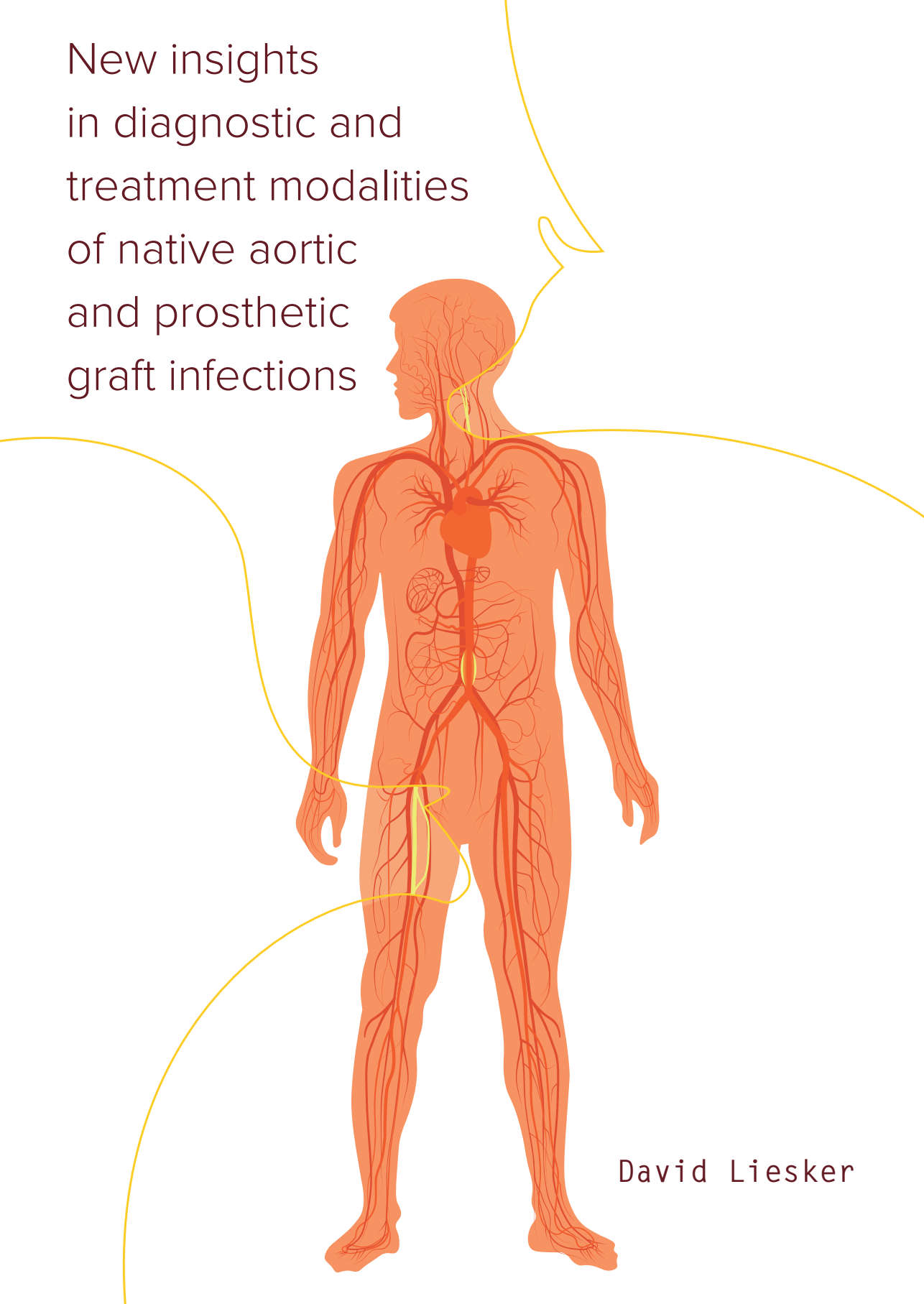
New insights in diagnostic and treatment modalities of native aortic and prosthetic graft infections



David Liesker

NEW INSIGHTS IN DIAGNOSTIC AND TREATMENT MODALITIES OF NATIVE AORTIC AND PROSTHETIC GRAFT INFECTIONS

David Jens Liesker

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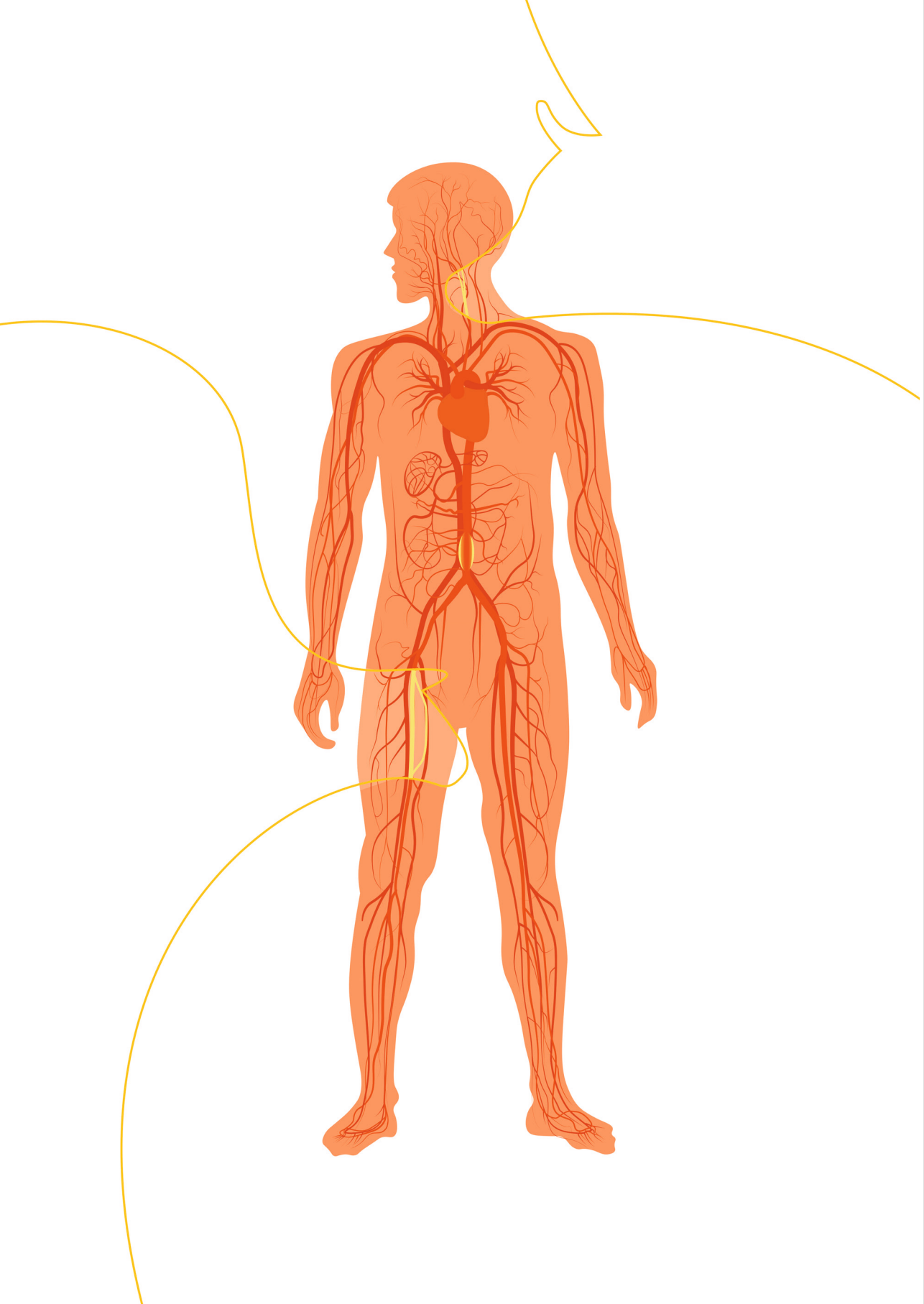


Chapter 1

General introduction

GENERAL INTRODUCTION

Over the past few decades, there have been significant advancements in the field of vascular surgery. For example, endovascular minimally invasive procedures have become increasingly popular due to their reduced morbidity and mortality rates and reduced recovery time compared to traditional open surgical approaches.[1,2] Despite these advancements, infection remains a major problem in vascular surgery, both in the form of native vascular wall infection and vascular graft and endograft infection (VGEI). Infection of a native vessel can occur in any blood vessel in the body, but is most commonly found in the aorta. When it is accompanied by an aneurysm it is called infective native aortic aneurysm (INAA).[3] VGEI occurs when bacteria or other microorganisms infect a vascular graft or endograft, while infection of the native artery occurs when the bacteria or other pathogens infect the patient's own blood vessels. In some cases and especially untreated, these infectious diseases can be life-threatening due to complications such as aneurysm formation or rupture. Further research is needed to better understand these infectious entities in vascular surgery.

Infective native aortic aneurysm

INAA, also known as mycotic aortic aneurysm (MAA), is defined as a dilatation of the aortic wall due to infection.[4] The first case description of this disease was published by Sir William Osler in 1885.[5] He used the term "mycotic aortic aneurysm" because he thought that the infected aneurysm, filled with pus, resembled a mushroom. The term mycotic however, is misleading, because most INAA are caused by bacteria rather than fungi.[6] A new, alternative term, INAA, was first described by Sörelius et al. in 2020. Two years later, a Delphi consensus was published with reporting standards on terminology, definition, classification, and diagnosis of INAA.[3,7] In Western countries, the incidence of INAA ranges from 0.6 to 2.6% in all people diagnosed with aortic aneurysms.[8] Histological studies showed inflammation of the vascular wall, infiltration of neutrophils, eventually leading to destruction of the intima and media.[4] Patients with an INAA usually have a symptomatic presentation. Symptoms range from localized symptoms, such as abdominal or back pain to systemic symptoms of infection, such as fever. The prognosis of the natural course of INAA is poor, because of its rapid expansion and therefore high risk of rupture. Although there are several studies on INAA, current literature is very heterogenous. Therefore, no clear guidelines are in place for diagnosis and treatment. Diagnosis of INAA is based on three aspects: 1. Clinical presentation (e.g. abdominal/back pain, fever, sepsis, and/or shock), 2. Laboratory findings (elevated C-reactive protein level and white blood cell count, positive blood- or tissue culture), 3. Computed tomography angiography (CTA) scanning findings (e.g. saccular/eccentric and/or multilobulated morphology, periaortic gas, periaortic inflammation, fat stranding, soft-tissue mass, lymphadenopathy, and rapid expansion).[9,10] In one out of three patients, the causative micro-organism is not cultured.[10] In these cases, broad spectrum empirical antibiotics that cover *Staphylococcus aureus* and gram negative rods

are prescribed. If a causative micro-organism is cultured, targeted antibiotics should be started. Recommendations regarding treatment of INAA are inconclusive. The European guidelines state that surgical techniques should be based on patient status, local and team experiences.[10] Open surgical treatment (including resection of the infected aneurysm, thorough debridement, and either in-situ or extra-anatomical repair) is the gold standard.[10] However, endovascular aortic repair is mentioned as an acceptable alternative to open repair or as bridge (to later open surgery) in patients who are not fit enough to undergo open repair.[10] In summary, INAA is a rare but dangerous disease affecting a heterogenous patient population with no golden standard in place for diagnosis and treatment.

Vascular graft and endograft infection

Another infectious entity in (cardio)vascular surgery is vascular graft and endograft infection (VGEI). VGEI is a complication after (cardio)vascular surgery and is associated with high morbidity and mortality.[11] The two year rate of VGEI in aorto-iliac position is 0.2%, without significant differences between open and endovascular grafts.[12] In the peripheral region, incidences of 2.5% are reported for femoro-femoral crossover bypasses and 2.8% for femoropopliteal bypasses.[13] The incidence of graft infection in the femoral position (i.e. in the groin) can be up to 6%.[14] Presentation depends on the location of the prosthesis. Patients with VGEI present with a variety of symptoms, including pain at the position of the graft, leaking surgical wound, inflammation of the skin at the site of the graft, a palpable mass, or systemic symptoms such as fever.[15] The presentation depends on the position of the infected grafts. Seventy percent of patients with an aorto-iliac VGEI experience fever and pain.[16] In patients with an infected peripheral reconstruction, the most common site of initial clinical presentation is the groin.[15] Since VGEI leads to high mortality and morbidity, accurate and early diagnosis is of utmost importance for management of VGEI.

