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General Introduction and Outline of the Thesis
INTRODUCTION

Abdominal aortic aneurysm

An abdominal aortic aneurysm (AAA) is defined as a 50% increase in aortic diameter compared with the healthy native aortic diameter or an absolute diameter larger than 3 cm.¹ The prevalence of AAA is estimated to be up to 14.2% in men and 6.2% in women, and risk factors include advanced age, male sex, family history, smoking, diabetes mellitus, atherosclerosis, and hypertension.¹⁻⁵ Three main processes are involved in the process of dilatation, which are inflammation, upregulation of proteolytic pathways, and smooth muscle cell apoptosis. Inflammation is associated with the production of reactive oxygen species and oxidative stress, which induces vascular smooth muscle apoptosis and promotes the proteolytic pathway that results in degradation of extracellular matrix proteins in the aortic wall. This, in turn, decreases the elastin concentration and increases the production of disordered collagen, thereby further weakening the aortic wall. Over time, the combination of elastin degradation and continuous hemodynamic load results in dilatation of the aortic wall.¹⁻⁴ Atherosclerosis can develop as a consequence of the changes in luminal flow, which can result in chronic inflammation and may accelerate the breakdown of collagen and elastin.¹⁶

Aneurysms are known to continue to grow over time. This increases the risk of rupture, which has a reported mortality rate of up to 85%.¹⁻⁷ Growth rates of 0.2 to 0.3 cm/year have been reported for AAAs between 3 cm and 5.5 cm, but larger aneurysms tend to expand faster compared with smaller aneurysms.³⁻⁸ Risk of rupture is sex-dependent, and despite the higher prevalence of AAA in men, the rupture rate is higher in women.⁵⁻⁸ Elective treatment for AAA is indicated when the risk of rupture is larger than the risk of the intervention. The 2018 Society for Vascular Surgery guidelines recommend elective repair for patients at low or acceptable surgical risk with aneurysms of >5.5 cm for men and >5 cm for women. AAAs with a growth rate of more than 1 cm/year should be repaired at a smaller diameter.³⁻⁸ In case of a high operative risk, the AAA diameter threshold of when to treat may be diameters between 6 cm and 7 cm. The decision whether to intervene is not only dependent on aneurysm size and risk of rupture, but comorbidities, physical status, and life expectancy should also be taken into account.⁸ Thus, the treatment strategy should be defined for each individual patient and aortic anatomy.

Treatment of AAAs

Treatment options for AAA are open surgery or endovascular repair. Open surgical repair has been practiced since its first description in 1952 and has been refined ever since.⁹ The procedure requires laparotomy, clamping of the aorta, aortotomy to
remove thrombus and debris from within, and subsequently, insertion of a prosthetic graft. Even in patients fit for surgery, there is a significant risk of complications: reported mortality was up to 4.2% and postoperative complications occurred in up to 13%.\textsuperscript{10,11}

Volodos et al.\textsuperscript{12} first described the endovascular aneurysm repair (EVAR) technique in 1986 as an alternative treatment approach for AAAs. During EVAR, arterial access is achieved through the common femoral arteries. An introduction sheath allows insertion of guidewires, over which catheters and the endograft's main body and limbs can be advanced.\textsuperscript{13,14} The main body needs an oversizing of 15% to 20% compared with the diameter of the infrarenal neck to create a radial force that provides fixation and withstands drag forces.\textsuperscript{15} In addition, hooks, barbs, and/or suprarenal bare-metal stents are incorporated to enhance fixation.

For infrarenal AAAs, the self-expandable endograft is positioned just below the lowest (most distal) renal artery orifice in the infrarenal aortic neck. The contralateral iliac limb is inserted after main body deployment, and if adequate proximal and distal seal is achieved, the aneurysm will be successfully excluded from the blood flow.\textsuperscript{14,16}

Approximately 30% of patients have AAAs with unsuitable proximal neck anatomy for a standard EVAR procedure. Hostile aortic neck anatomy includes short neck length (<10-15 mm), large aortic neck diameter (>30 mm), large infrarenal angulation (>60°), reversed taper, and/or large thrombus or calcium load. This may hamper the sealing and fixation of the endograft within the aortic neck.\textsuperscript{8,17–22} To circumvent these problems and to treat juxtarenal and suprarenal aneurysms, fenestrated, branched, or chimney EVAR procedures (F/B/ch-EVAR) can be performed. These procedures are generally more complex, because additional stents are deployed to maintain the blood flow to the renal and/or visceral arteries.\textsuperscript{22,23}

