CHAPTER 1

General Introduction
ABDOMINAL AORTIC ANEURYSM (AAA)

An abdominal aortic aneurysm (AAA) is a localized dilatation of the native aorta with an increase of its diameter with more than 50%.\textsuperscript{1} Approximately 80% of all aortic aneurysms occur between the renal arteries and the aortic bifurcation.\textsuperscript{2} The prevalence of AAAs is about 4% to 9% in men and 1% in women.\textsuperscript{3–6} Known risk factors are: smoking, male sex, age, white race, 1st degree family history of AAA and the presence of occlusive arterial disease.\textsuperscript{7}

Most AAAs are asymptomatic and are often diagnosed coincidentally on imaging studies. Despite the often asymptomatic presence of most AAAs, the rupture of an AAA is associated with high mortality rates.\textsuperscript{8} Therefore, prophylactic repair with insertion of a prosthetic graft is offered. As the size of the aneurysm increases, so does the risk of rupture. This risk of aneurysm rupture is not only related to the size of the AAA, but also to the expansion rate of the aneurysm and the gender of the patient.\textsuperscript{9} As in all surgical interventions, the benefit of the procedure has to be weighed against its harm. The risk of aneurysm rupture therefore has to be balanced against the risk of operation. Aneurysm repair should only be undertaken when the risk of rupture is considered high. Current guidelines recommend repair if an AAA has a diameter > 5.5 cm with men and > 5.0 cm with females.\textsuperscript{10}

HISTORY OF ANEURYSM TREATMENT:
SUCCESSFUL & UNSUCCESSFUL CONCEPTS

For many years there was no adequate treatment for an AAA. As the aneurysm often developed asymptptomatically and the patient was not aware of its presence, a rupture would come as a surprise and have often fatal consequences. From the 2nd century AD, proximal ligation of aneurysms in peripheral arteries was attempted, however abdominal arteries remained untreated.\textsuperscript{11} As ligation of the aorta did not seem successful, attempts to treat abdominal aneurysms consisted of trying to enhance the aneurysm wall by introducing thrombosis and fibrosis. In 1864 Moore, a British surgeon was the first to describe a procedure whereby metal wires (e.g. silver, iron, steel, copper-wire) were introduced in an effort to thrombose the aneurysm sac and thereby strengthening the wall.\textsuperscript{11} In an attempt to induce further coagulation, Alfonso Corradi in 1879, attached the metal wires to a battery.\textsuperscript{11, 12} This treatment principle was still used until up to 1968, whereby during the years the battery was removed and intra-operatively 100 volt of direct current was applied to the wires.\textsuperscript{13} In reports of this treatment concept, it was reported that wires with a length up to 700 ft (equals 213 meter) and a diameter of 32 gauge (equals 0.2mm) were inserted into the aneurysms.\textsuperscript{14}
Meanwhile in 1888, Matas had developed treatment of aneurysms by the means of aneurysmorrhaphy. With this treatment concept, the aneurysm sac was opened, the sac-content removed and the arterial orifices of the sac were sutured, thereby excluding the aneurysm sac from the circulation. Additionally, the wall of the aneurysm was sutured together to strengthen the aneurysmal wall and creating a normal size tubular conduit. This treatment concept was mainly exerted on peripheral arteries and not often on abdominal aneurysms.\textsuperscript{15}

In 1943 Paul Harrison introduced the concept of wrapping an aneurysm with cellophane, thereby inducing fibrosis and wall thickening. In this initial report, it was successfully performed on a subclavian aneurysm\textsuperscript{16}, but in 1948 it was as well performed on intra-thoracic and -abdominal aneurysms.\textsuperscript{17} On March 29 1951, Charles Dubost created a revolution in the treatment of an AAA by resecting the dilated native aorta and replacing it by a human homograft.\textsuperscript{18} This treatment concept was embraced by many physicians worldwide, and was introduced in the Netherlands by Maarten Vink in 1958 in the academic hospital of Leiden.\textsuperscript{19, 20} As, for obvious reasons, homografts were scarce, physicians soon searched for alternative materials. In 1954, artificial grafts made of Dacron were introduced by Michael DeBakey, resulting in the type of grafts which are still used nowadays.\textsuperscript{21} The last addition to the treatment concept was done in 1966, leading to the current standard of “Open Aneurysm Repair”. As the resection of the dilated aorta often gave may intra-operative difficulties, Oscar Creech decided not to remove the aneurysm sac, but left the sac in-situ and placed the graft in the sac and closed the sac afterwards, quite similar to the aneurysmorrhaphy.\textsuperscript{22}