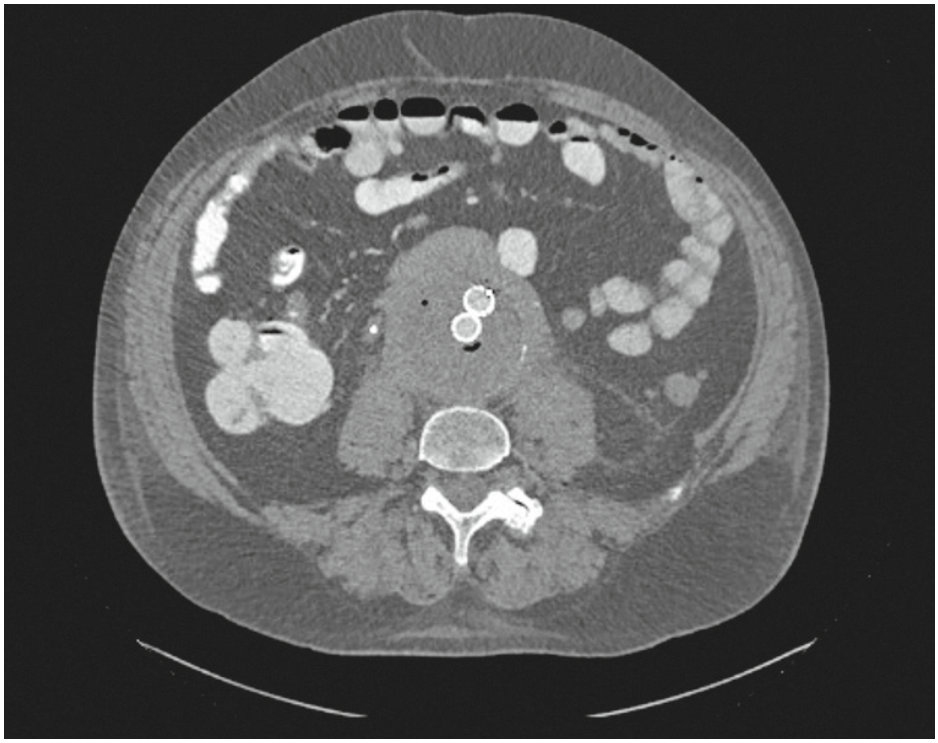
Diagnosis of VGEI can be difficult due to many factors, namely the non-specific clinical presentation and the difficulty to obtain cultures. Minor and major criteria based on clinical/surgical-, radiology-, and laboratory findings have been developed by the Management of Aortic Graft Infection Group (MAGIC) to diagnose VGEI. According to these criteria, VGEI is “suspected” if one major or two minor criteria are met, across three different categories. VGEI is “diagnosed” if at least one single major criterion and any other criterion from another category is met (Figure 1).[11,13]

Figure 1. Management of Aortic Graft Infection Group (MAGIC) criteria. Figure based on the reference of Lyons et al.[11]

	Clinical and Surgical	Radiology	Laboratory
MAJOR	▪ Pus around the vascular graft or in the aneurysm sac at surgery ▪ Open wound with exposed graft or communicating sinus ▪ Fistula ▪ Graft insertion in an infected setting (e.g., fistula, infective native aneurysm or pseudoaneurysm)	▪ peri-graft fluid on CT-scan ≥3 months after insertion ▪ Peri-graft gas on CT-scan ≥7 weeks after insertion ▪ Increase in peri-graft gas volume demonstrated on serial imaging	▪ Organisms recovered from an explanted graft, an intra-operative specimen, or a percutaneous, radiologically-guided aspirate of peri-graft fluid.
MINOR	▪ Localized clinical features (e.g., erythema, warmth, swelling, purulent discharge, pain) ▪ Fever ≥38 degrees Celsius with graft infection as most likely cause	▪ Other e.g., suspicious peri-graft gas/fluid/soft tissue inflammation; aneurysm expansion; pseudoaneurysm formation; focal bowel wall thickening; discitis or osteomyelitis; suspicious metabolic activity on FDG PET/CT; radiolabeled leukocyte uptake	▪ Blood culture(s) positive and no apparent source except graft infection ▪ Abnormally elevated inflammatory markers with graft infection as most likely cause (e.g., ESR, CRP, white blood cell count)

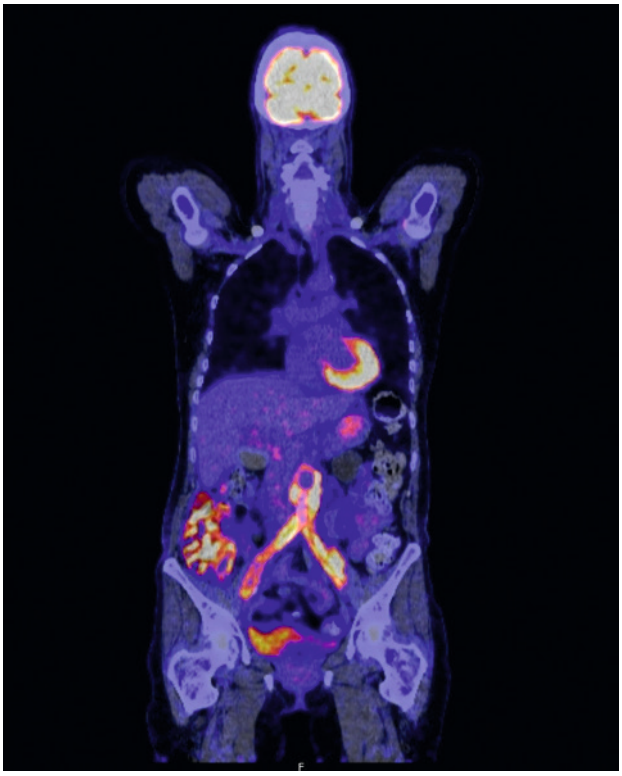
Consensus on the optimal imaging procedure for suspected VGEI is still lacking.[17] Ultrasound as a sole diagnostic modality is not recommended.[13] However, it can be used to differentiate between a hematoma or an abscess and it can be used for diagnostic punctures.[13] If VGEI is suspected within three months after initial surgery, computed tomography with angiography (CTA) is recommended.[13,15] An example of a CTA (transversal image) of a patient with an infected EVAR is shown in Figure 2. A large aneurysm sac with periprosthetic gas was observed.

Figure 2. Example of a CTA-scan (transversal image, level below the bifurcation) of a patient with an infected EVAR. The periprosthetic gas is a sign of VGEI.



Another imaging entity, besides CT(A), is ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG-PET/CT) scanning. In patients with a late (> 3 months after index surgical procedure) presentation of a suspected VGEI, [^{18}F]FDG-PET/CT is advised.[15] The combination of [^{18}F]FDG-PET and low-dose CT shows the metabolic activity of inflammation in addition to the patient's anatomy. Advantages of [^{18}F]FDG-PET/CT are the high sensitivity (ranging from 89 to 98%) and the ability to diagnose infection in other parts of the body.[17] Disadvantages include low specificity (ranging from 59-81%) and high false positive findings in the early post-operative period due to physiological inflammation.[17] In Figure 3, an example of an [^{18}F]FDG-PET/CT-scan (anteroposterior) is shown of a patient with an infected aorto-bifemoral graft (polyester).

Figure 3. Example of an ^{18}F-FDG PET/CT-scan (anteroposterior image) of a patient with an aorto-bifemoral polyester bypass with a strong suspicion of an infected prosthesis, both the body and the legs of the prosthesis are involved with distal extension on both sides towards the soft tissues.



Currently, the interpretation criteria as described in the European Society of Vascular Surgery (ESVS) guidelines for [^{18}F]FDG-PET/CT are the calculated maximum standardized uptake value (SUVmax), the tissue to background ratio (TBR), the uptake pattern (focal or diffuse), and the visual grading scale.[13] It is mentioned that a linear, diffuse, and homogeneous uptake is highly suggestive for VGEI.[13] In 2013, the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging published a guideline with general information about performing [^{18}F]FDG-PET/CT to localize and diagnose inflammation and infection.[18] However, a specific protocol including different criteria and/or characteristics to use for reporting a [^{18}F]FDG-PET/CT-scan of a suspected VGEI is yet to be established. Standardization of interpretation is needed to reduce heterogeneity and allow comparison between centers and across future studies.

Surgical treatment is important in the management of VGEI. Aggressive debridement and removal of all infected material (including the vascular prosthesis in its entirety) is necessary to prevent reinfection. This is due to the formation of a biofilm, which makes antvibiotics less effective.[15] However, not all patients are fit enough to undergo a major

vascular surgical procedure. If complete removal is not possible, surgical debridement and/or drainage of collections, in addition to antimicrobial suppression therapy, can be initiated. However, a disadvantage of this alternative approach is the higher mortality and post-repair re-infection rates.[19]

Various vascular graft materials are available for the treatment of both INAA and VGEI, including autologous vein, cryopreserved allografts, synthetic grafts (e.g. polyester), biosynthetic grafts (i.e. a combination of biological and synthetic material), and biological xenografts. Autologous veins (for example the great saphenous vein or the deep femoral vein) are the golden standard to be used in reconstructive surgery of VGEI. Although autologous veins offer good results with moderate resistance to infection, there are disadvantages. They are not always suitable or readily available. Another option to be used is a cryopreserved allograft. Though cryopreserved allografts are readily available and have low re-infection rates, they tend to have higher rates of graft degeneration leading to dilatation and rupture.[20–22] Synthetic prostheses are also readily available, but the re-infection rates are high compared to non-synthetic options.[13] In the group of synthetic grafts, silver impregnated or rifampicin soaked synthetic grafts have been used.[23–25] However, in patients treated with a rifampicin soaked graft, the occurrence microorganisms resistant to rifampicin (in about 30%) was shown.[23] Other alternatives for the treatment of VGEI are biological xenografts or biosynthetic materials (e.g. Omniflow® II, made of ovine-derived collagen and a polyester mesh endoskeleton). Earlier studies have demonstrated low infection rates of biosynthetic materials in elective surgery.[26] Furthermore, studies on Omniflow® II in septic environments also show potential infection resistance properties.[27,28] However, literature on the use of these grafts in abdominal and peripheral VGEI replacement surgery is still scarce.

History of biological xenograft materials used for vascular reconstruction

Vascular xenografts are grafts that are derived from one animal species and implanted into another species. The concept of using animal organs for human transplantation dates back to the early 20th century, but the first attempts at vascular xenografts were not successful due to rejection by the recipient's immune system. The use of biological xenograft material was pioneered in cardiac valve replacement surgery.[29] In the 1960s, researchers began experimenting with the use of immunosuppressive drugs to prevent rejection. One of the first successful vascular xenografts was performed in the sixties. In 1965, the first successful xenograft replacement of an aortic valve in a human was performed.[30] This graft was made of porcine material. In the following years, surgeons in France made extensive use of this valve substitute. Pig hearts were collected under sterile conditions and then kept frozen. Next, the valves were sterilized using purified glutaraldehyde and buffered at pH 7.4. A couple years later, an Australian research group used calf grafts instead of porcine grafts.[31] An advantage mentioned by this group, included the fact that there were no thrombo-embolic complications. In 1969, the French surgeon Alain Carpentier stated that "the use of biological tissue in surgery

springs from a natural tendency of man to consider with affection all natural material and with suspicion any artificial substitute".[32] Nowadays, more than 50 years later, biological materials are still being used in cardiovascular surgery.

Bovine pericardial patch

In the following decades, xenografts, most commonly made of bovine pericardium, were used for different indications in cardiac surgery, including reconstruction of the right ventricular outflow trajectory, pericardial closure, and correction of congenital heart defects, resulting in good outcomes.[33–35] Due to the safety and positive results of these biological xenografts in cardiac surgery, the bovine pericardial patch was introduced for carotid endarterectomy with patch angioplasty in the early nineties.[36] This patch is made of processed bovine pericardium stabilized in glutaraldehyde and stored sterile water with 1% propylene oxide. Surgeons appreciate its easy handling characteristics. Studies in the early 2000s concluded that the use of this material was promising for carotid endarterectomy with patch angioplasty.[37,38] In the following years, BPP gained increasing popularity. A Cochrane review (2021) demonstrated that BPP may decrease the occurrence of fatal stroke, infection, and mortality compared to other materials.[39] However, due to the rarity of events, the quality of evidence of this review was low. Currently there is still insufficient data to recommend BPP above other patches for carotid endarterectomy. Therefore, current recommendations state that the choice of patch material depends on the surgeon and the operating team.[40] In Figure 4, an example of a currently used BPPs (different sizes) are shown.

Figure 4. Currently available bovine pericardial patches in different sizes (LeMaitre, Vascular, Inc.)

