preoperative screening to evaluate suitability for inclusion in the study. The information collected consisted of a general health analysis including the Society of Vascular Surgery/ International Society of Cardiovascular Surgery (SVS/ISCVS) risk scores for diabetes mellitus, smoking, hypertension, hyperlipidemia, and cardiac, carotid, renal, and pulmonary disease, as well as American Society of Anesthesiologists (ASA) classification and ankle-brachial index. Preoperative AAA assessment included detailed spiral computed tomography (CT) scanning and angiography as described in a previous study with the Anaconda endovascular graft (ANA-004 study).<sup>19</sup>

### Study hypothesis and definitions

The primary objectives of the MANSA study were to examine the technical and clinical success of the Anaconda™ endovascular graft for the treatment of AAA with a severe angulated infrarenal neck. The outcome parameters were outlined in detail in ANA-004 and were in line with the previous published guidelines for reports concerning EVAR by Chaikof et al.<sup>20</sup> Clinical success is reported as short-term clinical success (30 days) and midterm clinical success (up to 4 years of follow-up).

### Device description

The Anaconda AAA Stent Graft System is a three-piece endovascular graft. The stents were made of multiple-element nitinol stents internally covered with woven polyester graft material. The top of the endovascular graft consists of a dual-ring stent design, resembling the Anaconda snake. The proximal ring stent is anchored in an infrarenal position by four pairs of nitinol hooks, which prevent device migration. The body is unstented, resulting in zero column strength and adaptability in angulated proximal vascular anatomy.

The iliac legs are fully supported with independent nitinol ring stents, which prevent kinking and provide

flexibility with fixation in tortuous distal iliac and femoral anatomy. The delivery device of the main body has an outer diameter of 20.4F or 22.5F (6.8-7.5 mm), depending of the stent graft neck diameter used. The delivery system for the iliac legs has an outer diameter of 18.3F (6.1 mm). The Anaconda™ AAA Stent Graft System can be fully repositioned by use of the control collar of the delivery system handle. The cannulation of the contralateral gate of the body is facilitated with a magnet system that uses a preloaded magnet wire to assist in the cannulation and deployment of the contralateral iliac leg.

### Operative procedure

All surgery was performed electively with a radiolucent table under fluoroscopic guidance. The endovascular graft was selected according to AAA anatomy, with special attention for at least 20%-30% oversizing of the prosthetic body in relation to the infrarenal neck diameter. The procedure was carried out under local (n=9), epidural (n=26), or general (n=1) anesthesia, by means of standard surgical exposure of femoral arteries with the use of surgical cut-down and arteriotomy. For anticoagulation during the procedure, intravenous heparin (100 IU/kg body weight) was given in accordance with standard endovascular procedures. A second heparin dose was given when the EVAR procedure exceeded 2 hours of operative time.

First, on both sides, a stiff .035 wire (Backup Meier; Boston Scientific, Natick, Mass) was introduced up to the aortic arch. When iliac and aortic angulations could not be straightened with the use of stiff wires, one or two endovascular sheaths (Cook Medical Europe Ltd, Limerick, Ireland) were used. The zero columnar strength of the body caused by the unstented segment is problematic in the severely angulated distal part of the infrarenal aortic neck. To prevent infolding of the body, the starting point of the release of the iliac legs in the body was therefore close to the proximal body stent rings at a distance above the level of the aortic rim and angulation. In this way, the body is supported in this crucial place and kinking or infolding was diminished. If applicable, the legs were extended to the common iliac bifurcation. All necessary operative details, overall outcome of the procedure, as well as any adverse event during operation were recorded.

### Follow-up protocol

The study included post-operative follow-up at discharge, 3, 6, 12, 18, 24 months and yearly thereafter to assess clinical success or failure. Each patient underwent postoperative CT-scanning at discharge and duplex-ultrasound or CT and biplane abdominal radiography thereafter. Recorded follow-up data included overall survival; death as a result of aneurysm-related treatment; conversion to open repair; endoleak; reintervention; aneurysm expansion or rupture; renal artery occlusion and endovascular graft infection, thrombosis, migration, dilatation or failure of integrity of exoskeleton structure.

### Statistical analysis

Only descriptive statistics were performed and mean, median or range are reported when appropriate.

## Results

### Patient and anatomical characteristics

Patient characteristics are summarized in table 2 and anatomical characteristics in table 3. Mean infrarenal neck angulation in this cohort AAA patients was 82 degrees (range 60-133 degrees). Mean aneurysm diameter was 71 mm, ranging from 45 mm (symptomatic small AAA) to 100 mm. In table 4 the outcome parameters up to four years follow-up are listed.

### Technical success

Primary technical success was achieved in 30 out of 36 patients (83%). There were two serious adverse events (SAE) during the initial EVAR procedure. In one patient an improper released Anaconda™ body below the aortic neck angulation could not be repositioned upstream due to the aortic rim at the level of the angulation and conversion to open repair was necessary.

In another patient deployment of the contralateral Anaconda™ leg failed. In the already deployed Anaconda™ main body an aorta-uni-iliac endovascular graft (Talent, Medtronic, Minneapolis, USA) with additional femoral-femoral crossover bypass was placed. This patient died of metastatic colonic malignancy in the fourth year of follow-up and developed in his last week a possible paraneoplastic occlusion of the Anaconda™ stent just distal from the renal arteries, which may have contributed to the death of this patient.

There were four type 1 endoleaks at the end of the implantation. Because of the adaptability of the two saddleshaped proximal stent rings, conservative treatment was initiated. Three of these four type I endoleaks resolved, with no signs of endoleak on the postoperative CT scan at discharge. The fourth patient with type I endoleak was initially treated with a proximal aortic extension cuff (Talent), and selective embolization of the type I endoleak. CT scanning on the fifth postoperative day demonstrated persisting type I endoleak and occlusion of the left renal artery. This artery was unintentionally partially covered by the aortic extension cuff. A partial conversion suturing the Anaconda body onto the native aorta was done. In the third-year follow-up, a type II endoleak was discovered and treated with coiling because of slight growth of the AAA. Unfortunately, after 49 months of follow-up, a contained AAA rupture caused by proximal anastomotic suture dislodging occurred. Resuturing of the proximal Anaconda™ body was performed successfully.

### 30 day clinical success

During the first 30 days the all-cause mortality was 0% (table 4). Mean and median hospital stay were 8 and 6 days (range 3-30 days), respectively. A total of 13 patients were hospitalized between 3 and 5 days.

One patient was re-admitted after 30 days, mainly because of respiratory problems. There were 11 type II endoleaks at discharge CT. The 30-day primary clinical success was 89% and assisted primary and secondary clinical success 94%. There were four 30-day clinical failures and SAEs (11%).

### **One year clinical success**

The first-year primary clinical success rate was 28/36 (78%). The primary assisted and secondary clinical success rates were 30/36 (83%). There were four additional clinical failures after 30 days, including two occlusions of the main body and two leg occlusions. In three of these four patients, additional interventions were necessary (femoralfemoral crossover bypass, recanalization of the stent body, conversion to an open bifurcated prosthesis). The fourth patient remained asymptomatic, and a conservative policy was followed. One patient died during the first year because of advanced age with general exhaustion.

### **Midterm clinical success**

After 4 years 2 patients were lost to follow-up. At four years the aneurysm related mortality was zero. All-cause mortality was 8 / 36 (22 %). The 4 year primary clinical success rate was 25 / 36 (69 %). The primary assisted and secondary clinical success rates were both 27 / 36 patients (75%). Eight out of 11 clinical failures and seven out of 10 SAEs occurred in the first post-operative year.

### **Other clinical failures, reinterventions and serious adverse events**

#### ***Occlusion of the Anaconda™ body***

One patient perceived a complete occlusion of the Anaconda™ body one week after a herniated nucleus pulposus operation. We speculated that during the operation in which the patient was resting on his belly and positioned with 90 degree hip flexion the Anaconda™ endovascular graft was inadvertently compressed. Complete conversion and implantation of a conventional Dacron aortabi-iliac prosthesis was performed.

In one patient an occlusion of Anaconda™ body occurred 11 months after the implantation. Percutaneous recanalisation of the body was established inserting two self-expandable stents at the level of the flow splitter. Four months later this patient presented with a contained AAA rupture. A complete conversion with insertion of a conventional Dacron aortabi-iliac prostheses was carried out.

#### ***Occlusion of a Anaconda™ leg***

One patient had a symptomatic occlusion of the left Anaconda™ leg 1 month after operation.

Thrombectomy was performed but re-occlusion occurred within 3 months. A femoral-femoral crossover bypass resolved the clinical symptoms, and a type II endoleak was coiled. One patient had a symptomatic occlusion of the left Anaconda™ leg. A femoral-femoral crossover bypass was done. One patient had a symptomatic occlusion of the right leg. In this patient thrombectomy and percutaneous transluminal angioplasty of the common and external iliac artery were successful.

One patient had an asymptomatic occlusion of the left Anaconda™ leg that was treated conservatively. Finally, another patient had an occlusion of the left leg, a stenotic right leg and migration of the stent with rotation, but was asymptomatic and treated conservatively.

### **Migration**

One patient had migration of the Anaconda™ body as the result of neck dilation producing a type I endoleak. Conservative treatment but also revision with the use of a triple fenestrated Anaconda™ extension are considered.

## Discussion

The present study, with a mean follow-up of 40 months, demonstrated that EVAR in patients with hostile neck anatomy outside Anaconda™ IFU criteria provided acceptable primary and secondary results without aneurysm-related mortality. The features of the second-generation Anaconda™ endovascular graft, such as repositionability of the two proximal stent rings during deployment and the unsupported and therefore more flexible main body, appear to expand the applicability of EVAR in AAA beyond 60 degrees of neck angulation. The number of leg occlusions was five out of 36 (14%) in total, and three of them occurred in the first year after implantation. As mentioned in the ANA-004 study, leg occlusion in the Anaconda endovascular graft was mainly observed in patients with small body diameter (<25 mm) and relatively large-diameter legs. The combination with steep neck angulations exacerbated the possibility of leg occlusions and could have propagated ultimately to body occlusion. On the basis of these observations, the sizing and reference chart of the Anaconda endovascular graft concerning the body leg combination was adjusted. A second modification to further reduce leg occlusion was the introduction of the Anaconda One-Lok system in 2011 (Fig); every leg fits in every body, abolishing body and leg mismatch. The One-Lok system was introduced after closure of the current study, and clinical results of the One-Lok system in AAA with severe angulated necks are not available yet.

Carpenter et al<sup>21</sup> mentioned in their study several causes of leg occlusion. Direct extrinsic compression of the limb in the iliac trajectory caused by vessel stenosis or tortuosity could provide a friction point for the introduction of twists. As a result of this, occlusion can occur. Also, a severe calcified and relatively narrow aortic bifurcation can become a fulcrum for the graft to bend or twist. Extrinsic limb compression caused by luminal thrombus within the aneurysm can compromise the limb outflow. With only one case of a migrated Anaconda™ body caused by neck dilation, the migration rate appears to be low. The mechanical characteristics of the Anaconda™ saddle-shaped proximal fixation and sealing rings including four hooks were clearly demonstrated in an experimental in vitro set-up comparing displacement forces (DFs) at proximal neck seal lengths of 15 and 10 mm in three different types of stents.<sup>22</sup> The Anaconda endovascular graft produced the second-highest DF in the neck and the highest DF in the distal fixation zone; distally, the “fish-mouth” configuration also increased the friction of the vessel wall.<sup>23</sup> The high DF migration of an appropriately oversized Anaconda endovascular graft is rare, even in very challenging environments such as highly angulated necks. latest-generation endovascular graft IFU include a neck angle varying between 60 degrees or less, with a minimum of 10-15 mm neck length, 75 degrees or less with the use of the Endurant, or 90 degrees or less with the use of the Aorfix, according to IFU. The IFU of the two endovascular grafts, including highly angulated infrarenal aortic necks, were not supported with midterm clinical data strictly applying the Chaikof criteria. Table V summarizes the IFU for EVAR indications for CE-approved stent prostheses.

Applying the Anaconda device in severe angulated necks outside the IFU challenged the participating EVAR teams in more than one way. In the present study, the operative procedures were custom-made in nearly every individual case.

Because of inclined (ie, nonperpendicular to the flow lumen) placement of the proximal stent rings in the severely angulated neck, significant mean oversizing (30%) of the body was applied. In this multicenter study, the participating hospitals were acknowledged EVAR experts. The patients were treated in their own regional hospital. They were visited by the proctors of the coordinating Anaconda™ study hospital (Medical Spectrum Twente, Enschede) during the specific EVAR procedure in the MANSAs study protocol. In this way, the local EVAR teams could be introduced to the Anaconda™ endovascular graft in difficult cases, expanding the indication for treatment. Introducing the Anaconda™ in different hospital settings could have implications for these study results. The four clinical failures in 30 days occurred in four different participating centers, including the center with the leading number of MANSAs patients. Two of the clinical failures were technical failures during operation and were reported at the beginning of the study in each particular hospital and reflect the difficulties in the use of the Anaconda™ stent in hostile neck anatomy.

A weakness of this study is the small inclusion of patients in most of the participating centers. There was no true learning curve with the use of the Anaconda in severely angulated aneurysms, although an experienced proctor was always available during the procedure. More than a decade of experiences with the Anaconda™ endovascular graft indicated that only in reversed conical and bell shaped necks it is challenging to obtain proper sealing and fixation of the Anaconda body. In line with Chauhuri, we disapprove the use of a (standard) endovascular graft outside the IFU in very short segmented necks ( $\leq 5$  mm).<sup>24</sup> Complications such as type I endoleak, neck dilatation, and endovascular graft migration were seen in angulated neck studies and represent the challenges of EVAR in these circumstances.<sup>25,26</sup> We anticipate that such an EVAR procedure must be primarily executed in high-volume centers. In this study, all participating centers were experienced in EVAR.

Long-term follow-up is thereby necessary because in general, reinterventions after the first year were still necessary in a significant part of this population.<sup>7-9</sup>

## Acknowledgements

We thank all participating physicians and hospitals for including patients in this MANSAs study. We are also grateful to Anja Stam, clinical research officer, for her help in gathering the relevant patient data.