The open repair, as described above, remained the golden standard of aneurysm treatment for many years. The next step in the evolution of aneurysm treatment took place in 1991 as the first endovascular grafts were placed transluminal in human aneurysms by Volodos in Russia\textsuperscript{23, 24} and by Parodi in Argentina.\textsuperscript{25} The concept consists of a minimally invasive procedure, which can be performed under regional or local anaesthesia and involves the deployment of a stent graft within the aneurysm sac, usually via the common femoral arteries. The stent graft is made of either polyester or polytetrafluoroethylene, attached to a metal stent. The metal stent provides both radial and longitudinal support, with the aneurysm being excluded from the circulation by the graft material. Nowadays, many different designs of grafts are available for the treatment of abdominal, juxta-renal and even thoracic aortic aneurysms, all with their own strong points. This treatment concept is now known as “endovascular aneurysm repair” (EVAR), and has proven itself to be a successful, minimal invasive, treatment modality for aortic aneurysms. In the last decade, there is much discussion if open repair or endovascular repair should be considered the golden standard for AAA treatment.\textsuperscript{26, 27}
Introduction

OPEN VERSUS EVAR: WHAT IS CONSIDERED THE BEST TREATMENT?

Since the introduction of EVAR, many physicians have been seduced by its enormous appeal. Understandably, the option of excluding a large aneurysm through two small incisions in the groin instead of through a large laparotomy is very compelling. To be able to compare the two treatment modalities, randomized controlled trials were conducted comparing the outcome of EVAR and open repair in patients eligible for both treatment concepts. The DREAM trial showed a significant advantage in the combined rate of peri-operative mortality and severe complications for EVAR (4.7%) compared to open repair (9.8%). However, this advantage disappeared after two years. Recently published, long term results from the same trial showed that 30% of the EVAR patients, compared to 19% in the open repair group, had to undergo a secondary intervention during the 6 year follow-up.

In the EVAR1-trial, the peri-operative mortality was 2.3% for the EVAR group and 6.0% for the open group. The long term results show that 28% of the EVAR patients and 10% of the open repair patients had undergone a secondary intervention in the 8 year follow-up period.

Both trials show a peri-operative advantage for EVAR, which disappears in the two years after the procedure and develops in a disadvantage as more secondary interventions are needed. The secondary interventions result in higher procedure related costs for the EVAR group, which makes open repair more cost-effective. However some of the open surgery related complications (e.g. renal failure) and its consequences, were not included in the calculations.

These results plea against EVAR as a superior technique when compared to the well-established open aneurysm repair, although it should be noted clearly that the cases included in these studies were all treated with 1st or 2nd generation EVAR-grafts. During the last ten years, vascular surgeons have increased their experience with and their knowledge of the EVAR treatment. Much progress is made in defining criteria which patients will benefit from an EVAR-procedure. Furthermore, every year, new, enhanced, further evolved EVAR grafts become available, hopefully diminishing procedure or graft related complications and necessary secondary interventions.
THE SHORTCOMINGS OF EVAR

Although EVAR has shown great potential and is starting to replace open repair as the standard treatment for abdominal aortic aneurysms, it still has some serious shortcomings. These shortcomings can roughly be divided in three categories:

I Anatomy related exclusion criteria.

II Procedure related complications.

II Follow-up related complications/burdens.

I. Anatomy related exclusion criteria

For the EVAR procedure to be a success, the surgeon is highly dependable of the anatomy of the aneurysm. Nearly all manufacturers of the commercially available endovascular grafts state that to guarantee an adequate proximal seal and fixation of their graft, the neck of the aneurysm should be at least 15 mm long, should be free of wall thrombus, should be straight and not conical. Timaran et al have shown that in 27% of AAA’s the anatomy of the aneurysm makes it unsuitable for EVAR because of insufficient neck length, large neck diameter or severe angulation. The angulation between the aneurysm neck and the iliac arteries may not be too severe as it may lead to kinking and migration of the graft. Not only the proximal anatomy of an aneurysm may lead to exclusion of treatment, but the distal anatomy can give severe problems, as accessibility is highly dependable of the iliac anatomy. Most stent grafts need a minimal diameter of 14–22 Fr for access of the bulky delivery sheath, which makes many aneurysms with strong tortuosity or occlusive disease of the iliac arteries, ineligible for treatment. The (infra-) inguinal incisions can furthermore cause seroma, haematoma or wound infection, adding morbidity to the procedure.