Compared with open repair, EVAR significantly reduces short-term cardiac and pulmonary complications and demonstrates lower early morbidity and mortality rates.\textsuperscript{8,24} This latter is especially beneficial in patients with high surgical risk. EVAR is also associated with shorter procedure and recovery times, reduced hospital and intensive care unit lengths of stay, and reduced blood loss.\textsuperscript{8,10,25} Reports on renal complications vary in literature, but appear to be dependent on follow-up duration.\textsuperscript{26} Acute renal insufficiency has shown lower incidences after EVAR (2%-19%) compared with open repair (11%-27%).\textsuperscript{27,28} At 3 years’ follow-up, however, increased renal impairment has been observed after EVAR (between 25% and 36%) than after open repair (up to 19%).\textsuperscript{27–30} The steady decline in renal function after EVAR can be attributed to the high contrast volumes required for continued postoperative computed tomography (CT) angiography (CTA) surveillance.\textsuperscript{31} Nevertheless, the rates of renal failure requiring dialysis are comparable to open repair procedures, ranging between 0.5% and 2%.\textsuperscript{28,32} On long-term follow-up, open aneurysm repair procedures demonstrate
higher freedom from reinterventions, largely because of the number of graft-related complications with EVAR.\textsuperscript{11,33,34} Whether EVAR is more cost-effective than open surgical repair remains unclear because of the many factors involved, including the preoperative imaging, implants, hospitalization duration, treatment of complications at the time of the initial procedure or during follow-up, and long-term imaging follow-up.\textsuperscript{8} Currently, EVAR is the preferred treatment strategy, largely due to its minimally invasive character and lower morbidity and postoperative mortality in young patients with low operative risk. However, FEVAR or open surgical repair should be performed in patients with unfit anatomy for standard EVAR.

**Role of imaging in EVAR**

**Preoperative assessment**

CTA is routinely performed during the preprocedural workup to visualize the aortoiliac trajectory. The protocol typically includes a multiphase acquisition: a noncontrast, arterial, and/or delayed-phase examination. The noncontrast CT acquisition is useful in differentiating calcifications. For the arterial phase, iodinated contrast medium is administered intravenously, and the acquisition is performed using bolus triggering. Ideally, slices are reconstructed to 1.0 mm to 1.5 mm. Delayed images can be acquired approximately 2 minutes after the contrast injection and are useful to assess slow endoleaks.\textsuperscript{35} Drawbacks of CTA are the use of radiation and iodinated contrast material that may induce nephrotoxicity.\textsuperscript{28} Contrast-enhanced magnetic resonance angiography (MRA) can be performed in patients who cannot receive iodinated contrast. MRA does not use radiation, but is more time consuming and expensive than CTA and is also not suitable for patients with metal implants.\textsuperscript{23,36} Even though both imaging techniques can be used for preoperative EVAR planning, CTA is considered the gold standard and the preferred imaging modality because it is readily available and fast.

**Intraoperative guidance**

Endovascular procedures are performed under fluoroscopy guidance and rely on the use of iodinated contrast media and ionizing radiation. By use of digital subtraction angiographies (DSAs) the location of the origins of the renal and internal iliac arteries can be visualized. DSAs can also visualize possible complications after endograft deployment.\textsuperscript{37,38} Because of the potentially nephrotoxic effects of iodinated contrast and carcinogenic factors of radiation, it is highly relevant to reduce the number of imaging series. Patients with pre-existing renal impairment are especially at greater risk for renal complications during follow-up.\textsuperscript{27,28} Moreover, reducing radiation
exposure and procedure time may be beneficial to both patients and specialists. The number of imaging series used greatly depends on the procedure complexity: more complex procedures proportionally increase the amount of administered contrast, radiation dose, and procedure time; for example, the radiation doses for complex EVAR procedures can be twice those of standard EVAR procedures.

Preprocedural imaging holds valuable information that is used for planning the procedures and sizing the endografts but can also be used during the endovascular interventions. New available three-dimensional (3D) image guidance tools allow for intraoperative use of preoperative CTA for continuous fusion guidance during these interventions. After rigid registration of preoperative imaging to an intraoperatively acquired cone-beam CT scan, the CTA images are overlaid on live fluoroscopy. Dijkstra et al. were the first to report the use of this 3D image fusion technique in patients undergoing FEVAR. The technique demonstrated reduction in contrast and radiation dose for EVAR and more complex EVAR procedures such as branched or fenestrated thoracic aortic aneurysm repair. Introduction of stiff guidewires and delivery systems during EVAR may influence the accuracy of the fusion images caused by deformation of iliac arteries. To fully rely on the use of the 3D image fusion technique and minimize contrast and fluoroscopy use, accurate registration of the images is of utmost importance.