Hospital	Physician	Number of patients
Medical Spectrum Twente, Enschede, The Netherlands	R.H. Geelkerken. MD, PhD	25
Antonius Hospital Nieuwegein, The Netherlands	J.P. de Vries, MD, PhD	2
Leiden University Medical Centre, The Netherlands	Prof. J.J. Hamming, MD, PhD	2
Ikazia Hospital, Rotterdam, The Netherlands	P.T. den Hoedt, MD, PhD	2
St Jansdal Hospital, Harderwijk, The Netherlands	W.L. Akkersdijk, MD, PhD	1
Rijnland Hospital, Leiderdorp, The Netherlands	P.P.A. Hedeman Joosten, MD, PHd	1
Gelre Hospital, Apeldoorn, The Netherlands	H.C.J.L. Busscher, MD, PhD	1
Erasmus Hospital, Rotterdam, The Netherlands	Prof. H.J.M. Verhagen, MD, PhD	1
TerGooi Hospital, Hilversum, The Netherlands	E.J.F. Hollander, MD, PhD	1
	<b>Total number</b>	<b>36</b>

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**Table 1** Inclusion and exclusion criteria.***Inclusion criteria***

Patient willing and available to comply with follow up requirements
Patient can comply with instructions and gives informed consent
Life expectancy > 2 years
AAA > 50 mm in diameter
Symptomatic small AAA
Infrarenal proximal neck diameter 18 - 31.5 mm
Infrarenal proximal neck length $\geq$ 15 mm
Infrarenal aortic angulation > 60°
Distal iliac fixation site diameter < 16 mm and > 30 mm in length
Access vessels > 7.5 mm in diameter

***Exclusion criteria***

Ruptured or symptomatic AAA
Juxta- or suprarenal extension of aneurysm
Low operative risk for open repair
Presence of serious concomitant medical disease or infection
Known allergy to contrast medium, nitinol or polyester
Inability to preserve at least one hypogastric artery
Connective tissue disease
ASA Grade IV or V
Need for surgical reconstruction of other visceral arteries
Presence of > 50% continuous calcification of proximal neck
Presence of > 50% thrombus in proximal neck

**Table 2** Patient characteristics

Demographic		Number of patients
Age (years)	Mean (range)	74 (61-84)
Gender	Male	30
	Female	6
ASA Grade	I	1
	II	29
	III	6
	Unknown	0
Diabetics	Normal	19
	Only diet controlled	6
	Diet + drugs	11
Smoking	Not in past 10 years	22
	Ex smoker	6
	Smoker	8
Hypertension	None	18
	1-2 Drugs	14
	3+/uncontrolled	4
Hyperlipidaemia	Normal	19
	Mild	6
	Diet + Drugs	11
Cardiac disease	Normal	18
	Asymptomatic - MI	7
	Angina etc.	11
Carotid disease	No disease	29
	Asymptomatic	1
	Transient stroke	6
	Completed stroke	0

Demographic		Number of patients
Renal disease	Normal	32
	Increased Creatinine	4
Pulmonary disease	Normal	28
	Mild	3
	Moderate	4
	Severe	1

**Table 3** Eurostar type of AAA morphology

		Range (median)	
Total number of patients		36	-
Eurostar type of AAA	A	9	-
	B	23	-
	C	1	-
	D	3	-
	E	0	-
Aetiology	Atherosclerosis	36	-
	Others	0	-
Shape aneurysm	Fusiform	35	-
	Saccular	1	-
	Others	0	-
Diameter infrarenal neck	D2a (mm)	23	16-31
	D2b (mm)	23	17-29
	D2c (mm)	23	17-31
Neckshape (Balm) <sup>4</sup>	=	24	-
	=/\	4	-
	=\	3	-
	=<>	2	-
	=><	3	-
Length	Mm	28	10-45 (30)
Circumferential thrombus	% D2 a-b-c	Max	80-20-20
Circumferential calcification	% D2 a-b-c	Max	10-20-30
Angulation aortic neck -AAA	Degrees	82	60-133 (80)
Aneurysm diameter	D3 (mm)	71	45-100 (68)
Diameter right common iliac artery	Proximal (mm)	14	9-19
	Mid (mm)	15	
	Distal (mm)	14	
Angulation	Degrees	51	0-150
Diameter left common iliac artery	Proximal (mm)	15	9-63
	Mid (mm)	14	
	Distal (mm)	15	
Angulation	Degree	41	0-180
Diameter right external iliac artery	Mm	10	8-14
Angulation	Degree	48	0-150
Diameter left external iliac artery	Mm	10	9-14
Angulation	Degree	48	0-180

Table 4 Clinical success

	30 days	1 <sup>st</sup> year	2 <sup>nd</sup> year	3 <sup>rd</sup> year	4 <sup>th</sup> year	Total <sup>++</sup>
N in cohort	36	36	35	31	27	36
Lost to follow-up			2			6 % (2/36)
Conversion	2	1	1			11 % (4/36)
All-cause mortality	0 % (0/36)	3 % (1/36)	6 % (2/35)	0 % (0/31)	19 % (5/27)	22 % (8/36)
Aneurysm-related mortality	0 % (0/36)	0 % (0/36)	0 % (0/35)	0 % (0/31)	0 % (0/27)	0 %
Primary clinical success	89 % (32/36)	78 % (28/36)	74 % (26/35)	71 % (22/31)	77 % (21/27)	69 % (25/36)
Primary assisted and secondary clinically success	94 % (34/36)	83 % (30/36)	80 % (28/35)	77 % (24/31)	81 % (23/27)	75 % (27/36)
Clinical failure*	11 % (4/36)	11 % (4/36)	3 % (1/35)	3 % (1/31)	4 % (1/27)	31 % (11/36)
Serious adverse events	11 % (4/36)	8 % (3/36)	3 % (1/35)	3 % (1/31)	4 % (1/27)	27 % (10/36)
Limb occlusion	1	2	1	3	0	14 % (5/36)
Freedom from re-intervention		89 % (32/36)	83 % (29/35)	80 % (25/31)		83 % (30/36)
Freedom from migration <sup>++</sup>		100 % (36/36)	100 % (35/35)	97 % (30/31)	97 % (26/27)	94 % (34/36)

\*Excluded: Death not aneurysm related. Included primary assisted and secondary clinically success (2 pts).

<sup>++</sup> Intention to treat.

**Table 5** Suitability for endovascular aneurysm repair (EVAR) according to instructions for use (IFU)

Type	: Infrarenal angulation and neck length
Anaconda <sup>a</sup>	: $\leq 60^\circ$ and $\geq 15$ mm
Zenith <sup>b</sup>	: $< 60^\circ$ and $\geq 15$ mm with suprarenal angulation of $< 45^\circ$
Excluder <sup>c</sup>	: $\leq 60^\circ$ and $\geq 15$ mm
Talent <sup>d</sup>	: $\leq 60^\circ$ and $\geq 10$ mm
Endurant <sup>d</sup>	: $\leq 60^\circ$ and $\geq 10$ mm with suprarenal angulation of $\leq 45^\circ$ : $\leq 75^\circ$ and $\geq 15$ mm with suprarenal angulation of $\leq 60^\circ$
Aorfix <sup>e</sup>	: $\leq 90^\circ$ and $\geq 15$ mm
AFX <sup>f</sup>	: $\leq 60^\circ$ and $\geq 15$ mm
Powerlink <sup>f</sup>	: $\leq 60^\circ$ and $\geq 15$ mm

<sup>a</sup>Vascutech, Terumo, Inchinnan, Scotland.

<sup>b</sup>COOK Medical Europe, Limerick, Ireland.

<sup>c</sup>W.L GORE and Associates, Newark, NJ. USA

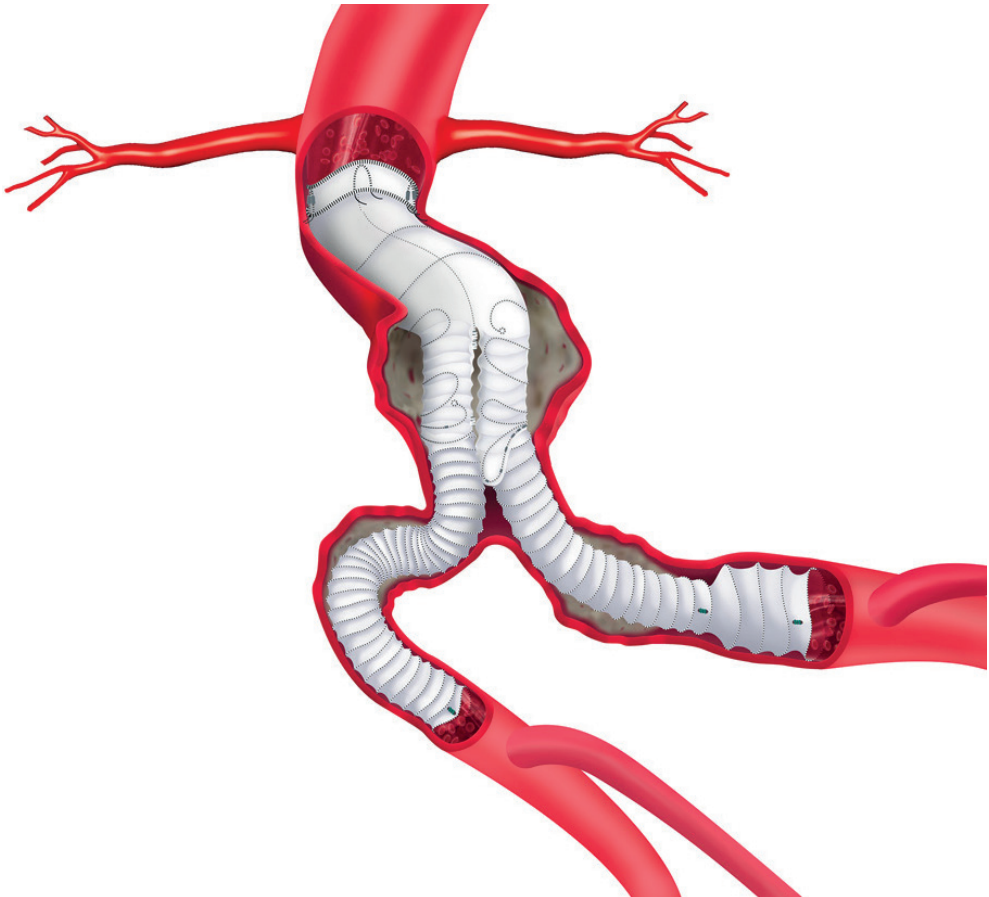
<sup>d</sup>Medtronic, Minneapolis, USA

<sup>e</sup>Lombard Medical Technologies, Didcot, UK

<sup>f</sup>Endologix, Irvine, USA

**Figure**

The Anaconda One-Lok endovascular graft (Vascutech, Terumo, Inchinnan, Scotland), introduced in 2011, is a modification of the Anaconda used in this study. Compared with the Anaconda used in this study, the One-Lok has two additional midrings in the region of the body and a universal diameter limb docking zone.







# Chapter

# 6

## Endovascular treatment of ruptured abdominal aortic aneurysm: is there a long-term benefit at follow-up?

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**Introduction:** Several studies have shown the feasibility of endovascular repair of ruptured abdominal aortic aneurysms (rEVAR). However, the role and value of rEVAR remains controversial due to selection bias and lack of long-term results. In the present study we describe our short- and long-term results of treating patients with rEVAR irrespective of hemodynamic condition and challenging anatomy.

**Methods:** In April 2006 we started the single centre prospective non-randomised Ruptured Aneurysm Study (RASA). During a four year enrolment period all consecutive patients presenting with infrarenal ruptured AAA (rAAA, N.=117) were assessed for preferential rEVAR treatment. A rAAA was defined as extravasation of blood or hematoma outside the AAA due to transmural tear in the infrarenal abdominal aorta wall documented by preoperative computed tomography (CT) angiography examination or during open repair. Patients with challenging anatomy (infrarenal neck length below 15 mm and neck angulation above 60 degrees) were included as part of a damage control concept. Complication and mortality rates were studied at 30 days and yearly afterwards.

**Results:** Thirty-five patients (33% of all admitted rAAA) were treated with rEVAR and 42% of them were considered hemodynamically unstable (systolic blood pressure <100 mmHg) and 30% had challenging AAA anatomy. The mortality rate at 30 days in the rEVAR group was 17%, in the open repair group 31%, and in the entire rAAA group (including abstained patients) 36%. During the first 30 days, 18 rEVAR patients experienced complications with nine re-interventions as a result. Long-term mortality of the rEVAR patients was 34% after a median follow-up of 3.4 years. All deaths after one year follow-up were non-AAA related. Multivariate analysis shows that Hardman index, presence of peripheral arterial obstructive disease and lowest systolic blood pressure during surgery are independently associated with long-term survival. Challenging rAAA anatomy was not associated with impaired survival.

**Conclusion:** Our study shows that rEVAR is feasible irrespective of hemodynamic condition and that it is associated with relative low mortality rates. Challenging rAAA anatomy may not affect overall long-term survival, but six out of ten patients remain unsuitable for rEVAR because of inappropriate anatomy.

## Introduction

In the last 50 years, open repair of ruptured abdominal aortic aneurysms (rAAA) remains lethal in up to 50% of patients despite rapid hospital transportation, early diagnosis, resuscitation and improvements in anaesthesia and intensive care treatment.<sup>1-3</sup> Our recent institution experience includes endovascular treatment of over 500 elective AAA patients with a 30-day mortality <1% and with good long-term success (own unpublished data). These elective results have led to the idea that using endovascular repair for ruptured aneurysm (rEVAR) also may improve survival in this high risk group of patients. Using standardized systems of treating patients with a rAAA, including rEVAR whenever possible, has proven to result in good outcome.<sup>4-7</sup> However, comparing rEVAR with previous or concurrent open procedures might be misleading due to selection bias.<sup>8</sup> Patients selected for rEVAR may be at a much lower risk as they are in general more hemodynamically stable or technically easier with longer infrarenal necks.<sup>9</sup> Furthermore, data on the long-term benefit of rEVAR in these high risk patients are scarce.

In the present study we describe our short- and long-term results of treating patients with rEVAR irrespective of hemodynamic condition and challenging anatomy. Finally, we review the current literature on long-term benefits of rEVAR.

## Materials and methods

### Study design

In April 2006 we started the single centre prospective non-randomised Ruptured Aneurysm Study (RASA) with the Anaconda™ Bifurcated Stent Graft System (Vascutek Terumo, Inchinnan, Scotland). The medical and anatomical inclusion criteria are listed in Table I. Approval of the study was obtained from the local ethics committee, and patients were included after written informed consent (Table I). Patient enrolment ended in March 2010. During the four year enrolment period all consecutive patients presenting with infrarenal rAAA were assessed for preferential rEVAR treatment. Our first choice of rEVAR treatment was the Anaconda™ stent graft, based upon our own experience as previously mentioned.<sup>9</sup> However, in the presence of extensive arterial obliterative disease at one of the access sites, the Talent aorto-uni-iliac device (AUI) or the Endurant prosthesis (Medtronic AVE, Santa Rosa, California) were selected. Patient characteristics, laboratory results, in-hospital transportation and operation time were recorded. Systolic blood pressure < 100 mmHg was defined as hemodynamic unstable. A patient was considered to have cardiovascular disease when coronary heart disease, peripheral vascular disease, or cerebrovascular disease was present (International Classification of Diseases (ICD)-9-CM (Clinical Modification) codes I20, I21, I63, I70, I73). Hypertension was defined as a systolic blood pressure of >160 mmHg or a diastolic pressure >90 mmHg, or when receiving antihypertensive medication. Diabetes mellitus and hyperlipidemia were defined by conventional American Diabetes Association and Adult Panel Treatment III criteria. Renal dysfunction was defined as a creatinine level >120 umol/L. Hardman index was assessed as previously described as it may predict short-term mortality in rEVAR patients.<sup>10</sup>

All rEVAR patients were followed with abdominal X-rays and regular duplex ultrasound or CT-angiography at 3, 6, 9, 12, 18, 24 months and yearly afterwards. Complication and mortality rates were studied at 30 days and yearly afterwards and were described according to the reporting standards.<sup>11</sup>

### Logistic procedure

All procedures were performed in a large teaching hospital with a regional referral pattern for rAAA. In our department the endovascular team consists of four vascular surgeons and four interventional radiologists, all with extensive EVAR experience. The EVAR team on call always consists of both an interventional radiologist and a vascular surgeon. None of the consecutive patients admitted with suspected rAAA in our emergency department were assessed for rEVAR at any of the referring hospitals.

Only patients who were able to make an informed choice and refused treatment were excluded from work up for treatment. After a first clinical assessment of vital signs in the emergency room (ER), all patients underwent emergency computed tomography angiography (CTa; non-enhanced and arterial phase acquisition) to confirm rAAA.

A rAAA was defined as extravasation of blood or hematoma outside the AAA due to transmural tear in the infrarenal abdominal aorta wall documented by preoperative CTA examination or during open repair. Upon confirmation of rAAA, patients were assessed for rEVAR treatment by an experienced member of our endovascular team, see also Table I. Anatomic inclusion criteria were not only those mentioned in the instructions for use, but also patients with a neck length of up to 8 mm or with an angulation of the infrarenal neck above 60 degrees were considered for rEVAR. These less favorable infrarenal necks were accepted as part of a damage control concept. During work up, systolic blood pressure was maintained around 80 mm Hg whenever possible (permissive hypotension).