II. Procedure related complications

During the last twenty years of EVAR treatment it has become clear that the treatment concept is one which may come with complications. The most important complications remain the presence of endoleaks type I-IV and endotension. Type I endoleak consists of blood flow into the aneurysm sac due to incomplete seal or ineffective seal at the end of the graft. This type of endoleak usually occurs in the early course of treatment, but may also occur later. With type II endoleak blood flows into the aneurysm sac due to opposing blood flow from collateral vessels. With type III endoleak blood flows into the aneurysm sac due to inadequate or ineffective sealing of overlapping graft joints or rupture of the graft fabric. Type IV endoleaks consist of blood flow into the aneurysm sac due to the porosity of the graft fabric, causing blood to pass through from the graft and into the aneurysm sac.
The significance of type II endoleaks remains highly discussed, however most vascular specialists agree that type I, III and IV can give severe complications such as sac rupture and almost always need re-intervention.\textsuperscript{41–44} Stent-migration and endoleaks cause high re-intervention-rates of up to 30 percent in the first year after deployment of the endografts.\textsuperscript{28, 45} Endotension (increased pressure in the excluded aneurysm sac without visible endoleak) remains a difficult complication to diagnose and treat.

Besides the hazards of endoleaks, other procedure-related complications may occur: the renal arteries can easily be unintentionally over-stented with an EVAR procedure, leading to renal ischemia; difficult manoeuvring due to hostile accessibility may lead to iliac dissection; iliac occlusions and false aneurysms in the groin after femoral access do occur. On longer term, stent graft iliac limb thrombosis or stenosis and subsequent iliac aneurysm formation may also occur.\textsuperscript{46}

III. Follow-up related complications

As complications (such as endoleaks, etc) may occur during follow-up, patients treated with EVAR, are intensively followed in the years following the procedure.\textsuperscript{10} During follow-up, patients have to be seen very often, especially in the first year after graft placement. Although there is a tendency to replace much of the follow-up CT-scans by ultrasound check-ups, still many ct-scans are made during the follow-up. This follow-up regime results in patients undergoing a high exposure to radiation\textsuperscript{47–49} and having a high risk of developing contrast nephropathy due to the necessary intravascular contrast.\textsuperscript{50, 51} Besides the physical side-effects, the many follow up exams and -studies, give the patient uncertainty if their aneurysm is definitively treated.\textsuperscript{52}

Recently published studies have shown that patients, who were treated with EVAR, suffered more long term procedure related morbidity when compared to an open repair cohort, often resulting in secondary endovascular or open interventions.\textsuperscript{29, 30} The long-term morbidity, the intensive follow-up, and the remaining uncertainty lead to less quality of life of EVAR patients when compared to open patients.\textsuperscript{29, 52} Finally, as stated above, the strict follow-up combined with the secondary interventions lead to a significant higher costs, when compared to open repair.\textsuperscript{30}

CUSTOMIZED AORTIC REPAIR: A NEW TREATMENT CONCEPT

As stated in the above paragraph, EVAR has some shortcomings, especially in its anatomic limitations. To overcome these disadvantages a treatment concept named “Customized Aortic Repair” (CAR) was devised by vascular surgeons Alexander de Vries and Hans Brom\textsuperscript{53}: a method of excluding the aortic aneurysm using endovascular techniques by injecting a biocompatible elastomer into the aneurysm sac (Fig. 1.1). The
non-polymerised liquid elastomeric solution is used to fill the aneurysm sac around a balloon-catheter. The thereby created endoluminal mould excludes the aneurysm sac after the in situ polymerisation. After balloon deflation a compliant elastomer cuff with a patent lumen is created. This treatment concept was originally known as “Aortic Customize”, however recently the developers have decided to change the name to “Customized Aortic Repair (CAR)”. Throughout this thesis, the original name will be used in the chapters, as this name was used in the publications in the several journals. Future publications will use the title “CAR”.