Figure 5. Omniflow® II biosynthetic graft.

Omniflow® II

Another vascular prosthesis (partly) made from animal-derived material is the Omniflow® II. This prosthesis consists of an ovine-derived collagen tube that is induced by subcutaneously implanting a polyester mesh endoskeleton into a sheep for several weeks. Hereafter it is explanted and made acellularized.[41,42] It is a tube shaped prosthesis that is available in different lengths and with diameter of 6 or 8 mm. See Figure 5.

Initially, the Omniflow® II was used for hemodialysis with encouraging results.[43,44] Due to these results, it is currently being used for several surgical procedures, including revascularization surgery in peripheral arterial disease patients, infected graft replacement surgery, and even in aortic reconstruction surgery.[45–48] In case of the latter indication, a (bifurcated) graft is created by the surgeon by spatulating and anastomosing two 8-mm tubular Omniflow® II prostheses. Several graft materials are available for the above-mentioned indications. However, currently available literature consists of studies with small samples sizes. The choice of graft material depends on multiple factors, including anatomical position, comorbidities of the patient, surgical indication, and preferences of the local surgical team.

Outline of this thesis

Part I of this thesis focuses on two infectious entities in vascular surgery, including infective native abdominal aortic aneurysms (formerly known as mycotic abdominal aortic aneurysms) and vascular graft and endograft infections. **Chapter 2** describes all patients with a INAA in a tertiary referral center in the Netherlands in order to give an overview of the diagnostic approaches and treatment in the last decade. **Chapter 3** further explores the reporting of [^{18}F]FDG-PET/CT for the diagnosis of VGEI, since there are no standards available yet. **Chapter 4** describes a case-report of a man with an abdominal aortic aneurysm with endovascular repair and atypical findings on the ^{18}FDG-PET/CT-scan which shows aortic wall inflammation to illustrate the problem this thesis is about. There is lack of knowledge on the use of biological materials, while these materials have the potential to be more infection resistant compared to synthetic alternatives. Biological xenograft materials with the potential to be infection resistant will be discussed in **Part II**. **Chapter 5** describes the use of Omniflow® II biosynthetic

prosthesis for replacement surgery of infected vascular graft and endografts. Besides, Omniflow® II is also used for other indications. Since both indications and position can influence the outcomes of vascular grafting (i.e. in general, infected setting and more distally located grafts yield poorer outcomes), in **chapter 6,** we evaluate the use of Omniflow® II for different indications in different anatomical locations within the femoral tract (i.e. femoral interposition, femoro-femoral crossover, femoro-popliteal, and femoro-crural) Biological materials are also used in surgery of the carotid artery (i.e. carotid endarterectomy with patch angioplasty). No recommendations are available in the guidelines regarding the choice of patch material. Therefore, **chapter 7** presents the 10-year single center results of the use of BPP and polyester for carotid endarterectomy with patch angioplasty. Furthermore, a suggestion of using autologous pericardium as patch material for carotid endarterectomy and our response on this suggestion are presented. Finally, to investigate if there are differences between readily available materials (e.g. polyester and BPP) and autologous venous patches in a larger group of patients, **chapter 8** presents the multicenter results of the comparison of bovine pericardial, polyester, and autologous vein patches for carotid endarterectomy with patch angioplasty. A summary of the findings derived from the above-mentioned chapters are discussed in in **Chapter 9**.

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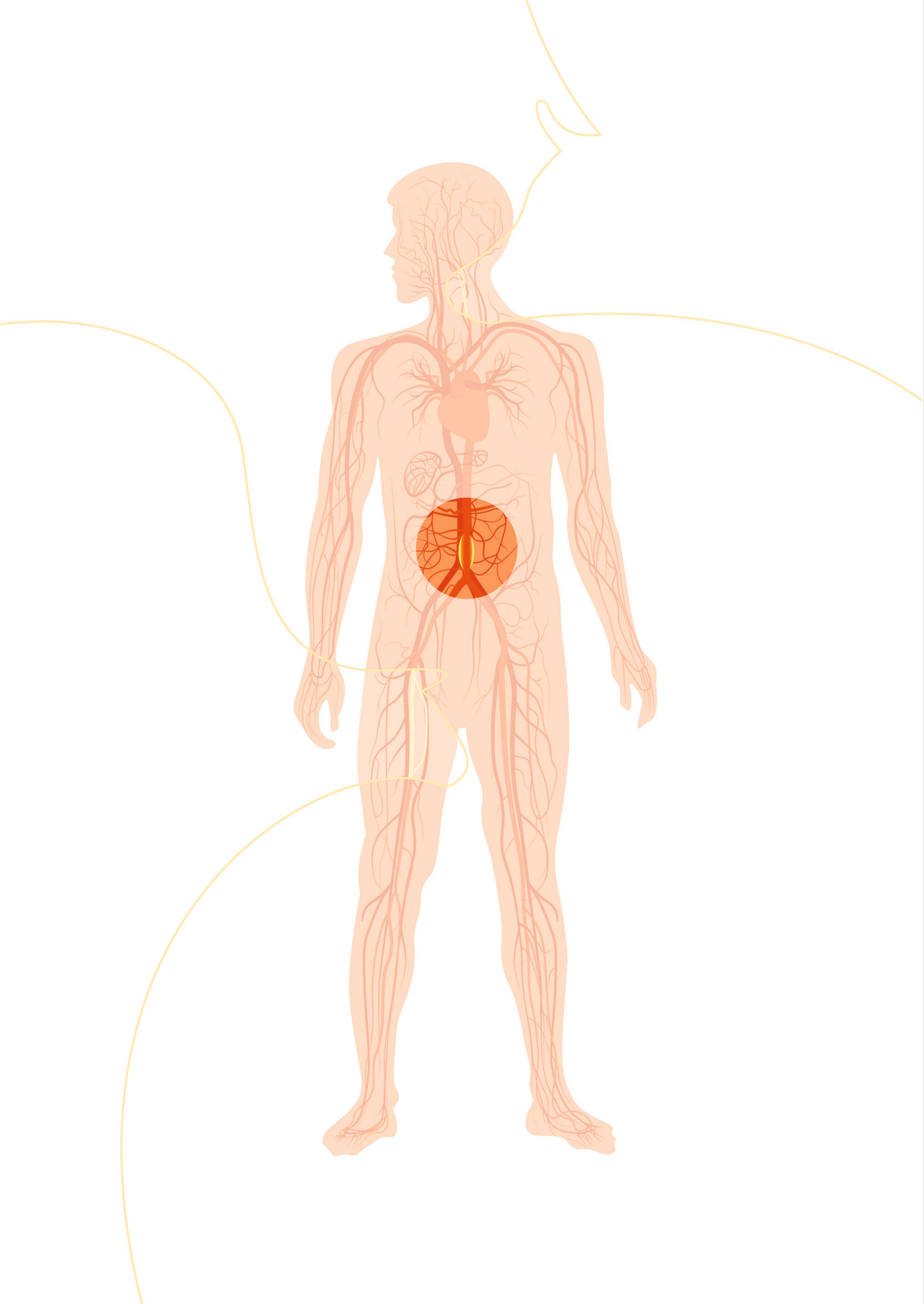

Chapter 2

Patient-tailored approach for diagnostics and treatment of mycotic abdominal aortic aneurysm

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ABSTRACT

Objectives

The existing literature on mycotic aortic aneurysm is scarce and focuses on treatment. This study evaluates the clinical characteristics, diagnostics, treatment, and outcome of patients with a mycotic abdominal aortic aneurysm treated in a tertiary referral center.

Methods

A retrospective cohort study was conducted including all patients with a proven mycotic abdominal aortic aneurysm admitted between May 2010 and July 2020. Primary outcome was mortality and secondary outcome included complications such as vascular graft/endograft infection.

Results

Twenty-four patients with a mycotic abdominal aortic aneurysm were included. Patients had a mean age of 68 ± 9 years and 20 (83%) were male. Thirteen patients (57%) had positive preoperative blood cultures. Streptococcus pneumoniae was most frequently isolated by blood culturing, pus, and vascular, or perivascular tissue cultures (17%). In 19 (83%) patients the mycotic abdominal aortic aneurysm was located infrarenally, in three (13%) patients suprarenally, and in one (4%) patient juxtarenally. Median follow-up was 20 (7–42) months. In 8 patients (33%) vascular graft and or endograft infection was diagnosed after surgical repair. Ten (42%) patients died during the follow-up period. The main causes of death were vascular graft/endograft infection-related (n = 4) and rupture of the mycotic abdominal aortic aneurysm (n = 3). No patient characteristics could be identified as predictive for mortality.

Conclusions

This study shows a large variation in presentation, diagnostic approaches, and surgical and antibiotic treatment of mycotic abdominal aortic aneurysm. The detailed information about the diagnostic approaches to this rare disease and its antibiotic and/or other treatment contributes to existing knowledge of mycotic abdominal aortic aneurysm. Because of the individual variation patients should be discussed in a multidisciplinary team with a vascular surgeon, infectious disease specialist, and clinical microbiologist.

INTRODUCTION

Mycotic aortic aneurysm (MAA) has a poor prognosis. Because of its rapid expansion the risk of rupture is very high. The underlying mechanism is an infection of the aortic wall. The incidence of MAAs in Western countries is 0.65 to 2% of all aortic aneurysms, and at the moment of presentation most patients are younger than those with non-mycotic aneurysms.[1,2] MAAs can develop from septic emboli, by hematogenous spread, or directly spreading from infected tissue adjacent to the vascular wall. The most common causative micro-organisms are *Staphylococcus* and *Salmonella species*.[3] Clinical presentation can be diverse and range from systemic symptoms of infection to more localized symptoms.[4] It is therefore important that MAAs be recognized early and prompt treatment be initiated.

Currently diagnosis is based on clinical characteristics (abdominal and back pain, pulsating mass, fever, and sepsis), medical history (prior infections, immunocompromised status due to disease or medication), laboratory markers (elevated C-reactive protein (CRP) or elevated leukocyte count, positive blood- or aortic tissue culture), radiological findings with duplex ultrasound, computed tomography (angiography) (CT(A)), and/or magnetic resonance imaging (MRI) (e.g., saccular/multilobular aneurysm, periaortic soft tissue mass or gas formation).[5] There are indications that ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) can play an additional role in the diagnosis of MAAs. The conventional treatment regime includes antibiotics combined with surgery (endovascular or open).[6,7]

Although several studies have been published, there are no clear guidelines for diagnosis, management, or treatment. The larger abdominal MAA studies are register-based, resulting in less detailed information; they are mainly focused on treatment and do not include conservatively treated patients.[8,9]

This retrospective study was conducted to evaluate clinical characteristics, diagnostic approaches, treatment, and outcome of patients with MAA admitted to our tertiary referral center.

MATERIAL AND METHODS

Study design and population

In a retrospective cohort study, data of all patients with an MAA admitted to our tertiary referral center between May 2010 and July 2020 were collected. Following the European Society for Vascular Surgery (ESVS) guidelines, the diagnosis was based on a combination of symptoms and clinical presentation (abdominal/back pain, fever, sepsis, and/or shock), laboratory markers (CRP and white blood cell count and/or a positive blood or aortic tissue culture), and radiological findings on CT.[10] Seven patients with a thoracic MAA were excluded, given the differences in presentation, imaging, and treatment with abdominal MAA.

The Medical Ethical Institutional Review Board granted dispensation for the study from the Medical Research Involving Human Subjects Act (WMO) obligation (registration no. METC 2020/0282). As a consequence, informed consent was not obtained. Patient data were processed and electronically stored in agreement with the declaration of Helsinki – Ethical principles for medical research involving human subjects.[11] Data were stored and analyzed anonymously.

Data extraction

Data were extracted from the electronic patients file (EPIC). The list was completed by identifying patients through searches on intervention codes and codes of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Missing data was added by contacting general practitioners and referring hospitals.

Patient characteristics

The following patient characteristics were collected: age (at time of presentation), sex, height, weight, body mass index (BMI), and medical history (e.g., tobacco use, hypertension, hyperlipidemia, diabetes mellitus, malignancy). Cardiac, pulmonary and renal status were evaluated. Tobacco use, hypertension, hyperlipidemia, diabetes mellitus, and cardiac, pulmonary, and renal status were classified by the Society for Vascular Surgery (SVS) system (class 0–3) according to the Ad Hoc Committee on Reporting Standard. Tobacco use was scored positive if there was current use or less than one year of abstinence (class 2 and 3 of the SVS system). Other variables collected using the SVS criteria were positive if the status was scored ≥ 1.[12]

Diagnostics

Clinical symptoms that were dichotomized (yes/no) included pain, fever (>38.5°C), unintentional weight loss, loss of energy, loss of appetite, nausea or vomiting, and changes in bowel habits. The inflammatory markers (laboratory findings) CRP level (mg/L) and white blood cell count (10^9/L) were collected. Timing of serum collection was at the initial presentation in the hospital.