### **Endovascular procedure**

All endovascular procedures were carried out in a fully equipped operating room (OR). Patients were prepared and positioned as for conventional open surgical repair on a radiolucent table. The preferred anaesthesia was local anaesthesia. Intravenous heparin was not administered in any of the rAAA cases. A full stock of AUI and bifurcated stent grafts (both Anaconda™ and Endurant) were permanently available in the OR. The procedure was carried out through surgical exposure of the femoral arteries by surgical cut down. Correct placement of the endovascular graft was guided by fluoroscopy and completion angiography was performed after successful deployment of the stent graft. As mentioned above, we have included patients with a relatively short infrarenal neck. In such cases with inherent risk of renal perfusion impairment by the stent graft, a stent was placed in both renal arteries. Femoro-femoral bypass graft surgery was performed to restore blood flow to the contralateral leg in patients with an AUI.

### **Statistical analysis**

Data are shown as mean  $\pm$  SD. The (independent) effects of variables on mortality were estimated with stepwise Cox regression analysis,  $P < 0.05$  was considered significant. Results were reported intention to treat as mean (range) and with a 95% confidence interval where appropriate. Student t-test was used to compare continuous variables. Significance was assumed at  $P < 0.05$ .

## Results

### Population

Within the present study period a total of 117 patients presented with a rAAA at our institution.

Figure 1 shows the flow chart of the rAAA patients. Twelve patients did not undergo repair of their rAAA. Of these 12 patients, 33% had disseminated cancer and 50% were unconscious, and/or unfit for treatment (all Hardman Index >3), and 17% refused repair of their rAAA. A rAAA was proven by CTA in eight of these twelve patients (75%). The other three patients were presumed to have a rAAA based on their history and a CTA was not performed because they died during cardiopulmonary resuscitation at the ER. A CTA was performed in all patients who received any form of rAAA exclusion (N.=105). Of these 105 patients, 33% underwent rEVAR and 67% were treated with conventional open repair.

The patient characteristics are described in Table II. Over 70% of the rEVAR patients had serious comorbidities, such as coronary heart disease and chronic obstructive pulmonary disease. On arrival, 42% of the rEVAR patients were considered hemodynamically unstable with a systolic blood pressure under 100 mmHg. All rEVAR patients underwent CTA and the anatomy details are described in Table III. Approximately 30% of the rEVAR patients had a challenging anatomy with an infrarenal neck length shorter than 15mm or neck angulation above 60 degrees. The majority of the rEVAR patients received an Anaconda™ stent graft (77%). Eight patients received an AUI or an Endurant stent graft due to inappropriate iliac access or fixation zone for the Anaconda™ stent graft. For instance, 5 patients also had an iliac aneurysm that needed coiling of the hypogastric iliac artery if a bifurcated stent graft was chosen. In the present study, such patients were treated with an AUI to save time and blood loss. All patients were directly transported from the CTA facility to the OR. In the meanwhile, the EVAR team assessed rEVAR suitability and decided which stent graft to use. The mean time between arrival at the emergency room and start of the femoral cut down in the OR was  $47 \pm 18$  minutes. Successful stent graft deployment and rAAA exclusion was reached on average after another 71 minutes (Table III). The actual operating time was much longer in some cases, as they needed for example femorofemoral bypass surgery. Two patients had an ongoing type 1 endoleak after the stent graft deployment, despite juxtarenal fixation and appropriate ballooning, and one of them was successfully treated with an open repair. After laparotomy and suprarenal clamping, the proximal ring stents of the Anaconda device were cut off and the remaining polyester graft section was end to end sutured to the native juxtarenal aorta. The other patient with an ongoing type 1 endoleak died due to profound shock during the rEVAR procedure. Two other patients needed conversion to open repair due to unmanageable gross haemodynamic instability. Five patients were treated with rEVAR despite a short infrarenal neck (Table III). In one patient this led to stenting of the renal arteries as the valleys of the proximal stent rings of the Anaconda™ stent graft were very close to the origin of the renal arteries. Also ten patients underwent rEVAR despite severe infrarenal neck angulation. We were not able to cannulate the contralateral gate of the Anaconda™ stent graft

main body with the intrinsic magnet wire in 4 patients due to a very large rAAA in combination with severe angulated common iliac arteries. In these cases, the main body was collapsed and brought down to the level of the aortic bifurcation to facilitate cannulation of the contralateral gate with the magnet wires and after successful cannulation the main body was repositioned to the infrarenal neck. The drawback of this procedure is that in cases with severe infrarenal neck angulation the collapsed body may get stuck at the level of the infrarenal neck edge.

### **Short term outcome**

Complication and mortality rates of the rEVAR patients are described in Table IV and V. Eighteen patients experienced at least one complication giving rise to 9 reinterventions. Two patients experienced leg thrombosis of their stent graft which was treated with thrombectomy and percutaneous transluminal angioplasty of the stent graft at the level of the flow splitter. The median stay at the Intensive Care Unit (ICU) was 3 days (range 0-15 days), within 12 patients staying less than 24 hours at the ICU. The mortality rate at 30 days in the rEVAR group was 17%. Three patients died of profound shock, one from myocardial infarction and two due to mesenteric ischemia. The mortality rate at 30 days in the open repair group was 31% and in the entire rAAA group (including abstained patients) was 36%.

### **Long term outcome**

Figure 2 shows the Kaplan-Meier survival curve for the rEVAR group. No patients were lost to follow-up. The mean follow-up was  $3.4 \pm 1.4$  years. The median survival was 42 months (standard error 4.8). The mortality rate after 1 year follow-up in the rEVAR group was 26% and after a mean follow-up of 3.4 years 34%. All deaths after one year follow-up were non-AAA related, including 2 myocardial infarctions and one case of disseminated cancer. Multivariate analysis shows that Harman index, presence of peripheral arterial obstructive disease and lowest SBP during surgery were independently associated with long-term survival. Challenging rAAA anatomy was not associated with mortality or reintervention rates.

## Discussion

Patients with rAAAs are increasingly treated with rEVAR which may offer many benefits as compared to open repair. However, the role of rEVAR remains controversial as selection bias may have influenced results from previous studies and others have not been able to prove superiority of rEVAR.<sup>8,12</sup> The results of our rEVAR study show a mortality rate at 30 days of 17% and after a mean follow-up of 3.4 years of 34%. This low mortality rate at 30 days is comparable to previous rEVAR studies. Veith et al. described the collected world experience of treating 1037 rAAA patients with rEVAR and observed a mean 30 day mortality rate of 21%.<sup>7</sup> In the present study we included 15 patients (42%) for rEVAR who were considered hemodynamically unstable on arrival. In the collected experience from Veith et al., 13 centers also used rEVAR in hemodynamically unstable patients. The mean 30 day mortality rate in these centers was 19.7%. These and our own results show that the 30 day mortality rate can be low in rEVAR selected cases. Extensive EVAR experience and the presence of a standardized emergency rAAA service may strongly influence these results in hemodynamic unstable patients. For instance, the mean ER to OR time, with permissive hypotension, in our study was just 47 minutes, which is short compared to a mean time of 71 minutes in a recent meta-analysis.<sup>13</sup> Obviously, a rapid throughput of patients is largely country depended, but may result in favourable hospital mortality, as was also found in another Dutch study.<sup>1</sup>

Unfortunately, long-term results of rEVAR are scarce. The Canadian aneurysm study observed that patients who survived open repair of a rAAA have a lower long-term survival as compared to those with elective AAA repair.<sup>14</sup> The mortality rate after 3 year follow-up in the Canadian study was 65%. A study from the Mayo clinics found that long-term mortality was related to cardiovascular disease and was not AAA related.<sup>15</sup> In our study we observed a rEVAR mortality rate of 34% after a mean follow-up of 3.4 years, which seems very low. In our study, long-term survival was associated with Hardman Index, presence of peripheral arterial obstructive disease and lowest systolic blood pressure during surgery. The majority of late deaths that occurred after 1 year follow-up in our study were related to CHD, like the Mayo clinic study. In a previous study we analyzed long-term mortality in a group of patients with rAAA (N.=34) and acute non-ruptured AAA (N.=22).<sup>5</sup> The mortality rates in the rAAA patients from that study were 18% at 30 days and 38% at 3 years. Hechelhammer et al. observed a mortality rate of 31% at 4 years follow-up after rEVAR, but Hinchliffe et al. were unable to prove superiority of rEVAR over open repair.<sup>12,16</sup> In a retrospective study over a 10-year period (N.=54) they observed a perioperative mortality rate of 37% and a mortality rate after 3 year follow-up of 64%. It is important to note that 15 patients in the study from Hinchliffe et al. were transported from another hospital where they were found medically unfit for open repair and their comorbidities may have influenced outcome. Egorova et al. analyzed the results of rAAA in 43033 Medicare beneficiaries of whom 1064 had rEVAR.<sup>17</sup> The survival analysis of patients

matched by propensity scores showed a benefit of rEVAR over open repair that persisted throughout the 4 year of follow-up. Long-term survival after rAAA repair correlated strongly with increasing annual surgeon and hospital volume and rEVAR experience.

Only 33% of the patients with a rAAA were anatomically suitable for rEVAR in our study, which is comparable to a previous studies from our group.<sup>18</sup> However, several systematic reviews have shown that approximately 60% of the patients with a rAAA should be suitable for EVAR.<sup>13</sup> Transport of patients suitable for rEVAR from hospitals who are not able to perform rEVAR to these larger centres with extensive rEVAR experience may in part explain the difference in rEVAR inclusion rates. Furthermore, we included patients for rEVAR with challenging anatomy. Approximately 30% of our rEVAR patients had an infrarenal neck shorter than 15 mm or a neck angulation greater than 60 degrees. Richards et al. observed that 34% of their rEVAR patients had a challenging anatomy.<sup>19</sup> More importantly, in their study challenging anatomy was associated with increased overall mortality over time. Especially an angulated neck greater than 60 degrees was associated with a hazard ratio of 2.15 (95% CI 1.13-4.08) for over-all mortality. However, it is important to note that these data were gathered over a 14-year period and in that time, procedures, imaging and stent grafts have changed. Indeed there is evidence that good results can be obtained in patients with challenging anatomy, probably related to experience, availability of different endograft options and high quality of imaging.<sup>20,21</sup> Challenging infrarenal neck anatomy was not associated with long-term mortality in our study. Finally, rEVAR can be used in a damage control concept accepting less favorable AAA anatomies. Fenestrated and branched stent grafts can be used for long-term AAA exclusion if the initial used stent graft in rEVAR fails. Endovascular techniques and possibilities for AAA repair are still growing and the newly introduced off-the-shelf fenestrated devices may further expand treatment possibilities of relatively stable rAAAs.

## Conclusion

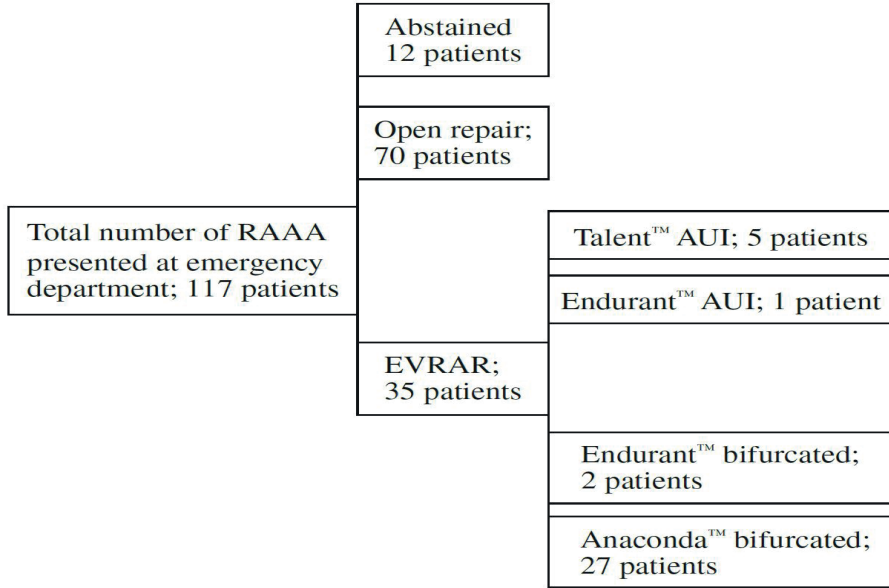
Our study shows that rEVAR with modern, mainly bifurcated devices, is feasible, also in hemodynamically unstable patients. Furthermore, it is associated with relative low mortality rates. Accumulating published data suggest that challenging AAA anatomy may not affect overall long-term survival, especially in centres with sufficient EVAR and open repair experience. Although challenging anatomies are being treated more over with rEVAR, still the majority of primary referral patients remain unsuitable for rEVAR.

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**Figure 1** Flowchart of the 116 patients presenting with a ruptured infrarenal aortic aneurysms in the RASA study period.



**Table 1** Inclusion and exclusion criteria of endovascular treatment of patients with ruptured infrarenal aorta-iliac aneurysms with the Anaconda™ endoprosthesis (RASA study).

**Inclusion criteria**

• Patients aged > 18 years
• Patient with a ruptured infrarenal AAA*
• Informed consent before or after treatment (in case of death consent by relatives)
• Infrarenal proximal neck diameter 18 – 31.5 mm
• Infrarenal proximal neck length > 8 mm
• Sealing and fixation zones; appropriate anatomy at the physician's discretion
• Access vessels: appropriate anatomy at the physician's discretion

**Exclusion criteria**

• Juxta or suprarenal extension of aneurysm
• Known allergy to contrast medium, nitinol or polyester
• Need for surgical reconstruction of other visceral arteries
• The patient chooses to be treated by open surgery
• Patients with cancer, with is likely to cause death within one year
• Patients not fulfilling the inclusion criteria

\* Rupture is defined as extravasation of blood due to transmural tear in infrarenal abdominal aorta wall documented by preoperative CT examination, or at laparotomy.

**Table 2** Characteristics of the rEVAR patients

	n
Age (years)	75 ± 8
Gender (male:female)	28 : 7
Current smoking	21
Coronary hearth disease (CHD)	18
Chronic obstructive pulmonary disease (COPD)	11
Hypertension (n)	25
Hyperlipidemia (n)	9
Stroke (n)	4
Renal insufficiency(n)	5
Peripheral arterial occlusive disease (PAOD)	7
Diabetes mellitus (n)	2
Systolic bloodpressure (SBP) on arrival at emergency room (ER)	112 ± 36
SBP < 100 mmHg (n)	15
Haemoglobin at ER (mmol /L)	6.7 ± 1.7
Creatinine at ER (mmol / L)	133 ± 100
Hardman index (median and range)	0.9 (0-3)

**Table 3** Anatomical and operative characteristics of the rEVAR patients (n=35)

Anatomy	
AAA diameter	78 ±18
Infrarenal neck length (mm)	25 ±13
Patients with an infrarenal neck length <15 mm	5
Infrarenal neck angulation (°)	46 ±28
Patients with an infrarenal neck angulation >60° (n)	10
Patients with also an iliac aneurysm (n.)	5
Operative	
Time between arrival ER and start femoral cut-down (min)	47 ±18
Time between start surgery and completion angiography (min)*	71 ±34
Time between start surgery and leaving operation room (OR) (min;range)	189 (70-340)
Lowest SBP during surgery (mmHg)	91 ± 28
Red blood cell (RBC) unit units given (N.; range)	4.3 (0-34)
Contrast used (mL; range)	140 (25-360)
X-ray time (min)	14 (3-50)

Data given as mean ± standard deviation unless otherwise specified.