Filling the aneurysm sac with an injectable biocompatible elastomer can realize a reduction in the wall stress and thereby a reduction in rupture risk, since aneurysm rupture occurs when the local wall stress exceeds the local wall strength.\textsuperscript{54, 55}

This treatment concept can function as a standalone treatment, but might also play a role as an adjuvant procedure to the current EVAR treatment (Fig 1.1). The elastomer
can be injected next to the inserted EVAR graft and will cure around the graft, taking on its form. The support of the elastomer could prevent dislocation and migration of the graft. With this technology, aortic aneurysms with less favorable proximal neck anatomy could be made suitable for EVAR.

THE ELASTOMER, POLYDIMETHYLSILOXANE (PDMS)

For the technique to succeed, a material was needed with specific chemical and mechanical properties. The material had to be non-toxic and cross-link isothermically in the presence of blood, without the release of toxic by-products. To be able to inject it through a 7 Fr catheter, the viscosity in the non-crosslinked form had to be low. The curing-time should be sufficiently long (5–10 min) to be able to complete the injection-process before the material becomes too viscous. When cured, it should be non-thrombogenic and the strength and durability had to be sufficient to withstand the pressure in the aorta, relieving the stresses from the native, dilated vessel wall.

Silicone-based elastomers meet the requirements of blood compatibility and have been successfully used intra-vascular by others.56–61

The elastomer was developed by the Technical University of Delft, the Netherlands (Prof. van Turnhout MSc PhD, van den Berg MSc PhD and Alili MSc) on assignment of CAR. After elaborate testing, one formulation was selected, which fulfilled all the criteria.53 The formulation consists of a two component room temperature addition-cure liquid silicone formulation, obtained from Viazym BV [ViaZym BV; Delft, The Netherlands]:

- A platinum containing Vinyl terminated polydimethylsiloxane (PDMS) with an optimized molecular weight with regard to viscosity versus mechanical properties of the cured end-product (elongation to break, modulus). This component further contains surface-treated amorphous silica and a sesquisiloxane-like material known as Vinyl Q, which is known to increase tear-strength of the final cured elastomer without much increase in viscosity
- A methylhydro-dimethyl-siloxane copolymer containing vinyl terminated polydimethylsiloxane (PDMS). This component further contains surface-treated amorphous silica and Vinyl Q.

Viscosity of the compound allowed infusion-rates of up to 2 ml per second using a standard angiographic pump with an injection-pressure of 1200 pounds per square inch.53

The substance has an average polymerisation time of approximately 5 minutes. After curing, the material had a yield-stress of approximately 400 kiloPascal (kPa), failing at more than 20% elongation. The density of the cured elastomer is 1.0167 g/cm3.53
A cast of the material with the added crosslinker and filler has been subjected to fatigue tests at 21 cycles per second with stresses comparable to the stresses in the human aorta. No signs of material failure or tear have been observed after one month, which is comparable to an exposure of 18 years in a circulation with a mean frequency of 70 beats per minute.\textsuperscript{53}

**POTENTIAL BENEFITS OF THE TREATMENT CONCEPT**

In theory, any AAA with a deviant anatomy will become endovascular treatable with elastomer sac-filling, when endovascular balloons will be available in different kinds of form and configuration. With current EVAR-techniques, severe angulations may lead to kinking of the graft material and eventually to migration of the graft.\textsuperscript{35–37} As no graft material is used, these problems are not likely to occur with CAR. The fluidity of the non-polymerized elastomer inherently causes adjustment to the geometry of the aneurysm, not only by filling the large aneurysm sac but also by diffusing into all wall irregularities and side branches. The elastomer mould will fixate itself as it customizes itself to the form of the AAA sac.

Another important exclusion criterion for the current EVAR therapy is strong tortuosity or occlusive disease of the iliac arteries. As stated above, a minimal diameter of 14–22 Fr is often needed for access of the bulky and rigid delivery sheath. To fill the sac with the biocompatible elastomer a fill catheter with diameter of minimal 7 Fr needs to be introduced transfemorally to the aneurysm sac.