Preoperative CTA and 18F-FDG PET/CT-scans were evaluated.[13,14] The location of the abdominal aortic aneurysm was classified into suprarenal, juxtarenal, and infrarenal. Morphology was either fusiform or saccular. The following dichotomous CTA characteristics were collected: appearance of the wall (multilobulated, yes/no), thickening of the aortic wall, interruption of aortic wall calcification, adjacent soft-tissue stranding, adjacent collection of gas, periaortic lymph nodes, rupture (contained in the retroperitoneal space or full-blown), cortex interruption of the vertebrae close to the aneurysm, and luminal ulceration (disruption of the plaque surface with adherent organizing thrombus).[15] The maximum anteroposterior aneurysmal diameter and the side-to-side diameter were measured in the transversal plane (mm). CTA data were collected by 1 author (DL) and checked by a second author (NP).

The following 18F-FDG PET/CT characteristics were collected: maximum standardized uptake values (SUVmax) at the level of the MAA (region of interest), tissue-to-background ratio , (calculated as: SUVmax of MAA divided by SUVmax of a liver region), patterns of uptake (homogenous or heterogenous), and a visual grading scale . The visual grading scale included the following categories: grade 1 = FDG uptake comparable to the background, grade 2 = low FDG uptake (comparable with that by inactive muscles or fat), grade 3 = moderate FDG uptake (clearly visible, but less than physiological FDG activity in the bladder), grade 4 = high FDG uptake (comparable with physiological FDG uptake in the bladder).[16] All measurements were taken by one author (DL) and checked by a second author (RS). The measurements were taken on EANM Research Lab (EARL) reconstructions.

Microbiological diagnostic approaches were evaluated. Results of cultures derived from blood (preoperative), preoperative para-aortic puncture material, and intraoperative pus/tissue were collected.

Treatment

Treatment modality was gathered, including open surgery (synthetic graft, biological xenograft or autologous graft), endovascular aneurysm repair (EVAR), or treatment with antibiotics only. Omental wrapping of the aorta was performed in open surgery with high risk of infection (for example MAA repair or replacement surgery in infected vascular endografts), except if too little (suitable) omental tissue was present. If open treatment had been selected, autologous venous reconstruction was preferred due to the lower (re)infection risk in comparison with synthetic grafts. If there was no suitable vein or in case of emergency surgery (and endovascular repair was not possible), a bovine pericardial xenograft was preferred.[17] Detailed information about antibiotic treatment (including dose and duration) were also collected. Complications of treatment were noted, such as graft infection and/or endoleak.

Follow-up

Date and reason of death were collected. If the patient survived the follow-up period, the last day of follow-up (i.e. outpatient clinic visit) was noted.

Statistical analysis

Categorical variables were described with frequencies (percentages). Distribution of continuous data were checked visually and supplemented by the Shapiro-Wilk test. Normally distributed data were presented as mean ± standard deviation (SD). Skewed distributed data were presented as median and interquartile range (IQR). Survival was estimated with the Kaplan-Meier curve. Univariate cox regression analyses were performed to determine whether one or more baseline characteristics were associated with mortality. The amount of effect on mortality was described with hazard ratios. No multivariate cox regression analysis was done because of the low number of patients and events.

Statistical significance was set at *alpha* <.05. Statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

RESULTS

Basic characteristics and comorbidities

Twenty-four patients with an MAA were included in the analysis following the listed criteria. Patients had a mean age of 68 ± 9 years and 20 (83%) were male; 15 patients (63%) were known with tobacco use (including current smokers or those with less than one year of abstinence) and 14 patients (58%) with hypertension. Hyperlipidemia, diabetes mellitus, and malignancy were present in 11 (46%), 5 (21%), and 6 (25%) patients, respectively (Table I).

Table I. Patient characteristics, clinical and laboratory findings in patients with mycotic aortic aneurysm.

Characteristic	N (%) or mean ± SD or median (IQR)
No. of patients	24 (100)
Age in years	68 ± 9
Sex, males	20 (83)
BMI (kg/m^2)	26 ± 3
Tobacco use	15 (63)
Hypertension	14 (58)
Hyperlipidaemia	11 (46)
Diabetes mellitus	5 (21)
Malignancy	6 (25)
Cardiac disease	8 (33)

Table I. Continued

Characteristic	N (%) or mean ± SD or median (IQR)
Pulmonary disease	7 (29)
Renal disease	7 (29)
Symptoms	
Pain	22 (92)
Fever	6 (25)
Weight loss	4 (17)
Loss of energy	9 (38)
Loss of appetite	6 (25)
Nausea or vomiting	8 (33)
Change of bowel habits	8 (33)
Laboratory findings	
CRP[b] (mg/L)	134 (67-231)[a]
White blood cell count (10^9/L)	17 (14-21)[a]

[a] median and IQR. IQR is written as: (first quartile-third quartile), [b] C-reactive protein.

Clinical presentation

Twenty-two (92%) patients presented with pain and 6 (25%) patients with fever. Laboratory findings included a median initial CRP level of 134 (IQR: 67–231) mg/L and a median white blood cell count of 17×10^9/L (IQR: 14–21) (Table I).

Diagnostic imaging

All patients underwent a CTA scan. In 19 (83%) patients the MAA was located infrarenally, in three (13%) suprarenally, and in one (4%) patient juxtarenally. The median anteroposterior diameter measured in the transversal plane was 51 ± 24 mm and from side-to-side 60 ± 35 mm. Twelve (52%) patients had a fusiform morphology and 11 (48%) a saccular aneurysm. The most common CTA characteristics were thickening of the aortic wall (n = 18, 78%), interruption of arterial wall calcification (n = 16, 70%), and luminal ulceration (n = 14, 61%). Six (26%) patients were demonstrated to have a contained rupture at presentation and one (4%) with a full-blown rupture. Other MAA-related characteristics are shown in Table II.

Table II. Anatomical details and signs of infection as found on computerized tomography angiography and ^{18}F-FDG PET/CT-measurements.

Characteristic	N (%) or mean ± SD or median (IQR)
Number of patients with CTA[a]	23[b] (100)
Location	
- Suprarenal	3 (13)
- Juxtarenal	1 (4)
- Infrarenal	19 (83)
Morphology	
- Fusiform	12 (52)
- Saccular	11 (48)
Wild multilobulated appearance	5 (22)
Thickening of aortic wall	18 (78)
Interruption of arterial wall calcification	16 (70)
Adjacent soft tissue stranding	8 (35)
Adjacent collection of gas	1 (4)
Periaortic lymph nodes	12 (52)
Contained rupture	6 (26)
Full-blown rupture	1 (4)
Cortex interruption (vertebrae)	2 (9)
Luminal ulceration	14 (61)
Maximum anteroposterior diameter (mm) transversal plane	51 ± 24
Maximum side-to-side diameter (mm) transversal plane	60 ± 35
No. of patients with ^{18}F-FDG PET/CT[c]	6 (100)
SUVmax[e]	5.9 (5.1-8.6)[d]
TBR[f]	2.5 (1.5-3.4)[d]
Heterogenous pattern of uptake	6 (100)
VGS[g]	3.0 (2.8-3.3)[d]

[a] Computed tomography angiography, [b] based on 23 patients, one CTA is missing, [c] ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, [d] median and IQR. IQR is written as: (first quartile-third quartile), [e] maximum standardized uptake values, [f] tissue-to-background ratio, [g] visual grading scale.

Figure 1 shows the transversal (1A) and sagittal (1B) CTA views of an infrarenal ventral saccular MAA of one of the patients.

Figure 1. Transversal (**A**) and sagittal (**B**) CT-angiography views of a thin stemmed infrarenal ventral saccular mycotic aortic aneurysm, with thickening of the aortic wall, soft tissue stranding, and mural thrombus formation. (**C**) Transversal ^{18}F-FDG PET/CT view of the same patient at the level as Figure **1A** that shows a heterogeneous uptake of ^{18}F-FDG in the aortic wall.

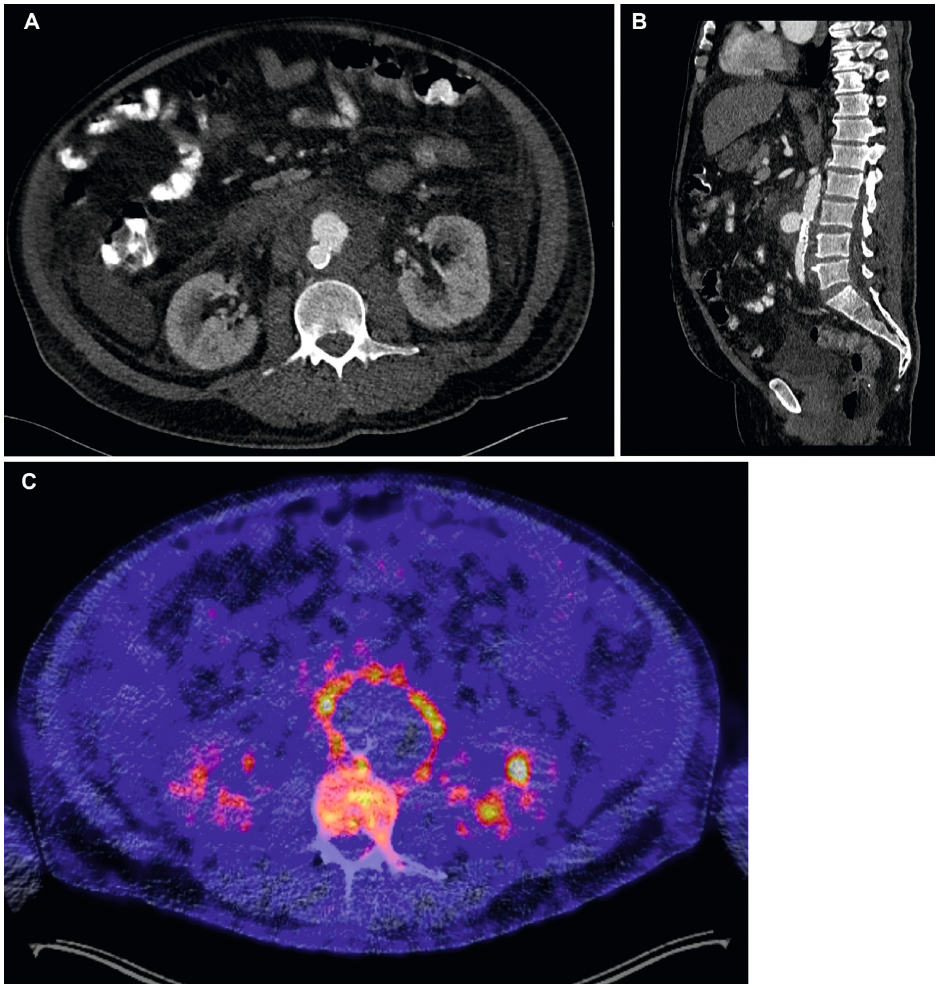


Table III. Overview of microbiological cultures, antibiotic therapy, surgical therapy, and outcome per patient.