\*time between start surgery and completion angiography as a measure of successful stent graft deployment and AAA exclusion

**Table 4** Thirty day complication rates in the rEVAR patients (n=35)

Type 1 endoleak (n)	2
Other types of endoleak (n)	0
Unintentional coverage renal artery (n)	0
Conversion (n)	3
Myocardial infarction (n)	3
Respiratory insufficiency (n.)	2
Mesenteric ischemia (n)	4
Multiple organ failure (MOF)	8
Abdominal compartment syndrome (n)	2
EVAR limb occlusion (n)	2
Mortality at 30 days (n)	6 (17%)

**Figure 2.** Kaplan-Meier survival curve for patients with endovascular repair of ruptured AAA. Median survival was 42 months (standard error 4.8).

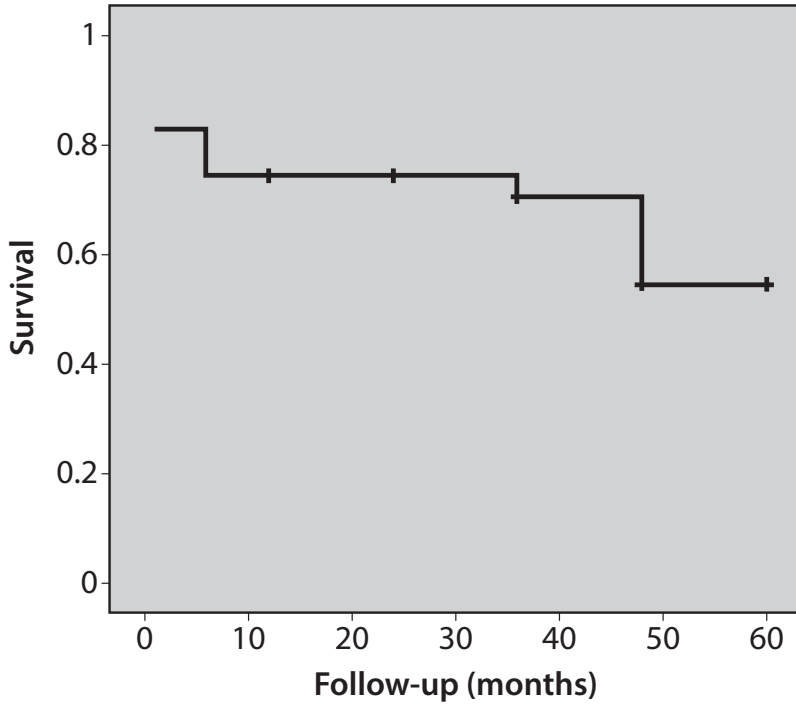


Table 5 Cumulative mortality and reintervention rates in the REVAR group (n=35)

	30 days	1 <sup>st</sup> year	2 <sup>nd</sup> year	3 <sup>th</sup> year	4 <sup>th</sup> year	Total
Number at risk	35	29	24	24	20	13
Mortality	6 (17%)	9 (26%)	9 (26)	10 (29%)	12 (42%)	12 (42%)
Cumulative causes of mortality*						
AAA related (n)	3	5	5	5	5	5
Coronary hearth disease (n)	1	2	2	3	3	3
Mesenteric ischemia (n)	2	2	2	2	2	2
Cancer (n)	0	0	0	0	1	1
Reintervention	9 (26%)	12 (34%)	12 (34%)	14 (45%)	14 (45%)	14 (45%)

\*:Mortality and reintervention rates assessed by Kaplan-Meier





# Chapter

# 7

## Incidence and treatment of limb occlusion of the Anaconda endograft after endovascular aneurysm repair

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**Purpose:** To evaluate the incidence and treatment of limb occlusions of the second- and third-generation Anaconda endografts.

**Methods:** A single-center retrospective study was conducted involving 317 consecutive patients (mean age 76 years; 289 men) who underwent endovascular aneurysm repair for elective asymptomatic, symptomatic intact, and ruptured infrarenal abdominal aortic aneurysm with 2 versions of the Anaconda device. From September 2003 to July 2011, the second-generation device was used in 189 patients (mean age 77 years; 169 men) and from July 2011 to September 2015, the third-generation device was implanted in 128 patients (mean age 75 years; 120 men). The rates of limb occlusion were compared between groups and according to compliance with the instructions for use (IFU); predictors were sought in multivariate analysis. The results of the latter are given as the hazard ratio (HR) and 95% confidence interval (CI).

**Results:** Kaplan-Meier freedom of occlusion estimates for second- and third-generation devices, respectively, was 96.6% and 95.0% at 1 year, 89.9% and 95.0% at 2 years, and 86.5% and 88.6% at 5 years. There was no significant difference in overall occlusion rate between the second-generation devices ( $p=0.332$ ) or with regard to use within the IFU ( $p=0.827$ ); however, there was a clinically relevant decrease in the occlusion rate for elective patients treated with the third-generation device (6.4% vs 13.1%,  $p=0.077$ ). There was an increase in the occlusion rate when the iliac limb diameter was  $\leq 13$  mm. In multivariate analysis, the only independent predictor of limb occlusion was a small distal prosthesis diameter (HR 0.732, 95% CI 0.63 to 0.86,  $p<0.001$ ). Symptomatic nonruptured and ruptured abdominal aortic aneurysm (AAA) interventions had an almost 2-fold increased risk of occlusion (HR 1.95, 95% CI 0.93 to 4.11,  $p=0.078$ ), though this did not reach statistical significance.

**Conclusion:** The Anaconda design has proven effectiveness in AAA exclusion in daily practice inside the IFU. However, efforts could be made to further reduce the limb occlusion rate.

## Introduction

From the first introduction of the Anaconda endograft (Vascutek/Terumo, Inchinnan, Scotland) in 1998, special attention was paid to the configuration of both body and limbs to achieve durable endovascular repair of challenging infrarenal abdominal aortic aneurysm (AAA) anatomy and to address some of the failures observed with other aortic stent-grafts in the 1990s, among them endograft limb occlusion.<sup>1-5</sup> In the second-generation Anaconda device with independent nitinol rings and zero columnar support, the infrarenal and iliac fixation and sealing was durable, but the observed number of limb occlusions was somewhat higher than expected. The ANA-004 study<sup>6</sup> and product registries suggested that limb occlusions were mainly observed with the combination of small body diameters and relatively large diameter limbs. As a consequence, the third-generation Anaconda device, the One-lok, was launched in 2011. In this third iteration, the docking zone limb diameter was standardized to optimize the body-limb combinations and ease the size selection. Two additional nitinol rings supporting the body were added to maximize lumen diameter and prevent possible kinking in angulated AAA neck anatomy. Device planning and selection were done using the instructions for use (IFU) and the product ordering information sheet.

In the second-generation device the limb design was straight; the third generation was designed such that the proximal part of the iliac limb attached to the body had a diameter of 12 mm. Three types of distal outflow configurations of the graft were designed in the third-generation endograft: a tapered limb if the iliac artery diameter was between 8.5 and 9.5 mm, a straight limb if between 10.0 and 11.5 mm, and a flared distal limb if between 11.0 and 23.0mm. Using the recommended product ordering information, the maximum oversizing should vary between 18% and 25%. The present study focuses on the incidence and treatment of limb occlusions of both second- and third- generation Anaconda devices.

## Methods

### Study design

A single-center retrospective study was conducted using prospectively recorded data from all consecutive AAA patients treated with the Anaconda device between September 2003 and September 2015. The second-generation device was used until July 2011, when the third-generation device became available. The primary outcome measure was limb occlusion, including symptomatic and asymptomatic. Only the first occlusion of an individual patient was used in the statistical analysis. Body occlusions were counted as one occlusion. The Ethics Committee of the University Medical Center Groningen waived the need for ethics approval or informed consent for the use of anonymized and retrospectively analyzed data.

Demographics and general health status, including the Society of Vascular Surgery/International Society of Cardiovascular Surgery risk scores,<sup>7</sup> the American Society of Anesthesiologist (ASA) classification,<sup>8</sup> as well as AAA anatomical characteristics, were collected. Patients were categorized as asymptomatic, symptomatic nonruptured, and ruptured AAA. The preoperative work-up was outlined in detail earlier.<sup>6</sup> Definitions according to Chaikof et al<sup>9</sup> were used.

### Patient population

A total of 317 patients (mean age 76 years; 289 men) were treated for infrarenal AAA with the Anaconda endograft during the observation period: 189 patients (mean age 77 years; 169 men) received a second-generation device and 128 patients (mean age 75 years; 120 men) received a third-generation device. Patient characteristics, anatomical characteristics, and characteristics of the endovascular aneurysm repair (EVAR) procedure are summarized in Tables 1 to 3, respectively. In 225 (71%) patients the EVAR procedures were performed electively (Table 4). Thirty-eight (12%) patients had a symptomatic nonruptured AAA and were treated within 24 hours. Fifty-four (17%) patients had a ruptured AAA and were treated in the acute setting. A total of 184 patients were treated within the IFU for Anaconda (Table 5).

### Follow-up protocol

Patients were seen in follow-up at 3, 6, 12, 18, and 24 months and yearly thereafter. The evaluations included duplex ultrasound and biplanar abdominal radiography or contrast-enhanced computed tomography angiography (CTA). Limb occlusion was detected using duplex ultrasound or CTA.

### Statistical analysis

Categorical variables are reported as numbers with percentages. The distribution of continuous variables were summarized as means or medians (with interquartile range), as appropriate. The relationships between type of Anaconda device and categorical data were analyzed using the chi-square test, while differences in continuous variables between the 2 types of devices were analyzed using a t-test (normal distribution) or Mann-Whitney U-test (skewed distribution), as appropriate. Normal distribution was tested using the Kolmogorov-Smirnov nonparametric test.

To compare the occlusion rate to data in the literature, a subanalysis was performed for second- and third-generation devices that were implanted following the criteria in the IFU. Time-to-event data were analyzed using the Kaplan- Meier method with log rank test or univariate Cox regression. Variables that were associated both with time-to-event and type of Anaconda (at  $p < 0.10$ ) were entered into a multivariate Cox regression model (stepwise, forward) to obtain a model identifying independent predictors of the time to occlusion. The generation of Anaconda device was forced into the model. The results are presented as the hazard ratio (HR) and 95% confidence intervals (95% CI). Significance was set at  $p < 0.05$ . Analyses were performed using IBM SPSS Statistics for Windows (version 22.0; IBM Corporation, Armonk, NY, USA).

### Results

Over a mean follow-up of 47 months (range 0–134), 31 (9.8%) index occlusions were diagnosed (4 body and 27 limb). The mean follow-up was 57 months (range 0–134) and 33 months (range 0–66) for second- and third-generation device cohorts. Freedom from occlusion estimates were 96.6% (95% CI 93.9% to 99.3%) and 95.0% (95% CI 91.1% to 98.9%) at 1 year, 89.9% (95% CI 85.2% to 94.6%) and 95.0% (95% CI 91.1% to 98.9%) at 2 years, and 86.5% (95% CI 80.8% to 92.2%) and 88.6% (95% CI 81.6% to 95.6) at 5 years, respectively (Figure 1A). There was no statistically significant difference in occlusion between the 2 generations of the devices ( $p = 0.591$ ). In the second-generation group there was a significant difference in the occlusion rate related to the timing of surgery, predominately because of the much higher occlusion rate in symptomatic patients compared with elective patients ( $p = 0.001$ ).

The cumulative number of occlusions during follow-up of the total cohort and the subcohorts with criteria inside the IFU is presented in Table 6. At 5-year follow-up the cumulative occlusion rate inside the IFU was 9.8% (18/184). The Kaplan-Meier freedom from occlusion inside the IFU for both types of devices is reported in Figure 1B. There was no significant difference in occlusion estimates between the second-generation devices ( $p = 0.827$ ). Freedom from occlusion estimates for second- and third-generation devices were 98.1% (95% CI 89% to 100%) and 95.9% (95% CI 91.4% to 100%) at 1 year and

94.8% (95% CI 90.3% to 99.3%) and 95.9% at 2 years, respectively. For the second-generation device the 5-year freedom from occlusion was 87.1% (95% CI 79.8% to 94.4%).

### **Treatment of leg occlusions**

In 31 patients experiencing one or more occlusions, one occlusion occurred in 15 patients treated with second-generation vs 9 patients with third-generation endografts. Two occlusion events occurred in 6 patients, all with second-generation devices. One patient with a third-generation device experienced 3 limb occlusions: one event in 1 limb and 2 events in the other limb. Limb occlusions did not result in any minor or major amputations.

In total, 5 (1.6%) conversions to open repair were performed for body occlusions in 4 cases and a contained rupture after initial successful thrombectomy of the body occlusion in the other. Further details of treatment are described in Table 7.

### **Uni- and multivariate analyses**

The following variables were related to time to limb occlusion at univariate analysis: timing of surgery, neck calcification, left external iliac artery diameter, right iliac artery angulation, proximal prosthesis diameter, distal prosthesis diameter (left and right), device length, additional procedures, direct postoperative endoleak, procedure time, and blood loss (all at  $p < 0.10$ ). Embolization of the internal iliac artery was not a significant factor for limb occlusion, although occlusion did occur in 2 patients with prior embolization of the internal iliac artery. Iliac diameter was also small in these 2 patients, that is, 10 and 11 mm on both limb sides.

In a forward, stepwise multivariate Cox regression analysis only the distal right prosthesis diameter (HR 0.732, 95% CI 0.63 to 0.86,  $p < 0.001$ ) was an independent predictor of time to occlusion; Anaconda generation (HR 0.996, 95% CI 0.41 to 2.44,  $p = 0.991$ ) and timing of surgery (HR 1.95, 95% CI 0.93 to 4.11,  $p = 0.078$ ) were not. When the generation of the Anaconda device was removed from the model, the outcomes for the remaining variables remained largely unchanged.

In the limb occlusion group, 19 (61%) of 31 patients had 1 or more iliac extensions compared with 98 (34%) of 286 patients without limb occlusion ( $p = 0.01$ ). In 54 (29%) of 189 patients with a second-generation device, the right iliac diameter was  $\leq 13$  mm; 11 of 21 occlusions occurred in this group. In 69 (54%) of 128 patients with a third-generation device, the right iliac diameter was  $\leq 13$  mm; 9 of 10 occlusions occurred in this group. This increase in the occlusion rate when the iliac limb diameter is  $\leq 13$  mm, which was confirmed in the multivariate analysis, suggests that a larger distal prosthesis diameter leads to fewer occlusions.

## Discussion

The most striking findings in this study were the relationship of limb occlusion to the timing of surgery in the second-generation group and to small distal prosthesis diameter, not to the generation of the Anaconda. In patients who underwent elective surgery there was a clinically significant decrease in the proportion of patients who developed a limb occlusion in the third-generation Anaconda; however, this did not reach statistical significance.

Comparing EVAR studies and especially limb occlusion rates in the literature is not straightforward. Variations in type of endograft device, selection criteria, treatment within or outside the IFU, follow-up protocol, multi- or monocentric study, and patient and anatomical characteristics make a balanced comparison between studies challenging.

Faure et al<sup>2</sup> published a literature overview on predictive factors for limb occlusion in various types of endografts. Mean follow-up varied between 1 and 77 months with limb occlusion rates between 0% and 7.2%. The limb occlusion rate of the present study after a mean follow-up of 47 months was 9.8% overall, but the rate was 6.4% for the third-generation device used in elective cases, which seems at the upper end of the acceptable range for limb occlusion.

Our reported rate of limb occlusion is higher than others have reported for the Anaconda device, but this may reflect the complexity of some of our cases outside the IFU and the inclusion of a substantial proportion of emergency cases. In their single-center study using the Anaconda, Freyrie et al<sup>10</sup> reported their results of 177 electively treated AAA patients with anatomical criteria inside the IFU. Mean follow-up was 33 months (range 1–77). The overall rate of iliac limb occlusion was 4.5% (8/177). In another single-center study, Karkos et al<sup>11</sup> reported a 4.8% occlusion rate at a mean 29 months. Of the 68 patients included, 5 patients had ruptured AAA. One body occlusion occurred on day 8 postoperatively likely, due to graft twist. One limb graft occlusion occurred after 43 months. An asymptomatic limb occlusion was managed conservatively. No specific causes were specified.