Beside the stand-alone treatment concept, the elastomer and injection-technique are more broadly applicable. The elastomer can already be used as an adjuvant with current stent-grafts when problems of endoleak or migration occur as depicted in Fig. 1.1. In these cases the elastomer can be used to fill-up the aneurysm-sac and secure the endovascular stentgraft.\textsuperscript{62}

The major complication of EVAR is endoleak after the placement of the EVAR graft. Type I endoleaks may still occur at the junction-sites of the elastomer mould and the native vessel-wall. However, addition of conventional stents might still be an option. We expect that the mould-grafting technique is free of type II endoleaks (branch-vessel leakage) because, like the aneurysm sac, branch-vessels will be occluded by the elastomer. Type III endoleaks are not likely to occur as the mould is cast in one piece and there is no graft material in which tears can occur. As the material is non-porous, type IV endoleaks are also not likely to occur.
POTENTIAL LIMITATIONS OF THE TECHNIQUE

Besides the potential occurrence of endoleak type I, the treatment option might have other shortcomings. It is not desirable to have leakage of the fluid elastomer (before the cross-linking) to the peripheral vessels (e.g. renal arteries), as this might act as an arterial embolus. However, the high viscosity ensures a safe delivery of the elastomer in the aneurysm sac and prevents leakage of the elastomer. As the contrast substance has a lower viscosity than the elastomer, it will be pushed out of the sac before the elastomer will. When all contrast is pushed out of the sac, it is filled with elastomer. Furthermore the amount of elastomer which has to be used can be calculated from pre-operative CT-volume measurements, thereby preventing potential “overfilling” of the sac, which may lead to extensive leakage.

Another theoretical disadvantage is that during the filling of the sac, the pressure may increase in such a way, that the AAA sac is at risk of rupture. If indeed such a rupture does occur, it may directly be sealed by the curing elastomer, however that remains speculation.

Every foreign material inserted in the human body may be toxic or may induce allergic reactions. Although PDMS has proven to be non-toxic, and is renown for its biocompatible properties, this was always when inserted in solid state. With CAR, the elastomer is inserted in liquid state and cures within the body. It’s potential effect on the human body is currently unknown as it has not been tested in-vivo. However, as the material cross-links isothermically in the presence of blood, without the release of toxic by-products, no major problems are expected with regard to biocompatibility.

OUTLINE OF THE THESIS

In Chapter 2 the effect of stent-graft compliance on aneurysm sac pressure and potential endotension will be discussed. Aim of the study was to see if with more compliant (stented or stentless) grafts, there was more pressure transmission from the graft into the excluded aneurysm sac, the so-called “diaphragm-effect”.

It is believed that the presence of intraluminal thrombus may diminish wall-movement and wall stress the “cushioning effect.” The hypothesis is that the stiffness of the thrombus and the wall influence the amount of wall stress. In a validated circulation model, the effect of aneurysm wall-thickness and the presence of intraluminal thrombus on the wall-movement of an aneurysm were investigated and the results are reported on in Chapter 3.

General aim of this thesis was to see if the concept of CAR is feasible. In the same circulation model as in Chapter 3, the new treatment concept was investigated in
**Chapter 4.** Aim of the study was to see if injecting the aneurysm sac with the elastomer would lead to diminishment of wall stress. As migration of endografts is an important shortcoming of the current EVAR-technique, the proximal fixation strengths of current available EVAR-grafts were investigated in an in-vitro tensile-tension set-up in **Chapter 5.** The hypothesis of the study was that a proximal seal of less than 15mm would lead to an insufficient proximal fixation. As fixation of the graft is dependable of the friction between graft wall and aneurysm wall\textsuperscript{69,70}, we believed that filling the area between the aneurysm wall and the outside of the graft with elastomer would improve the fixation strength of the grafts. The same model as in **Chapter 5** was used and the results of the experiment are discussed in **Chapter 6.** As an aneurysm sac may be filled through a small profile catheter from a distance, endoleaks should theoretically be treatable with it as well. **Chapter 7** focuses on the potential of the elastomer as a treatment modality for endoleaks type II-IV, which was investigated in the earlier mentioned circulation model. As PDMS in its original formulation is renowned for its biocompability and low thrombogenicity\textsuperscript{57–62}, it was selected as substance for sac-filling. In **Chapter 8**, the thrombogenicity of the current elastomer is investigated in an validated ex-vivo model\textsuperscript{71} and it is compared to the current golden standard, expanded polytetrafluoroethylene (ePTFE). One of the essential steps to clinical applicability are successful in-vivo experiments. The results of preliminary in-vivo porcine experiments with the new treatment concept are described in **Chapter 9.** The summary and the general discussion of this thesis can be found in **Chapter 10**, while the summary and discussion in Dutch are included in **Chapter 11.** Finally, **Chapter 12** consists of the acknowledgements, list of publications and the writer’s curriculum vitae.
REFERENCE LIST