	Blood cultures	Perioperative tissue and/or pus cultures	Puncture	Antibiotic treatment	Antibiotic course duration, preoperatively or postoperatively	Surgical treatment	Outcome
1	Negative	NP[a]	NP	Ceftriaxon 2g IV[b] BID[c]	2 days postop until failure	No	Mortality caused by MAA-rupture
2	Negative	NP	*Mycobacterium bovis*	Ceftriaxon 2g IV BID, Rifampicin/ Isoniazid 300/150mg oral BID, Moxifloxacin 400mg oral OD[d]	8 days Ceftriaxon preop, Rifampicin/Isoniazid postop lifelong, 2 months Moxifloxacin postop	Endovascular repair	Adverse events: no
3	Negative	NP	NP	Piperacillin/Tazobactam 4g/0.5g IV OD, Vancomycin 1100mg IV OD, Caspofungin 70mg IV OD	6 weeks postop	Endovascular repair	Adverse events: no
4	*Streptococcus agalactiae*	NP	NP	Benzylpenicillin 4000000 IE IV OD, Amoxicillin 1000mg oral OD	6 weeks Benzylpenicillin postop followed by Amoxicillin until failure	Endovascular repair	Adverse events: no
5	*Salmonella species*	*Salmonella species*	NP	Ceftriaxon 2g IV BID, Ciprofloxacin 500mg oral BID	2 weeks Ceftriaxon postop followed by 4 weeks Ciprofloxacin	Open reconstruction (autologous vein)	Cardiac-related mortality
6	NP	*Coxiella burnetii*	NP	Doxycycline 100mg oral BID, Hydroxychloroquine 200mg TID[e]	8 weeks Doxycycline, 6 weeks Hydroxychloroquine postop	Open reconstruction (Dacron)	Occlusion of L.a. femoralis communis requiring thrombectomy and vascular graft/endograft infection and infection-related mortality
7	*Staphylococcus aureus*	NP	NP	Flucloxacillin 12g IV OD, Rifampicin 450mg oral BID	2 weeks Flucloxacillin postop followed by 7 months Rifampicin	Open reconstruction (Dacron)	no
8	Negative	NP	NP	Augmentin 625mg oral TID, Cotrimoxazole 960mg oral BID	Postop until failure	Endovascular repair	Vascular graft/endograft infection for which treated with replacement surgery (xenograft, bovine pericardium)

Table III. Continued

	Blood cultures	Perioperative tissue and/or pus cultures	Puncture	Antibiotic treatment	Antibiotic course duration, preoperatively or postoperatively	Surgical treatment	Outcome
9	Negative	NP	NP	Augmentin 500mg/125mg oral TID	10 days postop	Open reconstruction (autologous vein)	Adverse events: no
10	Negative	*P. mirabilis*	NP	Cefotaxime 1g IV QID, Cotrimoxazole 800-160mg BID	2 weeks Cefotaxime postop followed by 4 weeks Cotrimoxazole	Open reconstruction (Dacron)	Adverse events: no
11	Negative	*E. coli, E. faecalis, Candida species*	NP	Ciprofloxacin 250mg oral BID, Fluconazole 200mg oral OD	Postop until failure	Open reconstruction (Dacron)	Vascular graft/endograft infection and pulmonary-related mortality
12	*Streptococcus pneumoniae*	*E. faecalis*	*E. faecalis*	Vancomycin 300mg IV BID, Ciprofloxacin 500mg oral BID	2 months postop	Open reconstruction (Dacron)	Vascular graft/endograft infection
13	*Salmonella*	*Salmonella*	NP	Meropenem 1000mg IV TID, Vancomycin 2400mg IV OD	6 months postop	Endovascular repair	Vascular graft/endograft infection, endoleak type I and infection-related mortality
14	*Staphylococcus aureus*	NP	NP	Flucloxacillin 12g IV OD, Clindamycin 600mg oral TID	6 weeks Flucloxacillin postop followed by Clindamycin until failure	Endovascular repair	Endoleak type I, vascular graft/endograft infection, for which treated with replacement surgery (xenograft, bovine pericardium) and infection-related mortality
15	Negative	Negative	NP	Ciprofloxacin 500mg oral BID, Clindamycin 300mg oral BID	Postop until failure	Open reconstruction (autologous vein)	Vascular graft/endograft infection and infection-related mortality

Table III. Continued

	Blood cultures	Perioperative tissue and/or pus cultures	Puncture	Antibiotic treatment	Antibiotic course duration, preoperatively or postoperatively	Surgical treatment	Outcome
16	Negative	*E. coli*	NP	Amoxicillin 500mg oral TID	2 months postop	Open reconstruction (Dacron)	Vascular graft/endograft infection
17	*Streptococcus equi*	NP	NP	Benzylpenicillin 12g IV OD	Starting 1 day preop continuing until 6 weeks postop	Open reconstruction (autologous vein)	Adverse events: no
18	*Streptococcus pneumoniae*	Negative	NP	Benzylpenicillin 18000000 IU IV OD	6 weeks postop	Open reconstruction (autologous vein)	Adverse events: no
19	*Streptococcus pneumoniae*	Negative	NP	Benzylpenicillin 12000000 IU IV OD	1 week	Open reconstruction (bio-prosthesis)	Adverse events: no
20	*Klebsiella pneumoniae*	NP	NP	missing	missing	No	Mortality caused by MAA rupture
21	Negative	NP	NP	Piperacillin/Tazobactam 4000mg/500mg IV OD, Augmentin 625mg oral TID	3 months Piperacillin/ Tazobactam postop followed by Augmentin until failure	Endovascular repair	Adverse events: no
22	*Staphylococcus aureus*	NP	NP	Flucloxacillin 12g IV OD, Clindamycin 300mg oral BID	6 weeks Flucloxacillin postop followed by Clindamycin lifelong until failure	No	Adverse events: no
23	*Streptococcus pneumoniae*	NP	NP	Piperacillin/Tazobactam 4000mg/500mg IV OD	Postop until failure	Open reconstruction (Dacron)	Malignancy-related mortality
24	*E. coli*	NP	NP	Augmentin 62 mg oral TID	2 weeks	No	Mortality caused by MAA rupture

[a] not performed, [b] intravenous, [c] twice a day, [d] once daily, [e] three times a day.

Microbiological diagnostic approaches

In total 18 patients (75%) had positive cultures (blood, intraoperative pus/tissue and/or pus puncture). In 23 (96%) patients' blood cultures were taken, 13 (57%) of which were positive. One patient did not have preoperative blood cultures because of an acute presentation with emergency surgery. Two patients had a preoperative puncture of a pus collection around the aneurysm and both cultures were positive. Ten patients (42%) had intraoperative tissue/pus cultures, seven (70%) of which were positive. Streptococcus pneumoniae was most frequently cultivated (n = 4, 22% of patients with positive cultures), followed by *Staphylococcus aureus* and *Escherichia coli* (n = 3, 17%) and *Salmonella species* (n = 2, 11%). See Table III for a detailed description of the diagnostics, antibiotic treatment, and outcome per patient.

Six patients underwent ^{18}F-FDG PET/CT scanning. The median SUVmax was 5.9 (5.1–8.6) and the tissue-to-background ratio 2.5 (1.5–3.4). All scans showed a heterogenous distribution of ^{18}F-FDG uptake within the aortic wall. The median score of the visual grading scale was 3.0 (2.8–3.3) (Table II). Figure 1C shows the transversal ^{18}F-FDG PET/CT view of the same patient at the same level as the CTA in Figure 1A. There is a heterogeneous uptake of ^{18}F-FDG in the aortic wall.

Modes of treatment

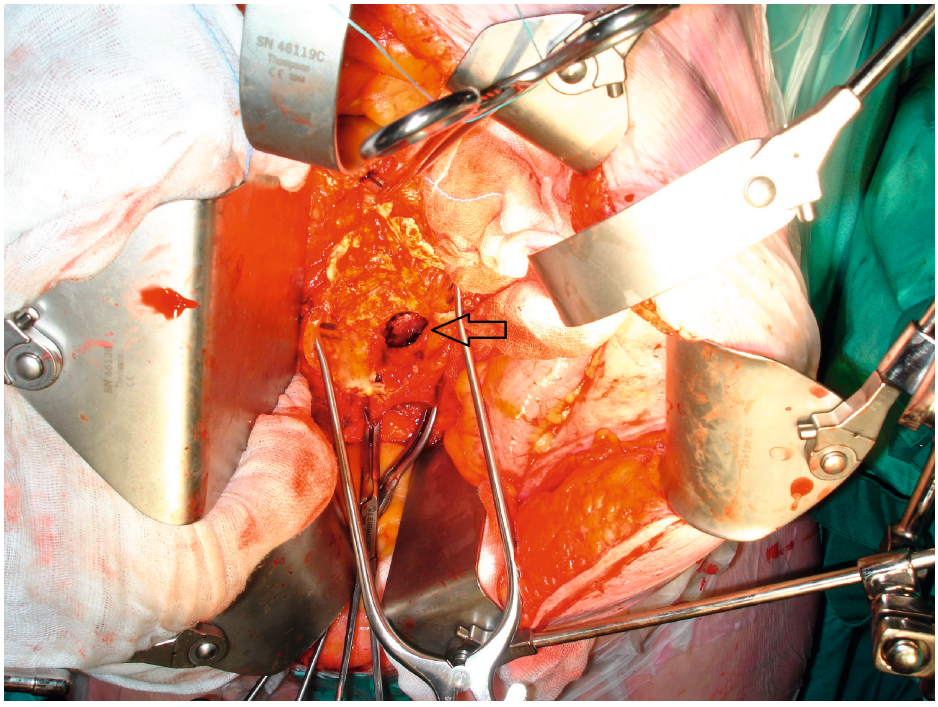
Invasive treatment was given to 20 patients (83%). Endovascular treatment was considered indicated whenever it seemed feasible (depending on the anatomy of the aneurysm), especially in critical ill patients or in case of emergency surgery. Thirteen patients (54%) underwent open surgery and 7 patients (29%) endovascular repair, possibly as a bridge to surgery. Finally, 2 of these patients indeed underwent open reconstruction after previous EVAR.

Open surgery was subdivided into conventional open surgery (replacement with a Dacron prosthesis) (n = 8, 61%), open surgery with an autologous vein (common femoral vein) (n = 4, 31%), and open surgery with a biological xenograft (bovine pericardial graft, named No-React Non-valved Conduit (Biointegral Surgical Inc, Mississauga, ON, Canada) (n = 1, 8%) (Table IV). Figure 2 shows a photograph taken during open surgical repair of a juxtarenal MAA, with clamping of the right renal artery, and the proximal and distal abdominal aorta. Four patients (17%) were not treated surgically. In 3 cases due to comorbidities and the fourth patient died because of a ruptured aneurysm after presentation, before treatment.

Table IV. Modes of treatment in patients with mycotic aortic aneurysm.

Variable	N (%)
Open repair	13 (54)
- Conventional (Dacron)	8 (61)
- Autologous	4 (31)
- Bio-prosthesis	1 (8)
Endovascular repair	7 (29)
Conservative (no surgery)	4 (17)

Figure 2. Photograph of infrarenal mycotic aortic aneurysm taken during open surgical repair, the infrarenal aorta (proximal) and the right and left common iliac artery are clamped. The arrow points a dorsally ruptured mycotic penetrating aortic ulcer.



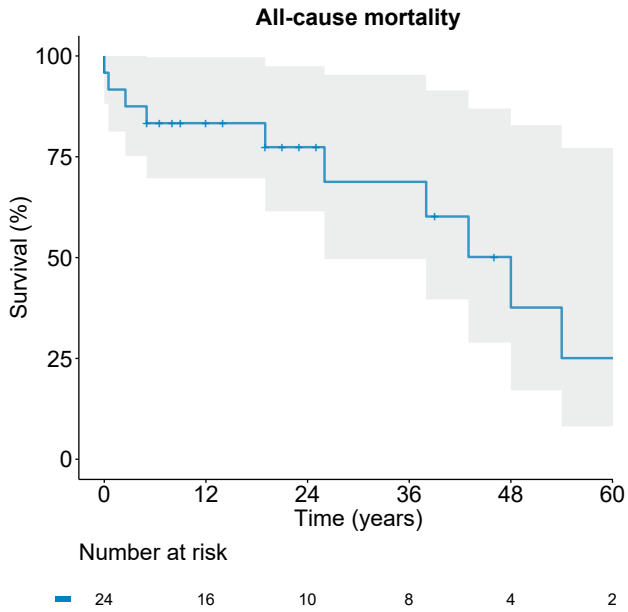
All patients were treated with antibiotics with varying durations in accordance with decisions from a multidisciplinary expert team with a vascular surgeon, clinical microbiologist, and infectious disease specialist (Table III).

Mortality and adverse events

Median follow-up was 20 (IQR: 7–42) months. Ten patients (42%) died during follow-up. Patient survival from first presentation until mortality or latest follow-up is shown in Figure 3.

Kaplan-Meier analysis demonstrated a cumulative survival of 83% (standard error: 5) at 1 year, 69% (standard error: 12) at 3 years and 25% (standard error: 14) at 5 years. Main causes of death were (central) vascular graft/endograft infection-related (n = 4, 40%) and MAA rupture (n = 3, 30%, all conservatively managed patients). Cardiac-, pulmonary- and malignancy-related mortality accounted each for n = 1 (10%).

Figure 3. Survival function of patients with mycotic aortic aneurysm.



The 30-day mortality rate was 0% in the group that underwent (open or endovascular) surgical repair and 50% (n = 2, both MAA rupture) in the conservatively treated patients. The in-hospital mortality rate in the surgically treated group was 10% (n = 2) and the overall mortality rate in the surgically treated group was 35% (n = 7) with a median follow-up of 24 months (IQR: 13–45).