Nano et al<sup>12</sup> reported just 0.8% limb occlusion among 118 patients at a mean of 48 months. One acute thrombotic limb ischemia occurred 15 months after the procedure. In a recently published study,<sup>13</sup> 2 generations of Medtronic endografts were compared in 221 patients (131 Endurant and 90 Talent) with an overall mean follow-up of 61 months. With the new Endurant endograft design, the number of complications at the level of the aortic neck was reduced, but the number of iliac interventions increased. However, an iliac limb occlusion occurred in 5.6% of the Endurant patients compared with 3.4% of the Talent patients, so an updated Endurant design was recently introduced.

In our multivariate analyses, distal prosthesis diameter was an independent predictor of time to limb occlusion, which is in line with earlier studies.<sup>1,2,14</sup> Mantas et al<sup>5</sup> could not prove this particular result in their study but suggested that an iliac angle  $\geq 60^\circ$ , calcification  $\geq 50\%$ , and endograft limb oversizing  $\geq 15\%$  of the common iliac artery diameter may increase the risk of occlusion fivefold. In the study of Faure et al,<sup>2</sup> a prediction model was constructed to divide EVAR patients developing limb occlusions into high- and low-risk groups depending on the anatomical criteria. Intensifying the follow-up schedules and promoting early awareness of possible problems could be a necessary prerogative for the high-risk patient cohort in the first 2 years. Correction of intraoperative factors for limb occlusion, such as stenting of a possible compromised device limb lumen, could reduce the limb occlusion rate.<sup>15</sup>

The strong point of the current study is the long-term follow-up and very low number of cases lost to follow-up. The substantial number of first limb occlusions presenting between 2 and 5 years suggested an ongoing interaction between the anatomical configuration and blood flow. However, this study is potentially biased with regard to the comparisons made between the second- and third-generation devices, as it was not designed as a randomized trial. Heterogeneity of both cohorts could also be a bias because the devices were implanted in 2 different time frames and improvement in experience and imaging quality likely occurred. Furthermore, the increase in the proportion of AAA patients treated today with EVAR (up to 90%) could jeopardize the clinical outcome

## Results

The Anaconda design has proven durable in AAA exclusion in daily practice both inside the IFU and in challenging AAA anatomy.<sup>16</sup> However, efforts could be made to further reduce the limb occlusion rate.

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**Table 1** Patient characteristics<sup>#</sup>

Demographic	Second generation device (n=189)	Third generation device (n=128)	Total number of patients (%)
<b>Sex</b>			
Male	169	120	289 (91.2%)
Female	20	8	28 (8.8%)
<b>Mean age years (range)</b>	77 (58-95)	75 (42-90)	76 (42-95)
<b>ASA Grade</b>			
I	1	4	5 (1.6%)
II	130	83	213 (68.3%)
III	18	20	38 (12.2%)
IV	4	4	8 (2.6%)
V	33	15	48 (15.4%)
<b>Diabetes mellitus</b>			
No	160	112	272 (86.1%)
Only diet-controlled	22	11	33 (10.4%)
Diet and drug controlled	6	5	11 (3.5%)
<b>Smoking</b>			
No	130	93	239 (71.2%)
Yes	55	35	98 (28.8%)
<b>Hypertension</b>			
No	65	36	101 (31.9%)
1 or 2 drugs	88	73	161 (50.8%)
3+ drugs or uncontrolled	36	19	55 (17.4%)
<b>Hyperlipidemia*</b>			
No	98	38	136 (43.3%)
Diet and-or drugs	88	90	178 (56.7%)
<b>Cardiac Disease</b>			
No	106	64	170 (53.8%)
Asymptomatic, MI	80	58	138 (43.7%)
Unstable angina, etc.	2	6	8 (2.5%)
<b>Carotid disease**</b>			
No	166	101	267 (84.5%)
Yes	22	27	53 (15.5%)
<b>Renal disease</b>			
No	175	116	291 (92.1%)
Yes	13	12	25 (7.9%)
<b>Pulmonary disease</b>			
No	150	108	258 (81.6%)
Mild	37	20	57 (18.0%)
Severe	1	0	1 (0.3%)

<sup>#</sup> Continuous data are presented as the mean (range); categorical data are given as number (percentage).

P-value Chi-Square (asyp.sig 2-sided)

\* P<0.05 (0.000)

\*\* P<0.05 (0.024)

**Table 2** Anatomical criteria

	Second generation device (n=189)	Third generation device (n=128)	Total group (n=317)
<b>Infrarenal aortic neck</b>			
Mean diameter in millimeter (range)			
- Proximal	22.6	23.1	22.8 (10-34 <sup>#</sup> )
- Mid	23.0	23.3	23.1 (14-32)
- Distal	23.5	24.1	23.7 (14-33)
Right common iliac artery	15.7	17.2	16.3 (7-100)
Left common iliac artery	14.3	15.2	14.7 (7-63)
Right common femoral artery	9.5	9.5	9.5 (5-22)
Left common femoral artery	9.6	9.2	9.4 (5-22)
<b>Mean aortic neck length mm (range)</b>	28.4	31.6	29.7 (10-146 <sup>§</sup> )
<b>Circumferential thrombus neck %</b>	8	9	8 (0-100)
<b>Circumferential calcification neck %</b>	8	7	7.9 (0-100)
<b>Mean angulation aortic neck (range)</b>	37 (0-133)	36 (0-100)	36.4 (0-133)
<b>Median angulation neck</b>	30	35	30
<b>Max AAA diameter, mean mm (range)</b>	64 (18-125)	65 (25-130)	64.2 (18 <sup>§</sup> -130)
<b>Angulation right common iliac artery*</b>	61 (0-180)	51 (0-180)	57 (0-180)
<b>Angulation left common iliac artery</b>	66 (0-320)	56 (0-180)	63 (0-320)
<b>Angulation right external iliac artery</b>	63 (0-180)	67 (0-180)	64 (0-180)
<b>Angulation left external iliac artery</b>	58 (0-180)	57 (0-150)	57 (0-180)
<b>Circumferential Thrombus (% , range)</b>			
right common iliac artery			
left common iliac artery	10	11	10 (0-100)
Circumferential calc. % (mean, range)	9	8	8 (0-100)
right common iliac artery	25	27	26 (0-100)
left common iliac artery	26	26	26 (0-100)

\* P < 0.05 (0.018)

# reversed conical neck

§ Iliac aneurysm

**Table 3** Characteristics of the EVAR procedure

Leg occlusion	Second generation device (n=189)	Third generation device (n=128)	Total group (n=317) (%)
<b>Type of anesthesia</b>			
General	22	22	44 (14%)
Regional	150	98	248 (78%)
Local	17	8	25 (8%)
<b>Additional PTA</b>			
No	174	117	291 (92%)
Yes	15	11	26 (8%)
<b>Additional distal extensions right</b>			
0 extensions	117	83	200 (63%)
1 extensions	64	43	107 (34%)
2- extensions	8	2	10 (3%)
<b>Additional distal extensions left</b>			
0 extensions	166	123	289 (91%)
1 extensions	22	3	25 (8%)
2- or more extensions	1	1	2 (1%)
<b>Endoleak during operation</b>			
No endoleak	138	65	203 (64%)
Type 1	8	3	11 (4%)
Type 2	43	60	103 (32%)
<b>X-ray time (min)</b>			
≤ 30	182	127	309 (97%)
31-60	5	1	6 (2%)
> 60 -177 (max)	2	0	2 (1%)
<b>Contrast use in ml (min)</b>			
≤ 100	89	76	165 (52%)
101-200	83	46	129 (41%)
> 200-360 (max)	17	6	23 (7%)
<b>Blood loss ml</b>			
≤200	133	88	221 (70%)
201-500	41	29	70 (22%)
501-1000	10	7	17 (5%)
> 1000-5000 (max)	5	4	9 (3%)

**Table 4** Timing of surgery and occlusion

Timing of surgery and occlusion	Second generation device		Third generation device		Total number of patients (%) (n=317)	
	Number of occlusion / number of patients					
Elective - Asymptomatic AAA	11/125	(8.8%)	7/100	(7.0%)	18/225	(8.0%)
Elective - Symptomatic	9/28	(32.0%)	0/10	(0%)	9/38	(23.7%)
<b>Total Elective</b>	20/153	(13.1%)	7/110	(6.4%)	27/263	(10.2%)
Emergency - Ruptured AAA	1/36	(2.8%)	3/18	(16.7%)	4/54	(7.4%)
<b>Total occlusion</b>	21/189	(11.1%)*	10/128	(7.8%)	31/17	(9.8%)

\* p<0.05

**Table 5** Instructions for Use# criteria Anaconda second and third generation

Infrarenal aortic neck	
Length (H1)	>15 mm
Thrombus	<50%
Calcification	<50%
Diameter (D2)	>16 mm and <31 mm Anaconda Second generation
Angulation infrarenal	<90 degrees*
Neck shape (Balm)	Parallel or conical
Iliac arteries	
Diameter AIC	>8.5 and <21 mm
Distal fixation length	>20 mm

# Elective surgery

§ 17.5 Anaconda third generation

\* In the ANA 004-study (6) IFU angulation infrarenal was <45 degrees, for this analysis =<90 degrees, the present maximum infrarenal angulation within IFU, was accepted for both cohorts

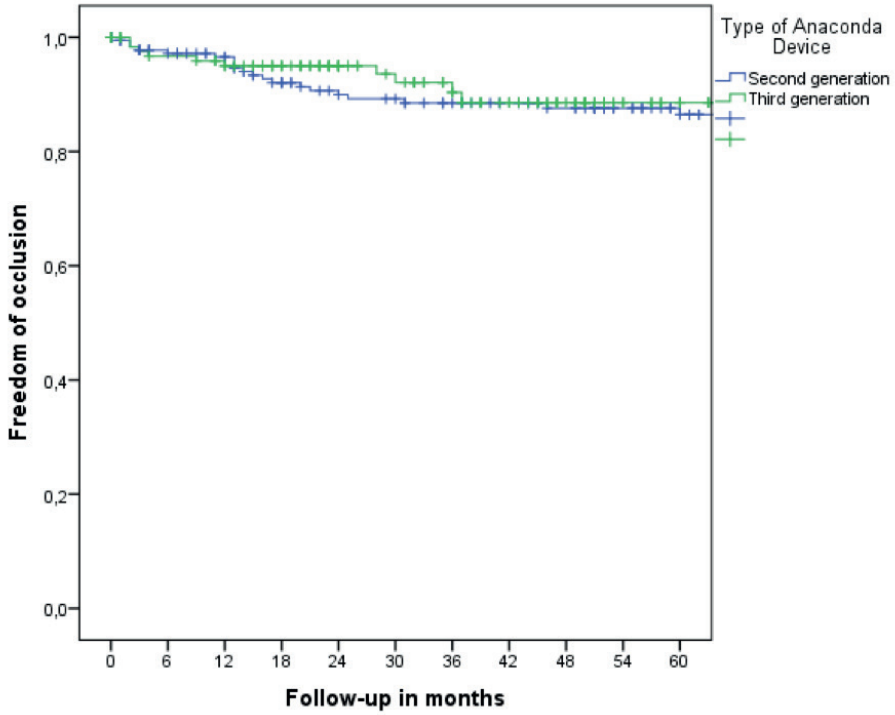
**Table 6** Cumulative number of occlusions during follow-up of the total cohort and the sub-cohorts with criteria Inside Instructions for Use (IFU), see also table 5.

	Total study cohort (n=317)	Total inside IFU cohort. (n=184)	Inside IFU cohort Second generation (n=108)	Inside IFU cohort Third generation (n=76)
<b>Time to occlusion</b>				
< 30 days	1/317 (0.3%)	0/184 (0.0%)	0/108 (0.0%)	0/76 (0.0%)
< 3 months	5/317 (1.6%)	3/184 (1.6%)	1/108 (0.9%)	2/76 (2.6%)
< 12 months	11/317 (3.5%)	5/184 (2.7%)	2/108 (1.9%)	3/76 (3.9%)
< 24 months	21/317 (6.6%)	9/184 (4.9%)	5/108 (4.6%)	4/76 (5.3%)
< 36 months	26/317 (8.2%)	14/184 (7.6%)	9/108 (8.3%)	5/76 (6.6%)
< 48 months	28/317 (8.8%)	17/184 (9.2%)	10/108 (9.3%)	7/76 (9.2%)
< 60 months	29/317 (9.1%)	18/184 (9.8%)	11/108 (10.2%)	7/76 (9.2%)
<b>Total</b>	31/317 (9.8%)	18/184 (9.8%)	11/108 (10.2%)	7/76 (9.2%)

**Table 7** Leg occlusions occlusion and type of intervention

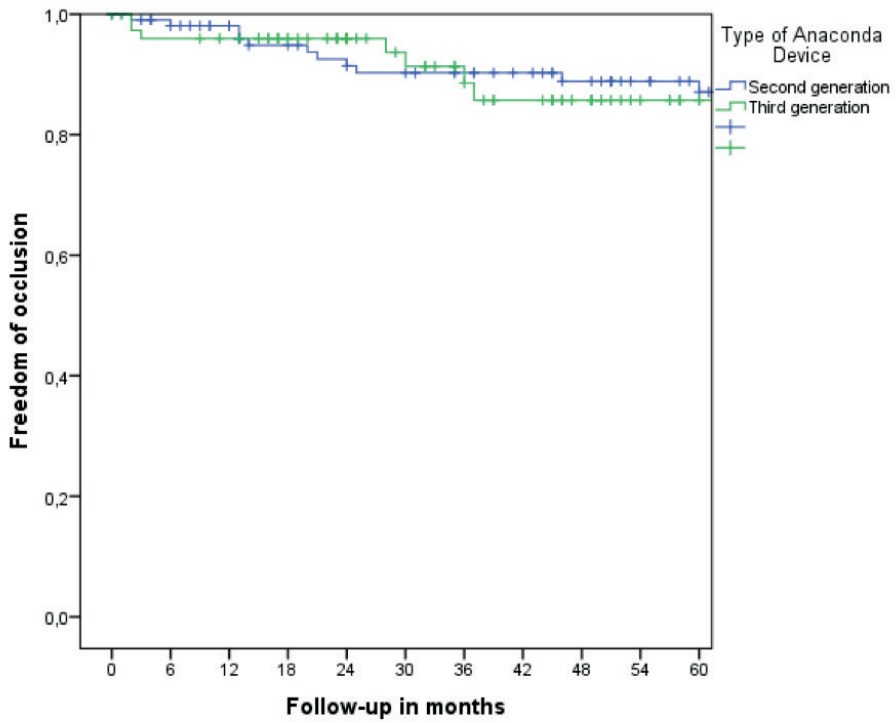
	Second generation device (pts)	Third generation device (pts)	Intervention	Second Intervention
<b>1 event</b>	2 5 2 3 3	1 1 4 2 1	Thrombectomy Thrombectomy with patch Recanalisation and stenting Conversion to open * Fem-fem cross over Conservative treatment	
<b>2 events</b>	1 3 1 1		Trombectomy Recanalisation and stenting Stent, thrombectomy (body) Thrombectomy	Recanalisation and stenting Recanalisation and stenting Conversion (contained rupture) Thrombectomy with patch
<b>3 events</b>		1	Recanalisation and stenting	Thrombectomy + Recanalisation and stenting
	21	10		

Fig 1A Kaplan-Meier curves with freedom of occlusion total cohort (p=0.591 log-rank)



Months		6	12	18	24	30	36	42	48	54	60
Second-gen	189	164	156	139	126	124	121	121	100	100	76
Std error(%)		1.2	1.4	2.1	2.4	2.5	2.6	2.6	2.7	2.7	2.9
Third-Gen	128	117	111	111	111	63	52	49	49	49	49
Std error(%)		1.6	2.0	2.0	2.0	2.8	3.2	3.6	3.6	3.6	3.6

**Fig 1B** Kaplan-Meier curves with freedom of occlusion inside IFU ( $p=0.827$  log-rank)



Months		6	12	18	24	30	36	42	48	54	60
Second-gen	108	100	100	86	86	78	78	78	64	64	49
Std error(%)		1.4	1.4	2.0	2.0	3.1	3.1	3.1	3.3	3.3	3.7
Third-Gen	76	71	71	71	71	71	32	30	30	30	30
Std error(%)		2.3	2.4	2.3	2.3	2.3	4.6	5.3	5.3	5.3	5.3





Chapter

8

**Summary and future  
perspectives**

# Summary and future perspectives

## Summary

This thesis focusses on three different aspects of abdominal aorta aneurysm (AAA) disease.