Postoperative EVAR surveillance and complications

Despite the improvements in endograft fixation (e.g., suprarenal fixation and anchoring hooks and pins), complications still occur in the long-term after EVAR. Follow-up imaging is therefore necessary to assess for late complications. Imaging is routinely performed by CTA at 1 and 12 months postoperatively, and in case of no complications, annual duplex ultrasound imaging is used thereafter. Some complications are similar to those observed after open repair procedures, such as graft infection, aortoenteric fistulas, graft occlusion, or thrombosis. Other complications are more EVAR specific and include the occurrence of endoleaks (i.e., persistent blood flow into the aneurysm sac) and migration of the implanted device.

Type I endoleaks occur due to incomplete sealing at the proximal (type IA) or distal (type IB) landing zones. Type II endoleaks arise from branch vessels that feed the aneurysm sac through retrograde flow, which can lead to sac enlargement. Type III endoleaks are usually structural failures (holes or defects) or separations of the endograft components. Type IV endoleaks represent porous endograft material that will spontaneously seal, and treatment is not required. Finally, type V endoleaks (or endotension) are described as an enlarging aneurysm sac without visible endoleak. Repair of type I and III endoleaks is advised when detected, because they can lead
to repressurization of the aneurysm, sac expansion, and ultimately, rupture.\textsuperscript{16,24,47–51}

The management of type II endoleaks continues to be debated: treatment is generally recommended for leaks with sac expansion of >1 cm, whereas surveillance suffices when no sac enlargement is observed. Endotension management should be individualized to the patient and can entail surveillance, relining of the endograft, or explantation.\textsuperscript{8}

Migration is defined as endograft displacement by more than 5 to 10 mm, which is often caused by dilatation of the aortic neck.\textsuperscript{16} If left untreated, migration may lead to late type I endoleaks and an increased risk of rupture.\textsuperscript{16,24,47–51} Secondary interventions after EVAR, which have been reported to have a rate as high as 20%, are ideally performed endovascularly.\textsuperscript{52–54}

**Proximal neck–related complications**

Reinterventions for type IA endoleaks and migration are required in up to 3.0% and 5.1% of the patients, respectively.\textsuperscript{34,55–58} A significantly higher occurrence of type IA endoleaks is observed in patients with hostile proximal neck anatomy.\textsuperscript{19} Initial treatment for type IA endoleaks is balloon angioplasty to remodel the proximal part of the endograft and promote apposition. In case of undersized, maldeployed, or migrated endografts, covered extension cuffs can be deployed to overcome the seal failures and create a new seal length of at least 15 mm. If this can only be achieved by extension superior to the renal arteries, FEVAR cuffs are the preferred treatment option to maintain renal blood flow. The Heli-FX EndoAnchor system (Medtronic Vascular, Santa Rosa, CA, USA) can also be used to prevent further migration of the endograft or treat type IA endoleaks by attaching the endograft to the aortic wall. Alternatively, coil or Onyx (ev3, Irvine, CA, USA) embolization can be performed to treat an endoleak. These can be useful in case of short infrarenal necks or when the aforementioned techniques are insufficient in treating the complication, and patients are not good candidates for open conversion. Lastly, when FEVAR cuffs cannot be deployed and there are no other endovascular options, bare-metal stents (e.g., Palmaz stents [Cordis Corporation, a Cardinal Health company, Milpitas, CA, USA] or AndraStent [Andramed, Reutlingen, Germany]) can be deployed to achieve adequate seal.\textsuperscript{20,59}

**EndoAnchors**

EndoAnchors are developed to improve seal and increase the migration resistance of endografts in the aortic neck. They can be used prophylactically to enhance proximal fixation and seal\textsuperscript{60–62} but are also commonly deployed in a therapeutic setting to resolve type IA endoleaks and to prevent further endograft migration.\textsuperscript{63,64} Four or six EndoAnchors should be circumferentially deployed, depending on aortic
neck diameter (≤29 mm or >29 mm), in which case the migration resistance can approximate that of a surgical hand-sewn anastomosis. Current reports on the use of EndoAnchors mainly come from the Aneurysm Treatment Using the Heli-FX Aortic Securement System Global Registry (ANCHOR; NCT01534819) that assesses worldwide use of EndoAnchors in patients with unfavorable aortic neck anatomy. The registry consists of a primary (prophylactic and therapeutic treatment for acute type IA endoleaks) and revision arm (therapeutic treatment for type IA endoleaks and/or migration during follow-up). Results demonstrated high technical success rates in the treatment of acute and late type IA endoleaks. In addition, prophylactic use of EndoAnchors resulted in a significant sac regression 2 years after EVAR compared with standard EVAR without EndoAnchors.