Postoperatively, 8 patients (33%) were diagnosed with an infected prosthesis (vascular graft/endograft infection) based on clinical, radiology and/or laboratory characteristics. Time of diagnosis ranged from 26 days till almost 3 years postoperative, with a median of 376 (IQR: 97–819) days. Five of them were initially treated with open surgery and replacement with a Dacron prosthesis and 3 with an endograft. In 2 patients the antibiotics were stopped at the time of diagnosis (after durations of 2 and 6 months, respectively). In 2 patients the same microorganism as from the preoperative cultures was found. Two patients did not have preoperative positive cultures, and in 4 patient's different microorganisms were cultured pre- and postoperatively. A total of 5 patients with a vascular graft and/or endograft infection died. All patients with a diagnosed infected graft were treated with antibiotics. Duration of antibiotic therapy was at least 6 weeks with possible extension based on symptoms, inflammatory markers (laboratory) and/or imaging. In addition to the antibiotic therapy, 3 patients were treated surgically. Two of these patients had an endograft infection. Hereafter, they underwent open surgery where the infected endograft was replaced by bovine pericardial xenograft, 3 and 13 months, respectively, after the initial procedure. The first patient had a good outcome

and had no signs of (re-)infection. The second patient developed graft infection and died 6 months after the replacement surgery as the result of infection related complications. One of the patients who had undergone an open MAA repair, had an infected Dacron prosthesis. The infected prosthesis of this patient was surgically replaced with autologous deep femoral vein. The surgery was complicated 2 months postoperative by an aorto-duodenal fistula, which was treated endovascularly first and later with a rifampicin soaked Dacron graft.

Other noted adverse events included endoleak type I after endovascular repair in 2 patients and postoperative occlusion of a femoral artery requiring thrombectomy in 1 patient initially treated with open reconstruction with a Dacron prosthesis (Table III). No patient characteristics could be identified that were predictive for mortality (Table V).

Table V. Univariate Cox regression analysis.

Characteristic	HR[a] (95% CI[b])	P-value
Age	1.06 (0.96-1.17)	0.27
Sex	0.36 (0.046-2.90)	0.40
BMI	1.10 (0.83-1.45)	0.50
Tobacco use	0.83 (0.17-4.03)	0.82
Hypertension	0.34 (0.72-1.62)	0.18
Hyperlipidaemia	1.40 (0.34-5.75)	0.65
Diabetes mellitus	0.40 (0.096-1.71)	0.22
Cardiac disease	0.78 (0.21-2.94)	0.71
Pulmonary disease	1.46 (0.40-5.27)	0.56
Renal disease	0.52 (0.12-2.35)	0.40

Abbreviations: [a] hazard ratio, [b] confidence interval.

DISCUSSION

Our study shows a mortality rate of 42% in patients with an MAA after a median follow-up of 20 months. The total survival rate of 83% at 1 year is comparable with the literature. The 5-year survival rate of 25% is lower than that found by Sörelius et al., at 59%.[9] This lower survival rate in our cohort could be attributed to the inclusion of patients who did not undergo surgery. These patients may not have been physically able to withstand surgery. As shown in Table III, 3 out of 4 patients who were not operated, died. Hsu et al. also included patients who were treated conservatively and found an overall 1-year survival rate of 25%.[16] In the group of patients that had undergone surgical treatment, the overall mortality rate was 35% (n = 7). However, the value of the 5-year

survival rate in our cohort is limited because of the low number of patients at risk at 60 months (n = 2, Figure 3).

Fifty-seven percent of the patients with preoperative blood cultures (96%) had at least 1 positive blood sample. This is comparable with the 56% found in the nationwide study on thoracic MAAs of Sörelius et al., but higher than the nationwide study of treatment of MAAs in the Netherlands of Dang et al.[8,9] Seventy percent of the intraoperative cultures (tissue and/or pus) were positive. From our viewpoint, if open surgery is performed, vascular tissue or pus should be cultured, to maximize the chances of finding the causative micro-organism in order to start targeted antibiotic therapy. In case of endovascular repair intraoperative cultures cannot be taken. This can lead to undertreatment, which will increase the risk of reinfection. Tagiwaga et al. described a case of CT-guided biopsy of periaortic wall after EVAR. This increases the chances of finding a causative agent, and thus finding the suitable therapy with the right antibiotic.[17] As shown in Table III, the second patient had negative blood cultures and underwent diagnostic puncture (and drainage) of an abdominal abscess close to the native aortic wall. Cultures showed *Mycobacterium bovis* and targeted antibiotic therapy was started. Later this patient underwent endovascular repair.

CT(A) is the preferred imaging method for diagnosing MAAs. The meta-analysis of Wang et al. showed a pooled sensitivity and specificity of CT of 82% and 93%, respectively.[18] ^{18}F-FDG PET/CT is potentially useful for diagnosing MAA in a non-acute setting.[19–21] Our study evaluated 6 patients with a preoperative ^{18}F-FDG PET/CT-scan. They all had a heterogeneous distribution of the ^{18}F-FDG uptake with a median SUVmax 5.9 and a median visual grade of 3.0. No cut-off points are described in the literature, but the SUVmax (5.9) is comparable with the 4.5–6.5 found in the systematic literature review of Hannsberger et al. SUV cut-off points for infection remain debatable.[22–24] The cohort study of Husmann et al. compared the diagnostic accuracy of PET/CT and contrast-enhanced CT in the detection of MAA and found a diagnostic accuracy of PET/CT higher than contrast-enhanced CT. They found a high sensitivity (probably because of the measurable SUVmax), and specificity was lower because of false-positive findings in inflammatory aortic aneurysms.[25] Next to the diagnostic value, serial ^{18}F-FDG PET/CT can potentially contribute in the follow-up to determine the duration of antibiotic therapy.[22,26] Furthermore, ^{18}F-FDG PET/CT can show infection in other parts of the body that could be the source of the MAA. Larger prospective studies are needed to estimate the diagnostic value of ^{18}F-FDG PET/CT for abdominal MAAs more accurately.

The treatment strategies found in our study were very heterogenous. Fifty-four percent of the patients had undergone open repair (Dacron prosthesis, venous reconstruction, or bovine pericardial xenograft), 29% had undergone endovascular repair, and 17% did not undergo surgical repair. Following the ESVS guidelines, open repair is the gold standard, but the use of EVAR has risen in the last decade. EVAR is minimally invasive

and can be used as a bridge to surgery in acute situations and/or in critically ill patients who would otherwise be given palliative treatment. Sörelius et al. shows a significant short-term survival benefit for EVAR without late disadvantages.[9] Following Heinola et al. open repair with biological grafts gives higher midterm survival compared to other methods, probably because of the lower risk of reinfection.[17] All patients got antibiotic treatment, with variances in duration. In the literature there are no clear recommendations and durations vary from 4–6 weeks to lifelong.[8–10,27] The antibiotic treatment is influenced by the cultured micro-organism, type of surgical repair, and clinical, and biochemical status of the patient.[10] Hence treatment of MAA patients should be based individually and discussed in a multidisciplinary team with a vascular surgeon, infectious disease specialist and clinical microbiologist. This patient-tailored multi-disciplinary approach is also the recommended strategy according to the recently published study by Berard et al.[30]

This study has some limitations. The first limitation is the retrospective design, which causes a heterogenous group of patients with different diagnostic approaches and differences in treatment strategies. Another limitation is the relatively low number of patients and the lack of a comparative control group (i.e., noninfectious AAA). This reduces the strength of the results. However, MAA is a rare disease, so the results of this study are still useful for guiding future studies.

Conclusion

In the present study heterogeneity in presentation, diagnostic approaches, and surgical and antibiotic treatment was observed in MAA. This relatively large single-center cohort study contributes to the current knowledge on MAA by providing detailed information about diagnosis and treatment and highlights the importance of a multidisciplinary approach.

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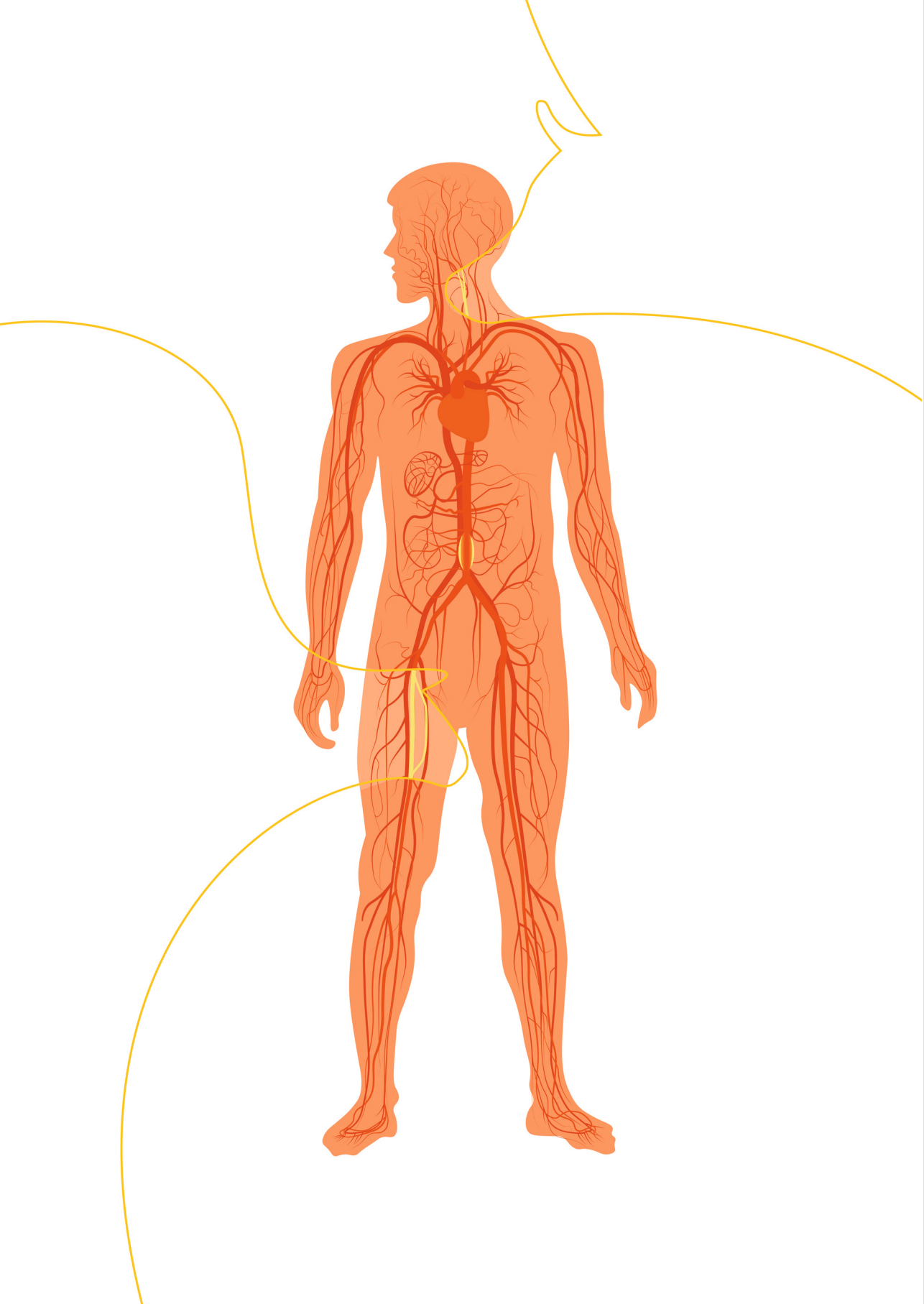

Chapter 3

Variability of [^{18}F]FDG-PET/LDCT reporting in vascular graft and endograft infection

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ABSTRACT

Objective

^{18}F-fluoro-D-deoxyglucose positron emission tomography with low dose and/or contrast enhanced computed tomography ([^{18}F]FDG-PET/CT)-scan reveals high sensitivity for the diagnosis of vascular graft and endograft infection (VGEI), but lower specificity. Reporting [^{18}F]FDG-PET/CT-scans of suspected VGEI is challenging, reader dependent, and reporting standards are lacking. The aim of this study was to evaluate variability of [^{18}F]FDG-PET/low dose CT (LDCT) reporting of suspected VGEI using a proposed standard reporting format.

Methods

A retrospective cohort study was conducted including all patients with a suspected VGEI (according to the MAGIC criteria) without need for urgent surgical treatment who underwent an additional [^{18}F]FDG-PET/LDCT scan between 2006 and 2022 at a tertiary referral centre. All [^{18}F]FDG-PET/LDCT reports were scored following pre-selected criteria that were formulated based on literature and experts in the field. The aim was to investigate the completeness of [^{18}F]FDG-PET/LDCT reports for diagnosing VGEI (proven according to the MAGIC criteria) and to evaluate if incompleteness of reports influenced the diagnostic accuracy.