First, pathogenesis and aetiology was elucidated stressing the importance of various factors related to the chance of rupture. These factors are of importance as they are directly related to the decision whether to intervene or not. As such a more patient tailored approach can be offered. Some of these factors can be visualized with computerized tomography scanning, which is also required to define whether endovascular aneurysm repair (EVAR) is possible, and to draw planning and sizing of the endograft. Obviously interobserver variability of EVAR suitability assessment using the CTA measurements determines accuracy of planning and sizing and may have consequences for final results with the chosen endograft, which is discussed in the second part of the thesis. The third part entirely focusses on one specific endograft, i.e. the Anaconda™ AAA Stent Graft System. During the years three generations of the device have entered the market. Outcome of EVAR in routine and challenging circumstances is studied. We aimed to find reasons why some of the endografts failed. As a consequence, changes to the device were introduced which in turn have influenced outcome. To study the consequences of these changes a comparison between the generations is made

The exact mechanism of aortic aneurysm growth is unknown, but the whole process seems to be multifactorial and further knowledge of biomechanical aspects could also be useful for stent graft design. Aneurysm specific characteristics such as aortic thrombus, calcification and other wall compliance related factors influence sealing and fixation of the endograft. As part of a book review regarding AAA disease and EVAR we presented a comprehensive overview on a variety of factors influencing AAA growth and rupture in [chapter 2](#). Results of basic research studies on pathophysiological processes in AAA thrombus and aortic wall are reported. Other risk factors such as diabetes mellitus and smoking are discussed using results from screening and cohort studies. Smoking is probably the single most important preventable risk factor for AAA development and growth. Understanding the role of intraluminal thrombus (ILT) as a possible factor promoting decrease of mechanical strength of the aneurysmal wall is explained. Influences of ILT, oxidative stress, neovascularisation and immune responses on the extra cellular matrix (ECM), related to the composition of the aortic wall in order to resist aorta arterial flow and pressure are described. Finally, possible pharmacological treatment options in reducing AAA growth and rupture are summarized.

If the indication for EVAR is made various anatomical patient specific factors influence the decision process of the preferred endograft to be used. The second generation Anaconda™ AAA endograft was

introduced in 2003 as one of the newer types of endograft at that time. In every new endograft design a doctor depended learning curve in selecting the proper endograft for the specific patient should be expected. To build a possible web-based e-learning environment for junior vascular specialists in which endograft selection could be trained in various types of anatomical patient data we conducted a validation study including three different brands of endografts mainly used in that time frame. In this study, as described in [chapter 3](#) a group of five experienced EVAR clinicians assessed anatomical data of 202 patients for suitability for three types of endografts. A total of 3030 assessments were made in which a quantification of the likelihood of success of effective and durable sealing and fixation had to be made. The Delphi method was used to determine consensus in the thinking process among clinicians and kappa analysis determined the proportion of variance in the assessment results. As a cohort, EVAR suitability estimation in a group of experienced clinicians appeared to be highly consistent with Cronbach values between 0.87 and 0.90. However, on an individual patient level suitability estimation could vary substantially. This chapter focusses on the interobserver variability in EVAR assessment with experienced EVAR clinicians. We speculated that proper development of EVAR suitability decision algorithms from a large panel of respected experienced vascular interventionalists could become the worldwide standard decision support system. Using a validated, continuously updated algorithm could possibly protect patients against individual clinical misinterpretation, learning curves of less experienced vascular interventionalists and against delay in the introduction of new or improved EVAR knowledge in the medical community.

Clinical introduction of a new type or significant changed endograft is -in general- followed by patient controlled prospective studies focusing on results inside the instructions for use (IFU). Positive study results in using the new endograft describing the technical success and clinical success will be of utmost importance to convince non participating centers to even consider the use of a new type of endograft design. In [chapter 4](#) of this thesis we present the results of the second generation Anaconda™ AAA endograft inside the IFU. The modifications of the second-generation stent included the introduction of proximal hooks connected to the proximal two-ring stents and the introduction of the zero-body support of the graft. The idea behind these modifications was to reduce the chance of stent migration and endoleak type-1. In an international multicenter, prospective, non-randomized controlled study a total of 61 patients from 9 different clinics were included. Primary technical 30 days success was 96.7 % and primary assisted technical success was 98.4%; one type-1 endoleak was treated with a proximal extension cuff. There were three clinical failures (4.9%) after 30 days including one conversion and seven failures (11.4%) at two-year follow-up. Nine re-interventions during follow-up were needed in which two were because of leg occlusion. There were no aneurysm related deaths and no device fixation failures at the proximal neck, migration or wire or hook fractures. There was a significant aneurysm sac diameter decrease from 57 mm to 45 mm after 24 months evaluation. We concluded that the second-generation Anaconda™ endograft allows easy placement and is effective at mid-term follow-up in patients with straightforward anatomy.

Gaining positive experience with the use of the Anaconda™ endograft inside the IFU with successful and durable exclusion of the AAA shifted the indications outside the borders of the IFU. One of the main exclusion criteria in a significant part of the AAA patients screened for EVAR is an angulated AAA anatomical neck. With a properly designed biomechanical match between a proximal angulated wall anatomy and endograft design durable sealing and fixation should be possible. Therefore, we conducted a multicenter study using the Anaconda™ endograft in AAA patients with a severe angulated infrarenal neck of which the results are described in [chapter 5](#). In previous studies, a severely angulated infrarenal neck of more than 60 degrees predicted adverse outcome. Modifications of the endograft with special attention to flexibility, proximal fit and sealing intended to decrease the chance of type-1A endoleak and endograft migration. Because of the design specifications of the Anaconda™ with zero body column strength and high flexibility of the delivery system during placement, theoretically the Anaconda™ could be used in severely angulated infrarenal necks outside the IFU. A total of 36 AAA patients, after properly informed consent, from 9 Dutch hospitals participated in this study. Mean follow-up was 40 months. Mean infrarenal neck angulation was 82 degrees (range 60-133 degrees). Mean aneurysm diameter was 71 mm, ranging from 45 mm (symptomatic small aneurysm) to 100 mm. Primary technical 30 days success was 83% and primary assisted technical success was 94 %. After 4 years aneurysm related mortality was zero and all-cause mortality was 22%. The four-year mid-term primary clinical success rate was 69% and primary assisted and secondary clinical success rates were both 75%. 8 out of 11 clinical failures occurred in the first postoperative year. A total of 5 limb occlusions and two body occlusions occurred during follow-up. One endograft migration occurred producing a type-1A endoleak. In this study the results of the leg occlusion rate were discussed. The study concludes that open AAA repair is still a preferable option in patients with challenging aortic neck anatomy and being fit for open surgery. Furthermore, because of the higher probability of type-1A endoleak, neck dilatation and endograft migration it could be beneficial to execute challenging EVAR procedures in high-volume centers.

With ongoing experience EVAR procedures were also applied during “contained” AAA ruptures. Results seemed beneficial for patients in terms of 30-days mortality, also in proven ruptured cases. Because of the repositionability of the body and the magnet system, which facilitates the rapid acquisition of short contralateral limb access, the prosthesis seems ideally suited for the treatment of ruptured AAA. As a consequence, a study protocol using the Anaconda™ endograft in acute cases was implemented. In [chapter 6](#) we studied the short- and long-term results of endovascular treated ruptured abdominal aortic aneurysm (rEVAR). In this single center prospective non-randomized study, a total of 117 patients presented with a ruptured AAA. Patient enrollment was from 2006-2010. Patients were assessed for rEVAR treatment during which permissive hypotension was maintained. A total of 70 patients were treated with open repair, 35 with EVAR in which 27 patients received an Anaconda™ bifurcated endograft and 8 patients received a Talent™ or an Endurant™ endograft due to inappropriate iliac access or fixation zone for the Anaconda™. About 30% of the rEVAR patients had a challenging neck anatomy with a neck

length shorter than 15 mm or a neck angulation of 60 degrees or more. The 30-day re-intervention rate was 26%. 30-day, 1-year and 5-year mortality were 17%, 26% and 42%, respectively. All deaths after one-year follow-up were non-AAA related. Challenging infrarenal neck anatomy was not associated with long term mortality in our study. We discuss in this study that rEVAR can be used in a damaged control concept accepting less favorable AAA anatomy and the possibility of more secondary re-interventions. This conclusion is confirmed in a systemic review with the conclusion that rEVAR in suitable patients is a reasonable alternative for open repair<sup>1</sup>.

During the course of conducted studies with the Anaconda™ endograft the leg occlusion ratio remained a matter of concern. Although not significantly more the ratio was consistently in the upper fourth quadrant of the reported figures with other types of endografts.

In [chapter 7](#) we evaluated the incidence and treatment of limb occlusion of the second- and third generation Anaconda™ endografts. In this third generation, called the Anaconda One-Lok™ and introduced in 2011 the docking zone-leg diameter was standardized for the body-leg combination. In this single-center retrospective study we used prospectively gathered data from a total of 317 consecutive patients from 2003 until September 2015. Primary outcome measure was limb occlusion. 189 patients received a second-generation device and 128 patients received a third-generation device. In 71% patients were treated electively, 12% were symptomatic and 17% had a rupture. A total of 184 patients were treated inside the IFU. After a mean follow-up of 47 months (range 0-134) 31 occlusions were diagnosed (4 body and 27 leg occlusions). Freedom from occlusion at five years were 86.5% for second generation and 88.6% for third generation devices. There was no statistically significance difference between the two generation devices. Limb occlusions did not result in any minor or major amputations. Five conversions to open repair were performed for body occlusions. Thrombectomy, recanalization and stenting, femoro-femoral cross-over bypass or conservative treatment were the treatments in the patients with one leg occlusion. There was a relationship between leg occlusion and smaller distal prothesis leg diameter independent of the endograft generation. With the second-generation devices timing of surgery was related to occlusion in the symptomatic group. In this study we concluded that the Anaconda™ has a proven effectiveness in AAA exclusion in daily practice inside IFU. A substantial number of occlusions presented between 2 and 5 years of follow-up promoting early awareness of possible problems in high risk occlusion groups. Using intensified follow-up schedules in this period could probably reduce the limb occlusion rate.

## Future perspectives

As with many diseases the definitive cure and / or prevention of Aorta Abdominal Aneurysm will start with a thorough knowledge of the factors initiating, promoting or exaggerating this disease. Inflammation, atherosclerosis with intraluminal thrombosis, and inherited factors are the pathways in which research is focused on primarily. Effects of Metformin, stem-cell therapy, and factors promoting the extracellular matrix synthesis are further studied. Non-surgical interventions should probably be started in an earlier stage of AAA development in which the diameter is still relatively small<sup>2</sup>.

Population screening for AAA for all men at the age of 65 years being beneficial is Class 1, Level A evidence now. European guidelines recommend to implement national screening programs for AAA-screening<sup>3</sup>. Nevertheless, the recent Dutch health care consul concluded that in the Dutch situation a population-based screening program would turn out negative in terms of risks and benefits. The AAA detection grade in the Netherlands with primary care physicians and the Dutch favorable results with the treatment of AAA compared to other countries makes the effort for national wide screening not as beneficial as previously thought. Although risk reduction will occur, concerns are raised about the emotional side effects for the screened population. With further optimization of primary care in prevention and awareness of AAA the necessity of nationwide screening could be further reduced<sup>4</sup>. Simple diagnostics such as duplex ultrasound are becoming more and more available in the primary care and could eliminate the nationwide screening programs in which ultrasound was not part of the primary care setting. Detecting AAA-development and growth with life style management and proper lifestyle interventions should be organized as part of the Dutch health care prevention program. Other nationwide screening questions such as detecting lung cancer in the high-risk smoking group using a pulmonary CT-scan could be combined with the first time AAA screening and thereby improving the benefit of otherwise screening nationwide.

With regard to interobserver variability in planning and sizing of the EVAR endograft, proper planning tools, uniform measurement of AAA anatomy and well supported clinical endograft selection guides could reduce interobserver variability<sup>5</sup>. It should be possible to create a sufficient large AAA database if the European Society of Vascular Surgery promotes an EU wide database in which all used types of endograft and the anatomical AAA data and patient characteristics are monitored. This should preferable be done in a prospective registry in which the European Union together with National health departments and the manufactures should fund these registries. The European Society of Vascular surgeons could coordinate these initiatives and vascular surgeons should financially be supported to organize and fill in the time-consuming registries data. Follow-up data has to be loaded nationally to make post implant EU surveillance possible.

During the first period of EVAR a voluntary multicenter registry -The European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR)- started in 1996 to include EVAR patients during their follow-up. In those days 60% were ASA III high risk patients, inclusion criteria were less strict than now with AAA diameter starting at 4 centimeters. This successful registry has produced results from the early generation endografts until the latest third generation endografts, ending patient inclusion in 2006. Latest results describing the effect of sex difference in 30-days and 5-years follow-up results after EVAR does highlight the advantage of a registry in which data is collected in daily clinical practice<sup>6</sup>. Although randomized clinical trials and systematic reviews are the scientifically gold standard, these registry data with long term information about a variety of included and updated endografts in time without manufacturer driven disclosures are important too.

When sufficient data is gathered this large data database can be analyzed using the newer analytical techniques such as Deep learning and Artificial Intelligence. These techniques could be very useful for data mining and exploring of possible flaws in the matching of endografts and patient related anatomical data and clinical outcome. Instructions for use can be modified if complications occur in specific patient categories and earlier recognition of endograft design failure could be possible.

Further insight in the behavior of the Anaconda™ endograft over time in relation with patient AAA anatomy is the objective of the currently running Longitudinal Study to Pulsatility and Expansion in Aortic Stent grafts (LSPEAS-study)<sup>7,8</sup>. The interaction process between the endograft and the patient abdominal aorta aneurysm is a time-dependent phenomenon in which the ultimate goal is prevention of rupture without complications and reinterventions<sup>9</sup>. Next step in the prediction of endograft behavior in individual patients in time is ECG-gated dynamic CT-imaging in which endograft and aorta wall motion can be monitored. During follow-up the continuous cyclic cardiac and aorta blood flow motion can alter the sealing and fixation of the endograft and knowledge of significant changes in these can eventually predict complications and failure in the (near) future.

Recent 3D-CT studies about the expansion and remodeling of the proximal Anaconda™ endograft in the aortic neck gave a unique insight in the mechanical properties in time of the saddle shaped Anaconda endograft. Although initially oversizing matters for effective sealing and fixation, the definitive endograft ring diameter will expand inside the aorta to near nominal diameter size as pre-operatively chosen within 6 months. This phenomenon is an adaptation of the patients' aortic wall anatomy<sup>10,11</sup>. Adaptation and migration are two distinct phenomena. Monitoring these phenomena with ECG-gated dynamic CT-imaging in the future could select patterns of the neck in which patients develop Type-1A endoleak or device related neck aneurysms. Intensive tailor-made follow-up is proposed for patient prone to these possible complications and in "prosperous characteristics patients" the intensity of follow up scheme

could be reduced. The increase in radiation load associated with this intensive follow-up protocol in selected patients is certainly within acceptable limits in this elderly patient group and with modern CT equipment.