To achieve fixation and resolve type IA endoleaks, EndoAnchors should be circumferentially and successfully deployed into the aortic wall (i.e., penetration of at least 2 mm). At 1-year follow-up of the ANCHOR study, 4% to 8% of patients demonstrated persistent or renewed type IA endoleaks. Reasons for type IA endoleak after EndoAnchor treatment need to be investigated to improve outcomes after the EndoAnchor implantation procedure. Individual analysis of EndoAnchor penetration depths, angles, and circumferential distribution will give insight in the association between EndoAnchor implantation and successful treatment of type IA endoleaks.

Even though circumferential distribution is recommended, EndoAnchors are frequently used in a targeted manner when treating type IA endoleaks. The EndoAnchors are often only deployed in or near the endoleak and not along the entire circumference, whereas during prophylactic use, they are more frequently deployed circumferentially. The effect on migration resistance of other than circumferential distributions needs to be analyzed to understand the possible long-term consequences of these other configurations.

**Distal seal complications**

Even though less attention has been paid to the distal endograft fixation, sufficient distal seal is important to prevent distal complications. Type IB endoleaks can develop due to dilatation of the common iliac artery or lack of radial force of the endograft limb within the vessel, which may lead to endograft limb retraction. Reintervention for type IB endoleaks is required in up to 2.3% of post-EVAR patients. Endograft limb failure can be treated by a branched iliac device or hypogastric embolization and limb extension into the external iliac artery. Alternatively, an open reconstruction can be performed.

Because of the dynamic surroundings of the endograft, subtle changes in the
position of the endograft may take place before migration or endoleaks occur. Vascular Imaging Analysis (VIA) prototype software (Endovascular Diagnostics BV, Utrecht, The Netherlands) was developed to detect these subtle changes in the proximal neck. The VIA prototype software uses 3D coordinates acquired from CTA images to define infrarenal aortic neck characteristics and endograft position and apposition. By analyzing CT scans during follow-up and visualizing the position and apposition of the endograft, the occurrence of proximal neck-related complications can be predicted. This same software may be able to detect subtle changes in position and apposition of the endograft limbs, which can provide information to predict distal complications. In case of complications requiring treatment, these are preferably performed electively. Thus, early detection of changes in endograft limb position that may be indications for future complications is important to prevent the need for urgent reinterventions.

Open conversion
When further endovascular salvage procedures may be unsafe or unfeasible, open conversion has to be considered. Explantation of an endograft may be technically challenging, and the risk associated with these procedures is considerable. Mortality rates of 3% to 10% have been reported. The number of early and late complications after EVAR may increase, because physicians seem to be pushing the boundaries by treating more complex cases. Consequently, this may also increase the rate of late open conversion after EVAR. It is important to understand the risks associated with late open conversions in an elective and urgent setting to come to a patient-tailored decision on when to perform the conversion.

AIMS AND OUTLINE OF THE THESIS

This thesis is divided into two parts. The first presents and investigates whether new imaging modalities can help to prevent complications in the treatment of obstructive and aneurysmal aortoiliac disease, and the second part is focused on outcomes of EVAR in complex anatomies.

Part I offers insights on new imaging modalities to help prevent and detect complications during and after treatment of aortoiliac obstructions and aneurysms. The two objectives of the first part of this thesis are to

- investigate the potential and accuracy of fusion imaging during endovascular aortoiliac interventions for obstructive and aneurysmal disease, and
validate the VIA prototype software for the analysis of the position and apposition of endograft limbs during EVAR follow-up.