Results

Hundred-fifty-two patients were included. Median diagnostic interval from the index vascular surgical procedure until [^{18}F]FDG-PET/LDCT scan was 35.5 (7.3–73.3) months. Grafts were in 65.1% located centrally and 34.9% peripherally. Based on the pre-selected reporting criteria, 45.7% of the reports included all items. The least frequently assessed criterion was FDG-uptake pattern (40.6%). Overall, [^{18}F]FDG-PET/LDCT showed a sensitivity of 91%, a specificity of 72%, and an accuracy of 88% when compared to the gold standard (diagnosed VGEI). Lower sensitivity and specificity in reports including ≤8 criteria compared to completely evaluated reports were found (83% and 50% vs. 92% and 77%, respectively).

Conclusion

Less than half of the [^{18}F]FDG-PET/LDCT reports of suspected VGEI met all pre-selected criteria. Incompleteness of reports led to lower sensitivity and specificity. Implementing a recommendation with specific criteria for VGEI reporting is needed in the VGEI-guideline update. This study provides a first recommendation for a concise and complete [^{18}F]FDG-PET/LDCT report in patients with suspected VGEI.

INTRODUCTION

Vascular graft and endograft infection (VGEI) is a major complication of vascular surgery and is associated with high morbidity and mortality.[1,2] The incidence of VGEI is difficult to assess, because the aetiology of this complication is complex and multifactorial including patient-related risk factors and pre-, intra-, and post-operative factors.[3] To improve early diagnosis and clinical outcomes, adequate treatment is important. However, diagnosis can be complicated due to the inability to take microbiological cultures because of a complex anatomical location or due to a subtle and non-specific clinical presentation.[4,5] VGEI can present early (within 4 months) or late (>4 months). Especially late VGEI can be challenging to diagnose due to lack of systemic signs of infection or elevated white blood cell count.[6]

In patients with a suspected VGEI, computed tomography angiography (CTA) is usually the preferred imaging modality to be performed.[6] However, nuclear medicine modalities may be needed to confirm the diagnosis and to analyse the extent and possible spread of the infection.[7] Literature has shown that ^{18}F-fluoro-D-deoxyglucose positron emission tomography with low dose and/or contrast enhanced computed tomography ([^{18}F]FDG-PET/CT) scan reveals a high sensitivity for the diagnosis of VGEI, but it should be performed preferably at least four months post-operative to avoid false positive findings.[3,5,7] False positive results can be caused by physiologic FDG-uptake due to a sterile inflammatory response after surgery.[5,7]

Reporting [^{18}F]FDG-PET/CT scans of suspected VGEI is challenging, reader dependent and report standards or interpretation criteria are still lacking. In contrast to VGEI, reporting standards on other specialities (e.g. oncology) are already available for a decade, are widely used and are known to improve clinical outcomes.[8–10] Interpretation of [^{18}F]FDG-PET/CT scans in VGEI patients can be performed in many ways: (1) visually, by uptake pattern (focal vs diffuse), uptake intensity, uptake outside vessel boundaries, uptake in regional lymph nodes, and/or (2) semi-quantitatively by SUV measurements, by comparison (ratios) with for example blood pool or liver. Different interpretation criteria exist, but no standardization of these criteria is accepted yet.[11,12] Therefore, the aim of this study was to evaluate variability of [^{18}F]FDG-PET/low dose CT (LDCT) reporting of suspected VGEI using a proposed standard reporting format based on findings in current literature and to evaluate if incompleteness of reports influenced the diagnostic accuracy.

MATERIAL AND METHODS

Subjects

All consecutive patients with a suspected VGEI who underwent a [^{18}F]FDG-PET/LDCT scan, at the University Medical Centre Groningen (UMCG) between September 2006 and September 2022 were included. Patients with an age below 18 years old were excluded.

Suspicion of VGEI was defined as undefined fever, localized clinical features of graft infection (e.g. erythema, swelling, warmth, pain and purulent discharge), elevated infectious variables in laboratory analysis (erythrocyte sedimentation rate, CRP and white blood cell count), undefined malaises, positive blood cultures and positive microbiology cultures in patients with previously implanted prosthetic grafts, as defined by the Management of Aortic Graft Infection (MAGIC) criteria.[13] Diagnosed VGEI according to the MAGIC criteria (VGEI was proven if there was at least one single major criterion and any other criterion from another category) was the gold standard.

The institutional review board approved dispensation in accordance with Dutch law on patient-based medical research obligations (registration no. METc 2022/453). Consequently, informed consent was not obtained. All patient-related data were processed anonymously and stored electronically in agreement with the Declaration of Helsinki – Ethical principles for medical research involving human subjects.[14]

Data extraction

Data were extracted from the electronic patient files (Epic Hyperspace®, Epic Systems Corporation). Suspected VGEI patients were identified through searches on intervention codes and International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes.

Patients' characteristics

Baseline patients characteristics included age (years) at time of [^{18}F]FDG-PET/LDCT, sex, body mass index (BMI), tobacco use, hypertension, hyperlipidaemia, and diabetes mellitus. The comorbidities were classified by the Society for Vascular Surgery (SVS) system (classes 0-3, for grading factor severity from absent to severe) according to the Ad Hoc Committee on Reporting Standards and were scored positive if the status was ≥ 1.[15]

Surgical procedure and [^{18}F]FDG-PET/LDCT scan

Vascular graft location was divided into central (aortoiliac position) or peripheral (other positions) and the surgical procedure into open repair and endovascular repair. The interval (months) between the index surgical procedure and the first [^{18}F]FDG-PET/LDCT in case of a suspected VGEI was calculated. Based on this interval the scan was labelled as early (≤4 months post-operative) or late (>4 months post-operative). Furthermore, the use of antibiotics at time of [^{18}F]FDG-PET/LDCT was noted.

VGEI treatment

The interval between the first [^{18}F]FDG-PET/LDCT scan and any surgical VGEI treatment (e.g. graft replacement) was calculated.

[^{18}F]FDG-PET-acquisition, image analysis and reporting assessment

[^{18}F]FDG-PET-scan imaging, whole body mode (i.e. from either the sole or halfway up the thigh to the crown of the head) was performed on two different PET/CT-scanners (Biograph Vision or mCT40, Siemens Healthineers, Erlangen, Germany). All scans were performed and reconstructed according to EANM guidelines.[9] Patients received FDG intravenously based on their weight (3 MBq kg-1), while fasted for at least six hours prior to scanning. All scans were performed 60 min after injection of ^{18}F-FDG. An additional continuous breathing low dose CT (80-120 kV, 20-35 mAs, and 5 mm slice thickness) was performed for attenuation correction and visualization of anatomical structures. Data was processed using standard software, applying an iterative reconstruction algorithm. For patients that received multiple [^{18}F]FDG-PET/LDCT scans during the diagnostic process, the first one was used as a baseline. The first scan was used to keep the influence of antibiotic treatment as small as possible and to create a homogenous cohort. All [^{18}F]FDG-PET/LDCT images have been analysed by a nuclear medicine physician. The original reports of the [^{18}F]FDG-PET/LDCT scans were used. The reporting nuclear physicians were noted and the years of experience during reporting were calculated.

All original [^{18}F]FDG-PET/LDCT reports were scored following pre-selected (by authors BS and RS) criteria (Table 1) that were formulated based on literature.[7–9,12] General criteria were based on the reporting guidance for [^{18}F]FDG-PET/CT imaging in oncology and included comparison to other diagnostic imaging modalities (if available), area of interest (i.e. total or part of the prosthesis involved, specific part described), uptake intensity (i.e. 1. uptake similar to the background; 2, low uptake, comparable with inactive muscles and fat; 3, moderate uptake, higher than the uptake in group 2, but distinctly less than physiologic uptake by the bladder; 4, strong uptake, comparable to the uptake in the bladder.), demarcation (i.e. which vessel, what side), comparison to physiological distribution (i.e. liver, spleen, digestive tract, ureters, and bladder), and body compartments.[11] Specific criteria for VGEI-related complications regarding inflammation and infection included locoregional involvement (e.g. lymph nodes, abscess, soft tissue induration), organ involvement (e.g. enteric fistula), prosthesis involvement (i.e. prosthesis involved or only the surrounding area), and uptake pattern (i.e. heterogenous, diffuse, linear, homogenous, focal, and/or patchy).[7–9,12]

Table 1. [^{18}F]FDG-PET/LDCT report characteristics

Criteria
Diagnostic imaging comparison (*with other imaging modalities if available*)
Locoregional involvement *(lymph nodes, abscess, soft tissue)*
Area of interest
Uptake intensity *(uptake similar to background, low, moderate, strong)*
Organ involvement *(i.e. enteric fistula)*
Demarcation *(which vessels affected, what side etc.)*
Physiologic distribution
Prosthesis involvement
Body compartments *(head/neck, thorax, abdomen/pelvis, musculoskeletal)*
Uptake pattern *(heterogenous, diffuse, linear, homogenous, focal, patchy)*

All original reports (written by nuclear physicians) were assessed and scored on assigned criteria by the first two authors (SL and DL). Consecutively, the scored reports were re-checked by an experienced nuclear medicine physician (RS) in case of uncertainties. The predefined (both general and specific) criteria were scored in three categories, consisting of 1. Equivocal: the criterion was evaluated by the nuclear medicine physician, but not interpreted (i.e. when images assessed using the specific criterion were not clearly suggestive or not suggestive for VGEI), 2. Evaluated: the criterion was evaluated and interpreted (i.e. when the application of the specific criterion allowed proper scoring of VGEI or normal findings), 3. Non-evaluated: the criterion was not evaluated (i.e. when the specific criterion was not used for the imaging interpretation).

[^{18}F]FDG-PET/LDCT conclusions and diagnosis

In order to investigate the level of agreement between the [^{18}F]FDG-PET/LDCT conclusions and diagnosis, the conclusions of the reports were scored according to three categories; 0 if the imaging was equivocal (nuclear physician not being able to diagnose or rule out VGEI) for VGEI; 1, meaning the nuclear physician concluded that the [^{18}F]FDG-PET/LDCT scan was positive for a VGEI; and 2, meaning the nuclear physician concluded that the [^{18}F]FDG-PET/LDCT scan was negative for a VGEI. The final diagnosis of VGEI was proven or rejected according to the MAGIC criteria (VGEI was proven if there was at least one single major criterion and any other criterion from another category).[13] Each MAGIC category (i.e. clinical and surgical, radiology, and laboratory) was scored (major, minor, or negative). Sensitivity, specificity, and accuracy were calculated for the total group and for subgroups (i.e. equivocal, positive, or negative conclusion), including completely evaluated reports (10 criteria evaluated) and less evaluated reports (≤8 criteria evaluated). These cut-off points were chosen to compare two groups with a sufficient number of reports and optimal separation between high and low scores (exclusion of scans with a score of 9 criteria).

Statistical analysis

Normal distributed continuous variables were reported as mean ± standard deviation and variables with a skewed distribution were reported as median and interquartile range (written as 25th percentile – 75th percentile). The distribution of continuous variables was checked visually using histograms and supplemented by the Shapiro-Wilk test. Categorical variables were presented as numbers with accompanying percentages. To compare the conclusion of the [^{18}F]FDG-PET/LDCT with the diagnosis of VGEI based on the MAGIC criteria, Cohen's Kappa (non-weighted), sensitivity, and specificity were calculated. Levels of agreement for Cohen's Kappa were; <0, poor; 0.01-0.20, slight; 0.21-0.40, fair; 0.41-0.60 moderate; 0.61-0.80, substantial; and 0.81-1.00, almost perfect. Statistical significance was set at *alpha* < .05. Statistical analyses were performed using SPSS (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp).

RESULTS

Patient characteristics

In total, 152 patients with the suspicion of VGEI underwent a [^{18}F]FDG-PET/LDCT scan and were included in this study. The mean age of the total group was 68.6 ± 8.8 years and 84.9% were male. Fifty-eight (38.2%) patients were current smokers, 84 (55.3%) patients had hypertension, 56 (36.8%) had hyperlipidaemia, and 39 (25.7%) had diabetes mellitus (Table 2).

Table 2. Patient characteristics

Patient Characteristics	N (%) or mean ± SD
Number of patients	152
Age in years	68.6 ± 8.8
Sex (males)	129 (84.9)
BMI in kg/m^2	26.0 ± 4.7
Tobacco use	58 (38.2)
Hypertension	84 (55.3)
Hyperlipidemia	56 (36.8)
Diabetes mellitus	39 (25.7)

Abbreviations: N=number, SD=standard deviation, BMI= body mass index, kg=kilogram, m=meter.