The infrarenal aorta neck shape with angulation from zero to ninety degrees or more is one of the critical factors in the selection of open or endovascular treatment of the AAA. The endograft distal landing zone behavior in time is important in predicting failure of endograft limbs. Occlusion of endograft limbs through thrombus in one of our studies with the Anaconda™ device was relatively high. In time the leg curvature seems to increase most prominently in the right iliac leg, which leg side was used to introduce the endograft. The very flexible Anaconda™ leg design mimics a vacuum cleaner tube. The drawback of the high flexibility is that the so called “Concertina effect” can result in a disturbance of the flow profile<sup>12</sup>. Bench model research can provide clues for optimizing the flow profile without jeopardizing the high kink resistance of the leg design. Using contrast-enhanced ultrasound particles during follow-up to characterize real-time flow patterns in iliac anatomy one could be able to predict nearby aorta-iliac leg occlusion<sup>13</sup>. This imaging modality could be used to prevent this specific complication.

Combining the knowledge and experience of vascular interventionalists and technical medicine engineers together in one vascular team should be the gold standard in AAA clinical and research programs.

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Chapter

9

**Nederlands samenvatting**

**Dankwoord**

**Curriculum vitae**

## Nederlandse samenvatting en toekomstig perspectief

Dit proefschrift gaat inhoudelijk in op drie verschillende aspecten van het abdominaal aorta aneurysma (AAA). In het eerste deel, **hoofdstuk 2** wordt de pathofysiologie en ontstaanswijze ontrafeld waarbij de verschillende factoren die van belang kunnen zijn voor AAA worden beschreven. Deze factoren zijn van belang om verdere groei van het aneurysma met verschillende interventies te kunnen bestrijden, zodat een voor de patiënt op maat gemaakte behandeling besproken kan worden. Sommige oorzaken van de AAA-groei kunnen met een computertomografie (CT)-scan in beeld gebracht worden.

Ook voor de endovasculaire behandeling ofwel in het engels “endovascular aneurysm repair” afgekort EVAR is een CT-scan noodzakelijk om te kijken of de EVAR technische mogelijk is en om de te gebruiken endoprothese te configureren. Het is bekend dat verschillende specialisten bij beoordeling van de CT-scan gegevens van een patiënt ook tot verschillende afwegingen kunnen komen om een EVAR-behandeling te doen. De planning van en de keuze voor een bepaalde prothese kan hierbij dus variëren tussen specialisten en hiermee dus ook de eventuele uitkomst van behandeling. Dit wordt besproken in **hoofdstuk 3** van dit proefschrift.

Het derde deel (**hoofdstuk 4-7**) gaat inhoudelijk over één type endoprothese, te weten de Anaconda™ AAA Stent Graft System. Gedurende de afgelopen jaren zijn er drie generaties/ opeenvolgende types van deze endoprothese op de markt gekomen. We bestuderen hierbij de resultaten van de tweede en derde generatie endoprothese bij gebruik in “normale” AAA-anatomie en meer uitdagende AAA-anatomie. We proberen hierbij oorzaken te vinden waarom sommige gebruikte endoprothese in de verschillende generaties bij sommige patiënten toch geen goed resultaat geven bij de behandeling. Mede door deze resultaten zijn ook aanpassingen aan de prothese doorgevoerd in de derde generatie die wat betreft uitkomsten van behandeling in de derde generatie weer vergeleken worden met de tweede generatie endoprothese.

Het exacte mechanisme van AAA-groei is niet bekend, maar multifactoriële invloeden evenals biomechanische aspecten spelen een rol, waarbij deze laatste factor ook van belang is voor het ontwerp van de endoprothese. Aneurysma specifieke eigenschappen zoals trombus, verkalking maar ook andere wand gerelateerde factoren beïnvloeden de afdichting en houvast van de endoprothese in de aorta. Als onderdeel van een hoofdstuk uit een boek betreffende AAA en EVAR geven we in **hoofdstuk 2** relatief beknopte samenvatting en overzicht van factoren die de groei en ruptuur kans van een aneurysma beïnvloeden. Basaal onderzoek over pathofysiologische processen in het wandstandige AAA-trombus wordt beschreven. Effecten van andere bekende risicofactoren uit screening en cohortstudies zoals diabetes mellitus en roken worden beschreven. Roken is hierbij waarschijnlijk de belangrijkste te vermijden risicofactor voor het ontstaan van AAA en zijn verdere groei. Uitleg wordt gegeven omtrent

het samenstel tussen de wandstandige (intraluminale) trombus (ILT) en de aortawand als oorzaak van verzwakking van de aanvankelijk sterke aortawand. Hoe deze ILT eventueel beïnvloed kan worden om de aortawand minder te laten verzwakken wordt eveneens besproken. Invloed van deze ILT, maar ook andere factoren zoals oxidatieve stress, neovascularisatie en aanwezige immuunrespons bepalen allemaal de sterkte van de onderdelen van de aortawand, samengevat in de extracellulaire matrix (ECM). Deze ECM-sterkte bepaalt mede de weerstand en souplesse van aortawand tegen de continue bloeddrukveranderingen veroorzaakt door de bloedstroom. De mogelijkheid om deze AAA-groei en ruptuurkans eventueel te verminderen met medicijnen wordt ten slotte in dit hoofdstuk ook nog beschreven.

Als de mogelijkheid voor een EVAR beoordeeld wordt, bepalen anatomische patiënt specifieke factoren het keuzeproces van de te gebruiken type endoprothese. De tweede generatie Anaconda™ AAA-endoprothese werd in 2003 als een van de nieuwe endoprotheses geïntroduceerd. Bij gebruik van een nieuw type endoprothese moet de vaatchirurg ervaring krijgen in het bepalen van de optimale maten van de prothese bij een specifieke patiënt, hierbij wordt de chirurg ook ondersteund door de fabrikant. Het opbouwen van deze ervaring, met name voor junior vaatchirurgen kan in principe ook versneld worden via e-learning modules. Wij testen en valideren een leeromgeving waarbij de anatomische AAA-maat gegevens van verschillende patiënten gepresenteerd worden. In deze leeromgeving kunnen drie verschillende merken endoprotheses gekozen worden die in die tijd ook daadwerkelijk gebruikt werden in de dagelijkse praktijk.

In deze studie, beschreven in [hoofdstuk 3](#), analyseert een groep van 5 ervaren EVAR-vaatchirurgen de anatomische gegevens van 202 patiënten met een AAA en beoordeeld hierbij de mate van geschiktheid van elk van de drie types endoprothese die hij kan gebruiken.

In totaal worden er 3030 beoordelingen gedaan waarbij een gekwantificeerde uitspraak wordt gedaan omtrent de ingeschatte kans op een succesvolle afdichting en fixatie van de endoprothese in de AAA. De Delphi-methode wordt hierbij als statistiek gebruikt om de mate van overeenstemming in besluitvorming tussen vaatchirurgen te beoordelen. De kappa analyse wordt gebruikt om de variatie in deze besluitvorming tussen de gegeven antwoorden te bepalen. Als cohort patiënten bekeken is de mate van overeenstemming van de gekwantificeerde uitspraak tussen ervaren vaatchirurgen behoorlijk groot met een Cronbach waarde tussen 0.87 en 0.90. Bekeken op individueel niveau van patiënt beoordeling kon er een behoorlijke variatie in de gekwantificeerde uitspraak zijn tussen de vijf vaatchirurgen. Dit hoofdstuk kijkt naar de variatie in dit keuzeproces tussen verschillende ervaren EVAR-vaatchirurgen. We schatten in dat goed ontwikkelde algoritmes in een beslissing ondersteunende omgeving de keuze van een specifieke endoprothese bij EVAR bij een specifieke patiënt mede kunnen helpen te bepalen

en dat dit systeem dan ook internationaal als standaard ondersteuning te gebruiken zou zijn. Met deze gevalideerde en met continue verbeteringen aangepaste algoritmes voor protheses kan de patiënt beschermd worden tegen onopgemerkte fouten in de interpretatie van gegevens, kunnen eventuele leercurves versneld worden en kunnen nieuwe versies van endoprotheses met internationaal input van experts in de algoritmes bij gebruik in de dagelijkse praktijk eerder mede beoordeeld worden op geschiktheid.

De introductie van een nieuwe endoprothese gaat in het algemeen samen met een patiënt gecontroleerde prospectieve studie om de klinische resultaten te monitoren bij gebruik van de endoprothese volgens de toegestane gebruiksvoorschriften - "instructions for use" (IFU)- van de fabrikant. Het is belangrijk bij gebruik van de nieuwe endoprothese dat de technische en klinische studieresultaten gelijk of gunstiger zijn in vergelijking met de tot dan toe gebruikte endoprotheses, anders is het niet te verwachten dat vaatcentra die niet met de studie meedoen de endoprothese ooit gaan gebruiken

In **hoofdstuk 4** van dit proefschrift beschrijven we de resultaten van de tweede generatie Anaconda™ AAA endograaft binnen de gebruiksvoorschriften. De tweede generatie endoprothese heeft proximale haakjes die verbonden zijn met de proximale dubbele ringstents zonder ondersteuning van ringstents in de endoprothese body. Het idee van de haakjes was het verminderen van de mogelijkheid van verzakken van de endoprothese vanuit de "hals" in het aneurysma zelf, maar ook de kans van zogenaamde type-1 lekkage van bloed langs de buiten-en bovenzijde van de endoprothese tussen de aortawand en de prothese in het aneurysma van de aorta zelf. In een internationale multicenter, prospectieve, niet gerandomiseerde studie worden in totaal 61 patiënten in negen verschillende klinieken geïncludeerd. De primair technische succesvolle behandeling (30 dagen) was 96.7% en met een extra operatieve interventie tijdens de ingreep in de vorm van een proximale cuff i.v.m. een type-1 endoleak zelfs 98.4%. Er waren drie "clinical failures" (4.9%) na 30 dagen waarbij 1 conversie naar een open operatie nodig was. Na 2 jaar follow-up waren er in totaal 7 clinical failures waarbij de endoprothese niet voldeed aan de vooraf gedefinieerde eisen van succesvolle plaatsing en aanwezigheid van de prothese bij de patiënt. Er werden negen herstel behandelingen uitgevoerd waarvan twee keer voor dichtzittende pootjes van de endoprothese. Er is niemand gedurende de studie overleden aan de gevolgen van het aneurysma zelf. Ook is de endoprothese niet los gaan zitten in de hals en zijn de metalen onderdelen van de endoprothese niet gebroken tijdens de studieperiode. De omvang van het aneurysma zelf is van 57 mm naar 45 mm significant kleiner geworden in de 24 maanden van de nacontrole van patiënten.

We concluderen in deze studie dat de tweede generatie Anaconda™ endoprothese makkelijk te plaatsen is en ook effectief is in zijn werking gedurende de geanalyseerde studieperiode bij binnen bepaalde grenzen gedefinieerde AAA-anatomie.

Met de gunstige ervaringen van het gebruik van de Anaconda™ binnen de gebruiksvoorschriften van de fabrikant werd door de vaatchirurgen ook EVAR-indicaties buiten de voorgeschreven gebruiksvoorwaarden gekozen. Een van de belangrijkste exclusie-criterium bij AAA-patiënten die gescreend worden voor EVAR is een (te) sterke hoek tussen de aorta nek waar de prothese zich moet vasthouden en de daadwerkelijke AAA zelf. Met een goed ontworpen endoprothese waarbij biomechanisch de prothese zich stevig kan fixeren aan de wand van de gehoekte hals overgang naar het aneurysma kan langdurige endoleak type-1 vrije fixatie mogelijk zijn. Om dit te onderzoeken beschrijven we in **hoofdstuk 5** de resultaten van een multicenter studie waarbij de Anaconda™ endoprothese in fors gehoekte infrarenale hals anatomie is geplaatst.

Uit eerdere studies was al bekend dat bij ernstige infrarenale hals hoeken van meer dan 60 graden de uitkomsten van EVAR minder gunstig zijn. Aanpassingen van endoprotheses met speciale aandacht voor flexibiliteit, proximale houvast en goede afsluiting bij de halswand kan de kans op type-1 endoleak en endoprothese migratie verminderen. Door de specifieke eigenschappen van de Anaconda™ met het prothese lijfje zonder stent ringen en het flexibele inbreng systeem van de endoprothese kan, in theorie de Anaconda™ zeker geschikt zijn voor plaatsing in gehoekte infrarenale hals anatomie buiten de gebruiksvoorwaarden.

In deze studie participeerden in totaal 36 AAA-patiënten uit 9 Nederlandse ziekenhuizen. Een totale follow-up duur van 40 maanden werd bereikt waarbij de infrarenale hals hoek gemiddeld 82 graden was (60-133 graden). De gemiddelde aneurysma diameter was 71 mm, variërende tussen 45 mm (symptomatisch klein AAA) tot 100 mm.

De primair technische succesvolle behandeling (30 dagen) was 83 % en met een extra operatieve interventie 94 %. Er is niemand gedurende de studie van 4 jaar overleden aan de gevolgen van het aneurysma zelf, maar wel 8 patiënten aan andere oorzaken. De 4-jaars primair klinische succesvolle behandeling was 68% en met extra interventie direct 75% en in latere fase ook 75%. 8 van de 11 klinische failures traden op in de eerste 12 maanden. In de totale studie-periode zijn 5 endoprothese pootjes en 2 prothese lijfjes dicht gaan zitten met stolsels (occludeerden). Deze minder gunstige resultaten werden in deze studie eveneens uitgebreid besproken. Er was 1 endoprothese die uitzakte vanuit de hals zodat een type-1 endoleak kon optreden. In deze studie concluderen we dat open AAA-herstel bij AAA-anatomie met een forse hals hoek nog steeds de voorkeur heeft indien de patiënt ook lichamelijk fit genoeg is voor deze open ingreep. Het lijkt verstandig te zijn indien EVAR alsnog wordt toegepast bij uitdagende anatomie zoals een sterk gehoekte aorta hals, deze procedure mede vanwege de hogere kans op type-1 endoleak, hals verwijding en uitzakken van de prothese, in centra met ervaring in complexe anatomie uit te voeren.

Door de toename in gebruikservaring werd de EVAR wereldwijd ook gebruikt bij de (contained) geruptureerde AAA-patiënten. Met name de 30-dagen mortaliteit na EVAR bij AAA-ruptuur leek gunstiger te zijn t.o.v. de uitkomsten na open AAA-operatie.

In **hoofdstuk 6** beschrijven we de korte en lange termijn resultaten van de Anaconda™ bij EVAR bij AAA-rupturen (rEVAR). In deze studie wordt in 1 ziekenhuis prospectief, niet gerandomiseerd een totaal aantal van 117 patiënten met een AAA-ruptuur geïnccludeerd in de periode 2006-2010. De patiënten werden tijdens de opvang beoordeeld middels CT-scan op anatomische geschiktheid waarbij een gecontroleerde hypotensie werd nagestreefd totdat duidelijk was op welke manier de operatie van het AAA het best mogelijk was. In totaal zijn 70 patiënten middels open uitschakeling van het AAA behandeld, 35 met EVAR waarbij 27 patiënten de Anaconda™ bifurcatie prothese geplaatst kregen en 8 patiënten de Talent™ of de Endurant™ endoprothese door ofwel niet geschikte iliacale toegang ofwel niet geschikte fixatie voor de Anaconda™ endoprothese. Ongeveer 30% van de rEVAR patiënten had eveneens een uitdagende hals anatomie met een halslengte korter dan 15 mm ofwel een hals hoek van 60 graden of meer. Na de rEVAR werd binnen 30 dagen bij 26% een re-interventie uitgevoerd. De 30-dagen, 1 jaar en 5 jaar mortaliteit na rEVAR was 17%, 26% en 42 % respectievelijk. Alle overleden patiënten na 1 jaar follow-up waren niet aneurysma gerelateerd. Ook een uitdagende hals anatomie was niet extra nadelig voor de sterftcijfers.