More complex EVAR procedures will demand an increase of radiation exposure and contrast use, and innovations in intraoperative imaging are being sought to minimize this. Chapters 2 and 3 report on the use of a 3D image fusion technique in endovascular procedures. For the fusion imaging to be fully incorporated in clinical practice, it is important to investigate its registration accuracy and understand the benefits of intraoperative use during endovascular procedures. Chapter 2 therefore investigates the registration accuracy of the use of this multimodal image fusion technique in endovascular obstructive iliac artery interventions and the effect of the insertion of stiff guidewires on fusion accuracy. Chapter 3 analyses the potential of the 3D image fusion technique in EVAR procedures to reduce the amount of contrast media used, radiation dose, procedure time, and fluoroscopy time.

Postprocedural imaging is regularly performed after EVAR to assess for complications; however, small positional changes in endograft limbs may be missed on regular CT scans. The VIA prototype software has demonstrated that it can accurately visualize and predict proximal neck–related complications. To prevent late distal seal complications, Chapter 4 validates the VIA software to determine endograft limb position and apposition in iliac arteries during follow-up after EVAR.

Part II is subdivided into two sections. The first section is specifically focused on the analyses of the position of individual EndoAnchors and subsequently investigates the effect of EndoAnchors on resolving type IA endoleaks and providing fixation and seal. The second section focuses on the outcomes of EVAR and late conversions after EVAR in patients with complex anatomies.

The objectives of Part IIa are to:

- demonstrate a novel method for analysis of aortic wall penetration and position of individual EndoAnchors and its effect on resolving type IA endoleaks, and
- investigate distribution patterns along the aortic neck circumference to improve EndoAnchor use in preventing endograft migration.

To treat or prevent type IA endoleaks and migration by use of EndoAnchors, successful circumferential deployment is recommended. Yet, complications still develop or persist after EndoAnchor use. The influence of anatomic characteristics on successful deployment of EndoAnchors needs to be reviewed to understand the occurrence
of proximal neck–related events. Therefore, Chapter 5 reports a novel method to quantify EndoAnchor penetration depths into the aortic wall. All EndoAnchors from a cohort of ANCHOR patients receiving therapeutic EndoAnchors for type IA endoleaks are investigated and classified into one of three categories: good, borderline, or no penetration. Predictors of successful EndoAnchor penetration are assessed, and the predictors for persistent type IA endoleaks after EndoAnchor use are established.

EndoAnchors should be deployed within the seal zone, and calcified regions or areas with thrombus >2 mm thickness should be avoided. Because penetration for nearly 47% of EndoAnchors was inadequate, Chapter 6 investigates EndoAnchor deployment beyond recommended use. EndoAnchor implantation above the endograft fabric or within gaps of >2 mm between the endograft and aortic wall (e.g., below the aortic neck, large endoleaks, or within thick thrombus) is defined as beyond recommended use. In addition, the individual EndoAnchor analyses of the previous study are expanded by assessment of deployment angles, distribution, and location along the circumference of the aortic neck. This will increase the understanding of endoleak persistence after EndoAnchor deployment.

A large variety in EndoAnchor distribution patterns along the aortic circumference was observed in the investigated ANCHOR cohort, even though a circumferential distribution is desired. An understanding of the consequence of these other distributions is important, because they may result in late complications. In Chapter 7, an experimental model is developed to investigate the effect of different EndoAnchor configurations on displacement resistance of the endograft. This study defines displacement of the proximal endograft when part of the endograft migrates by 3 mm and illustrates the importance of different EndoAnchor distributions on proximal fixation.

The objectives of Part IIb are to:

- discuss the long-term outcomes of EVAR with EndoAnchors, and
- review the outcomes of late open conversions after failed EVAR.

Current reports on the outcomes after EndoAnchor use are mainly from the multicenter ANCHOR database consisting of many different centers and user experiences. In addition, EndoAnchors can reduce gutter formation after ch-EVAR procedures, but outcomes after these procedures with the addition of EndoAnchors are limited. Therefore, Chapter 8 reports the midterm clinical outcomes of patients treated by (ch-)EVAR procedures with additional EndoAnchors in a single center. End points include the occurrence of type IA endoleaks, need for proximal neck–related reinterventions, and aneurysm–related mortality.
Late conversion can be considered when endovascular salvage procedures prove insufficient to treat complications after EVAR. **Chapter 9** provides a comprehensive systematic review of the literature investigating the 30-day mortality rates for urgent and elective late open conversions. The outcomes can be used to accurately inform the patients about the risk associated with late open conversion after primary EVAR. Finally, **Chapter 10** concludes this thesis with a summary, general discussion, and future perspectives.
REFERENCES


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PART I

Can New Imaging Modalities Help Prevent Complications in the Treatment of Aortoiliac Disease?