In deze studie bespreken we dat rEVAR gebruikt kan worden als een “damaged controle” operatie principe waarbij minder gunstige anatomie ook middels EVAR kan worden geopereerd indien de mogelijkheid van een toename in secundaire interventie hierbij als nadelige consequentie geaccepteerd wordt. Deze conclusie is recent ook bevestigd in een systematische review waarbij rEVAR in geselecteerde patiënten een goed alternatief is in plaats van de open AAA uitschakeling<sup>1</sup>.

Gedurende dit promotietraject bleek ook in de door ons uitgevoerde studies met de Anaconda™ endoprothese dat het aantal dichtzittende/getromboseerde Anaconda™ pootjes meer te zijn dan verwacht. Hoewel dit aantal in vergelijking met andere type endoprothesen in de literatuur niet significant hoger was, bleek het wel in de onderlinge vergelijkingen met andere (ook oudere) endoprothesen in de hoogste groep van dichtzittende pootjes te zitten. In **hoofdstuk 7** evalueren we de incidentie en behandeling van de dichtzittende poten in zowel de tweede generatie als de derde generatie Anaconda™ endoprothese. De derde generatie prothese die de Anaconda One-Lok™ wordt genoemd werd geïntroduceerd in 2011. Hierbij werd de Anaconda One-Lok™ lijfje met poot combinatie voor de verschillende te kiezen afmetingen gestandaardiseerd.

In deze retrospectieve studie wordt in 1 ziekenhuis prospectief de gegevens verzameld van in totaal 317 geïnccludeerde patiënten van 2003 tot aan september 2015. De primaire uitkomst parameter was poot

occlusie. In 189 patiënten werd de tweede generatie Anaconda™ endoprothese geplaatst en bij 128 patiënten de derde generatie Anaconda One-Lok™.

Bij 71% van de patiënten werd de operatie electief gepland uitgevoerd, bij 12% was er sprake van een symptomatisch AAA en bij 17% was er sprake van een AAA-ruptuur. In totaal werden 184 patiënten binnen de gebruiksvoorschriften van de Anaconda™ geopereerd. Na een gemiddelde follow-up duur van 47 maanden (range 0-134 maanden) werden initieel 27 dichtzittende pootjes en 4 dichtzittende lijfjes gediagnostiseerd. Van de tweede generatie Anaconda™ was 86,5% van de patiënten na 5 jaar occlusie vrij en 88,6% voor de derde generatie Anaconda One-Lok™ endoprothese. Dit was niet statistisch significant verschillend. Poot occlusie resulteerde in dit cohort niet in kleine of grote amputaties. In totaal vijf patiënten werden open geopereerd door occlusie van het lijfje van de endoprothese. Indien 1 pootje dicht zat werd trombectomie, rekanalisatie van de poot met stenting, femoro-femorale bypasschirurgie ofwel conservatieve behandeling verricht. Er was een verband tussen poot occlusie en kleinere distale prothese poot diameter bij zowel de tweede als de derde generatie prothese. In de tweede generatie bleek dat de timing van de operatie ook gerelateerd was aan meer poot occlusie, wat bleek uit procentueel de meeste occlusies in de symptomatische AAA-operatiegroep.

We concluderen met deze studie dat de Anaconda™ endoprothese een bewezen geschikte endoprothese is voor AAA-uitschakeling in dagelijks gebruik binnen de gebruiksvoorschriften van de fabrikant. Een substantieel aantal occlusies manifesteren zich tussen de 2 en 5 jaar follow-up zodat alertheid in diagnostiek in risicogroepen voor occlusie zinvol is. Het gebruik van intensievere follow-up programma's in deze jaren kan het aantal poot occlusies waarschijnlijk verminderen.

## Toekomstig perspectief

De definitieve behandeling en/ of preventie van het abdominaal aorta aneurysma behoeft als basis een diepgaande kennis van de factoren die het AAA laten ontstaan, laten groeien en verder laten verslechteren tot en met de eventuele ruptuur van het aneurysma. Ontsteking, arteriosclerose met intraluminale trombusvorming en erfelijke factoren zijn de onderzoekslijnen waar primair het wetenschappelijk pathofysiologische AAA-onderzoek op gericht is. De effecten van metformine, stamcel behandeling en factoren die de extracellulaire matrix verstevigen worden verder onderzocht. De niet chirurgische behandelingen moeten met name gestart worden in de vroegere fases van AAA-ontwikkeling waarbij het aneurysma diameter nog beperkt is<sup>2</sup>.

Bevolkingsonderzoek voor AAA-screening bij mannen van 65 jaar is klasse 1, level A-bewijs als zijnde effectief. De Europese richtlijnen raden dan ook aan een nationaal bevolkingsonderzoek te starten voor AAA screening<sup>3</sup>. In een Nederlands onderzoek van de Gezondheidsraad daarentegen wordt geconcludeerd dat voor de Nederlandse situatie een AAA-bevolkingsonderzoek negatieve gevolgen zou hebben in termen van risico's en opbrengsten. De opsporing van AAA in Nederland middels een bevolkingsonderzoek met de huidige goed georganiseerde huisartsenzorg en de gunstige resultaten van de Nederlandse AAA-behandeling in vergelijking met omliggende landen is niet zo gunstig meer als men aanvankelijk dacht. Hoewel er wel een risico reductie optreedt, maakt me zich ook zorgen omtrent de emotionele belasting van de screening voor de op te roepen bevolkingsgroep. Door verder optimalisatie in de eerstelijns zorg met betrekking tot preventie van en alertheid op de AAA kan het nut van de screening nog verder geminimaliseerd worden<sup>4</sup>.

Eenvoudige in te zetten diagnostiek zoals echo-duplex onderzoek is in opkomst in de eerstelijns zorg en kan het nut van AAA-screeningsprogramma's nog meer reduceren. Het detecteren van AAA-aanwezigheid en groei kan ook onderdeel worden van een breder Nederlands gezondheid en ziekte preventieprogramma. Andere nog op te zetten bevolkingsonderzoeken zoals longkanker detectie middels thorax CT-scans bij hoogrisico groepen zoals rokers kan zelfs gecombineerd worden met eenzelfde CT-scan voor het eerste moment van AAA- screening. De totale gezondheidswinst van deze gecombineerde screening kan zelfs meer zijn dan verwacht.

Met betrekking tot de interobserver variabiliteit in het plannen en meten van de EVAR-endoprothese zijn juiste meet instrumenten met uniforme afspraken omtrent AAA-anatomie meting zinvol. Ook het gebruik van goed uitgewerkte klinische relevante selectie en "decision support" programma's kunnen onwenselijke interobserver variatie verminderen<sup>5</sup>.

Het moet toch ook mogelijk zijn om een grote AAA-database te creëren waarbij de European Society of Vascular Surgery een EU brede database opzet waarbij alle type endografts en de anatomische AAA-data en patiënt karakteristieken in opgenomen worden. Dit zal bij voorkeur in een prospectief register gedaan moeten worden waarbij de Europese Unie samen met de nationale gezondheid organen zorgt dat de bedrijven van de endoprotheses hier een significante bijdrage in leveren om dit te financieren. De European Society of Vascular surgeons zal hierbij een ook een financiële bijdrage moeten ontvangen om het tijdrovende invullen van de database te organiseren en (op nationaal vaatchirurgisch niveau) te financieren. De follow-up data zal dan nationaal ingebracht kunnen worden om de noodzakelijke “post-implant surveillance” Europees mogelijk te maken.

Gedurende de eerste periode van EVAR is vanaf 1996 al een vrijwillig multicenter register van start gegaan - The European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) waarbij EVAR- patiënten gedurende de follow-up bijgehouden worden. In de EVAR-begintijd waren 60% van de patiënten ASA III hoog risico waarbij de inclusiecriteria minder strikt dan nu met AAA- diameters vanaf 4 centimeter. Dit succesvolle register heeft vanaf de eerste generatie tot en met de derde generatie endoprothese onderzoeksresultaten gegeneerd, waarbij de inclusie in 2006 is geëindigd. Recente onderzoeksresultaten waarbij het effect van gender op de 30- dagen en 5-jaars follow-up resultaten na EVAR beschreven worden, geeft nogmaals het belang weer van een register waar data verzameld wordt vanuit de dagelijkse klinische praktijk<sup>6</sup>.

Hoewel gerandomiseerde clinical trials en systematische reviews wetenschappelijk de gouden standaarden zijn, is een goede lange termijn registratie waarbij verschillende type endoprothesen en updates in tijd bijgehouden worden zonder eventuele inhoudelijke beïnvloeding van de fabrikant zelf ook erg belangrijk. Wanneer de database zodanig groot is dat “big data” analyse nodig is kunnen zelfs modernere analysetechnieken als Deep Learning / Artificial Intelligence ingezet worden. Deze technieken zijn waardevol voor data-analyse waarbij patroonherkenning onderzoek gedaan kan worden in de combinatie endoprothese en patiënt gerelateerde anatomische data en klinische uitkomst. De gebruiksvorschriften (Instructions for use) kunnen dan aangepast worden als complicaties optreden in specifieke patiëntgroepen en vroegere herkenning van potentiële endoprothese ontwerpfouten kan dan beter mogelijk zijn.

Inzicht in het gedrag van de Anaconda™ endoprothese in de tijd in relatie met de AAA-anatomie van de patiënt is het doel van de onderzoekslijn “Longitudinal Study to Pulsatility and Expansion in Aortic Stent grafts (LSPEAS-study)”<sup>7,8</sup> Het interactieproces tussen de endoprothese en het AAA van de patiënt is een tijdsafhankelijke fenomeen waarbij het ultieme behandeldoel is het voorkomen van de aneurysma ruptuur zonder allerlei bijkomende complicaties of noodzakelijke heroperaties<sup>9</sup>.

De volgende stap in de voorspelling van het gedrag van de endoprothese in individuele patiënten in de tijd is gebruik te maken van ECG-getriggerde dynamische CT-scanning waarbij de endoprothese en de aorta wand gedurende de beweging geobserveerd kan worden. Gedurende de follow-up periode heeft de continue cyclus van hartslag en aorta bloeddorstrooming invloed op de afdichting en fixatie van de endoprothese tegen de aortawand waarbij kennis van optredende veranderingen hierin gebruikt kan worden om complicaties en eventuele clinical failures van de prothese in de nabije toekomst te voorspellen.

Recente 3D CT-onderzoek omtrent het uitzetten en remodelleren van de proximale deel van de Anaconda™ in de aorta hals geeft een uniek inzicht in de mechanische eigenschappen in de tijd van de zadelvormige proximale deel van de Anaconda™ endoprothese. Hoewel in het begin "oversizing" (kiezen van een grotere maat prothese t.o.v. de aorta hals diameter) belangrijk is om goede grip en afdichting te krijgen, zie je ook dat de definitieve endoprothese ring diameter zich zodanig gaat hervormen in de aorta dat de normale diameter van de endoprothese van voor het inbrengen weer binnen 6 maanden zo'n beetje bereikt wordt. De aorta wand tpv aortahals van de patiënt past zich hierbij dan ook aan de uitgangsvorm van de endoprothese aan<sup>10,11</sup>. Vervolgen van dit fenomeen met behulp van ECG-getriggerde dynamische CT-onderzoek kan mogelijk in de toekomst hals anatomie eigenschappen voorspellen die vatbaar zijn voor Type-1A endoleak of endoprothese gerelateerde hals aneurysma's.

Intensievere op maat gemaakte follow-up schema's kunnen dan gemaakt worden voor patiënten die vatbaar zijn voor de mogelijke complicaties en minder stringente schema's zijn dan mogelijk voor de "recht toe recht aan" patiëntencategorie. De toename in röntgenstralen belasting bij intensiever follow-up schema's bij geselecteerde patiënten blijft daarbij wel binnen de limieten gezien de leeftijd van patiënten en de continue verbeteringen in CT-apparatuur. De infrarenale hals vorm met mogelijke hoeken vanaf 0 tot wel 90 graden of meer een belangrijk selectiecriteria voor open ofwel EVAR-behandeling van het AAA.

Ook het voorspellen van complicaties van de endoprothese in de distale landingszone in de bekkenslagaders is onder invloed van de werking van tijd. We zagen dat het dichtzitten van de endoprothese poot door trombus vorming relatief hoog was in 1 van onze Anaconda™ studies. In de tijd lijkt de uitbocht van de poot van de endoprothese met name aan de rechter iliacale zijde toe te nemen, de zijde die ook gebruikt wordt voor het inbrengen van de endoprothese. De flexibele Anaconda™ poot ontwerp heeft de vorm van een stofzuigerbuis maar het nadeel van de hoge flexibiliteit is het optreden van het zogenaamde "Concertina effect" wat kan resulteren in verstoringen van het doorstromingsprofiel in de poot<sup>12</sup>. Aanvullend onderzoek kan mogelijk aanwijzingen geven hoe het doorstromingsprofiel van de poot verder verbeterd kan worden zonder de flexibiliteit van de poot hiervoor op te geven

Met gebruik van contrast-versterkende echo deeltjes gedurende de follow-up kan de karakteristieke real-time doorstromingsprofielen in de iliacale anatomie gecontroleerd worden met als doel eerder voorspellen en voorkomen van mogelijk aorta-iliacale poot occlusie in de aankomende follow-up periode<sup>13</sup>.

Het combineren van de kennis en ervaring van vaatchirurgen, interventie radiologen en technisch geneeskundige gezamenlijk in een vasculair team zal de gouden standaard moeten zijn in de klinische en wetenschappelijke vaatprogramma's.

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**Steffan**



## Curriculum Vitae

Steffan Gerhardus Johannes Rödel was born on juli 14th 1972 in Doetinchem, The Netherlands. He grew up in Doetinchem with his parents Sep and Irma and his older brother Hans. He studied at the Gemeentelijke scholen Gemeenschap Doetinchem were he graduated the VWO in 1990.

That year he started his study Medicine at the Rijks University of Groningen. In 1993 he started his second study Mechanical Engineering at the Twente University following the path of his brother Hans. The first year was conducted in the affiliation of Leeuwarden so Steffan could follow classes in Groningen and Leeuwarden. In 1995 he moved to Enschede to complete the technical study and to start his co-schappen in the Medical Spectrum Twente Hospital in Enschede. In 1999 he finished Medical School to become a medical doctor.

Steffan started his working career in the Euregio project "knee surgery" in which he conducted research in knee laser surgery and knee ligament reconstruction under supervision of Prof. Dr. P.A.M. Vierhout and Dr B. Lo.

On saturday 13 May 2000 the city of Enschede was struck by the explosion of a firework depot. Due to this disaster the focus of his work shifted to the research related to this disaster. Results were published in the ministrial report commissie Oosting and in the NTVG.

On july 13th 2001 he finished his Mechanical Engineering study to become Ingenieur.

He started his surgical training in Enschede from 2001-2005 under supervision of Prof. Dr P.A.M. Vierhout and Dr W.J.B. Mastboom and finished his recidency in Groningen in 2007 under supervision of Prof. Dr H.J. ten Duis. He went back to Enschede as a surgeon for his fellowship lungurgery under supervision of Dr H.J. Mulder.

In 2009 he started as a chef the clinic in the Martini Hospital Groningen in which he became a senior consultant in 2011. Nowedays he holds a registration in lung surgery, trauma surgery and surgical oncology.

Steffan is married to Mariëtte.