Index surgical procedure and [^{18}F]FDG-PET/CT reporting

Sixty-five percent (n=99) of the patients received a central graft at the index procedure and the remaining patients a peripheral graft (n=53, 34.9%). Seventy-two percent (n=109) underwent open surgical repair (n=104 synthetic prostheses, n=2 bovine peri-

cardial prostheses, n=2 Omniflow® II biosynthetic grafts, and n=1 autologous venous reconstruction) and 28.3% (n=43) endovascular (all synthetic endografts). The median interval from index surgery until [^{18}F]FDG-PET/LDCT scan was 35.5 (7.3-73.3) months, with 82.2% (n=125) of the scans defined as late. Forty percent (n=60) of the patients received antibiotic therapy at the time of the [^{18}F]FDG-PET/LDCT scan. Over the whole study period, in total 12 different nuclear medicine physicians were involved in the reporting. The nuclear medicine physicians had median 8 (3-15) years of experience at time of reporting the scans and analyzed with a median of 12.5 (1.3-19.3) [^{18}F]FDG-PET/LDCT scans in patients with a suspicion of VGEI.

Evaluation of [^{18}F]FDG PET/CT criteria

Fourteen [^{18}F]FDG-PET/LDCT reports from external hospitals were not available for scoring and were excluded from this part of the analysis (only the conclusion was present). In Table 3 an overview of the pre-selected criteria is shown. In total, 63 (45.7%) [^{18}F]FDG-PET/LDCT reports had 100% score, meaning that all pre-selected criteria were evaluated. Diagnostic imaging comparison was the most often evaluated criterion in 100% of the reports. This criterion was followed by locoregional involvement (99.3% evaluated), region of interest (98.6% evaluated), and uptake intensity (97.8% evaluated). FDG-uptake pattern was the least evaluated criterion (59.4%).

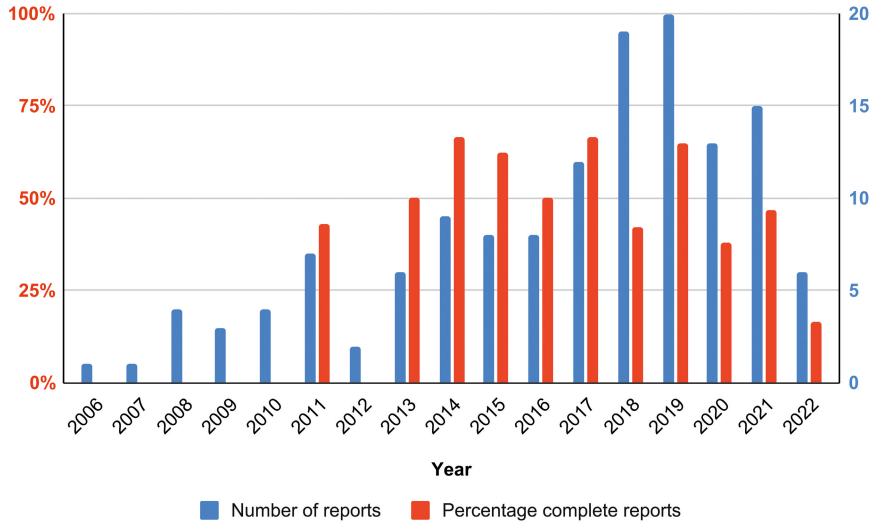
Table 3. Evaluated [^{18}F]FDG-PET/LDCT criteria

Characteristics (N=138)[a]	**Equivocal** N (%)	**Evaluated** N (%)	**Non-evaluated** N (%)
Diagnostic imaging comparison	0 (0)	138 (100)	0 (0)
Locoregional involvement	0 (0)	137 (99.3)	1 (0.7)
Area of interest	0 (0)	136 (98.6)	2 (1.4)
Uptake intensity	0 (0)	135 (97.8)	3 (2.2)
Organ involvement	0 (0)	134 (97.1)	4 (2.9)
Demarcation	1 (0.7)	130 (94.2)	7 (5.1)
Physiologic distribution	0 (0)	129 (93.5)	9 (6.5)
Prothesis involvement	14 (10.1)	122 (88.4)	2 (1.4)
Body compartments	0 (0)	121 (87.7)	17 (12.3)
FDG uptake pattern	0 (0)	82 (59.4)	56 (40.6)

[a]14 scans were from external hospitals, therefore the report was missing.

A positive trend over the years was observed in number of [^{18}F]FDG-PET/LDCT reports for suspected VGEI, see Figure 1. Furthermore, the percentage of reports in which all criteria were evaluated is shown, and fluctuated per year (Figure 1). The highest percentages of complete reports (66.7%) were observed in 2014 and 2017.

Figure 1. Number of [^{18}F]FDG-PET/LDCT reports for suspected vascular graft and endograft infection and percentage of reports in which all criteria were evaluated over the years



Definitive diagnosis of VGEI

In total, 123 (80.9%) patients were diagnosed with VGEI according to the MAGIC criteria. The clinical and surgical MAGIC category scored major in 70 (56.9%) patients, minor in 13 (10.6%) patients, and negative in 40 (32.5%) patients. In the radiology MAGIC category, 55 (44.7%) patients scored major, 60 (48.8%) scored minor, and 8 (6.5%) scored negative. In the laboratory category, 83 (66.7%) scored major, and 41 (33.3%) scored minor. Eighty-nine (81.7%) patients with an open graft got the diagnosis VGEI and 34 (79.1%) patients with an endovascular graft (p=0.819). In patients with a diagnosed VGEI, the most common VGEI specific characteristic was soft tissue induration (n=46, 37.4%), followed by 22 (17.9%) patients with an abscess, 18 (14.6%) patients with positive FDG-uptake in peri-prosthetic lymph nodes, and 17 (13.8%) patients with a fistula. The [^{18}F]FDG-PET/LDCT conclusions and definitive diagnosis (based on the MAGIC criteria) are shown in Table 4. This resulted in a Cohen's Kappa of 0.64 (moderate agreement). In total, 9 (5.9%) reports had an equivocal conclusion, 116 (76.3%) reports had a positive conclusion (i.e. suspected VGEI), and 27 (17.8%) reports a negative conclusion (i.e. not suspected VGEI). When adding the equivocal [^{18}F]FDG-PET/LDCT conclusions to the false positives or false negatives, the general performance of [^{18}F]FDG-PET/LDCT for the detection of VGEI resulted in a sensitivity of 91%, a specificity of 72%, and an accuracy of 88%. In the false-negative group, 5 (83.3%) patients were on antibiotic therapy at time of the [^{18}F]FDG-PET/LDCT scan. When evaluating the diagnostic value of [^{18}F]FDG-PET/LDCT reports with lowest number of criteria evaluated (≤8 evaluated criteria, n=26) and reports with the highest number of criteria evaluated (all criteria evaluated, n=63), a

sensitivity of 83%, a specificity of 50%, and an accuracy of 73% were observed for the less evaluated reports and a sensitivity of 92%, a specificity of 77%, and an accuracy of 89% were observed for the completely evaluated reports. In the completely evaluated group, there were no equivocal [^{18}F]FDG-PET/LDCT conclusions noted and in the less evaluated group five equivocal conclusions were present.

Table 4. [^{18}F]FDG-PET/LDCT conclusions and definite diagnosis according to the MAGIC criteria

		Diagnosis VGEI (MAGIC[a])		
		Proven	*Rejected*	*Total*
[^{18}F]FDG-PET/LDCT conclusion	*Equivocal*	5	4	9
	Positive	112	4	116
	Negative	6	21	27
Total		123	29	152

Abbreviations: [^{18}F]FDG-PET/CT= 2-deoxy-2-[^{18}F]fluoro-D-glucose-positron emission tomography and low dose computed tomography, VGEI=vascular graft and endograft infection, MAGIC=Management of Aortic Graft Infection.
[a]At least one single major criterion and at least one minor criterion from another category. Sensitivity: 91%, specificity: 72%.

VGEI treatment

Eighty-six (69.9%) of the 123 patients with a diagnosed (according to the MAGIC criteria) VGEI underwent surgical treatment in addition to antibiotic therapy. From the (diagnosed VGEI) patients who underwent surgical treatment, 80 (93.0%) patients got intraoperative tissue or graft cultures of which 66 (82.5%) were positive. In 41 (62.2%) patients the culture result was polymicrobial, in 23 (34.8%) patients it was monomicrobial, and in two (3.0%) patients the culture results were positive, but the microorganism was missing. The other patients were treated with antibiotics alone. The latter group of patients were often not fit enough to underwent surgical repair or were clinically stable with antibiotic suppression therapy. The median interval from [^{18}F]FDG-PET/LDCT scan to surgical VGEI treatment was 27.5 (7.0-90.5) days.

DISCUSSION

In this retrospective study, we assessed the completeness of [^{18}F]FDG-PET/LDCT reports of suspected VGEI patients based on ten predefined criteria as reported in current literature. Less than half of all [^{18}F]FDG-PET/CT reports contained all criteria. The least frequently assessed criterion was the pattern of [^{18}F]FDG-uptake, despite its critical significance to determine the diagnosis of VGEI.[12] A sensitivity of 91%, and specificity of 72% were found in the overall cohort, which is comparable with the existing literature.[3,5,7,16] Furthermore, a higher sensitivity and specificity in fully evaluated reports compared to reports using fewer evaluation criteria were observed. This is an important

finding since it demonstrates the additional value of striving for standardized reporting including all predefined criteria to increase the diagnostic accuracy. Accordingly, standardized and complete reports should be recommended in the new guidelines for patients with suspected VGEI.

The importance of the uptake pattern has been already addressed when [^{18}F]FDG-PET/LDCT or [^{18}F]FDG-PET/CTA are used in other clinical situations, such as in the diagnosis of infectious endocarditis and in patients with suspected infections after a Bentall procedure.[17,18] In these settings careful assessment of the presence of persistent host versus biomaterial coating reaction, the sewing ring of the valve, chronic tension, or friction exerted on anchor points as well as of all the factors affecting the intensity of [^{18}F]FDG uptake (i.e. time elapse from surgery, surgical and post-surgical complications, ongoing antimicrobial treatment, specific strains) has been demonstrated of fundamental to maintain high specificity when using [^{18}F]FDG.[19] If the proper protocol for patients' preparation and imaging acquisition are followed and specific imaging interpretation criteria are used sensitivity and specificity can reach 91% in case of infective endocarditis and 97% and 73% in case of Bentall procedures.[17,18]

The presence of para-physiologic, [^{18}F]FDG-uptake along the wall of the vascular grafts representing reactive granulomatosis is often visible and validated semi-quantitative SUV cut-off points are lacking. Therefore, describing the uptake pattern remains of utmost importance.[7,16,20] The uptake pattern has a comparable sensitivity, but a significant higher specificity compared to the common description of the intensity of [^{18}F]FDG-uptake against the SUVmax or tissue-to-background ratio (TBR).[16,21] Indeed, focal or heterogeneous uptake along the vessel is a hallmark of VGEI as compared to linear, diffuse, and homogenous uptake which does in general not represent infection.[11,22,23] Therefore, to increase the diagnostic accuracy of [^{18}F]FDG-PET/LDCT in VGEI, it is necessary to provide a combination of visual uptake pattern with [^{18}F]FDG-uptake intensity.[7] The some less frequently observed criterion of [^{18}F]FDG-uptake pattern in the current study is maybe due to dated reports with less attention to uptake patterns in VGEI. The [^{18}F]FDG-uptake intensity in our cohort was scored using a four-point scale which has been validated in our centre, used for several years, and has been recommended in previously published literature.[7] Recently, in 2015, Sah et al. proposed a new scoring method that consists of a five-point scale.[24] In the future, researchers in the field of [^{18}F]FDG-PET should be aware of this and a comparison should be made between these two scoring methods.

A recently published study has shown that the presence of positive (defined as follows: visual uptake of grade two or four and/or a short axis diameter >10 mm on LDCT) locoregional lymph nodes on [^{18}F]FDG-PET/CT imaging has a high specificity (96%) and positive predictive value (95%) for VGEI.[25] However, these findings were accompanied by a low sensitivity. Therefore, the positive locoregional lymph nodes could have a

positive influence on the specificity of new interpretation criteria. The current study corroborates to the conclusion that further research is needed to evaluate the diagnostic accuracy of lymph nodes for detecting and diagnosing VGEI, as positive lymph nodes in the area surrounding the vascular graft were observed in only 14.6% of the patients with a diagnosed VGEI.

In the first half of the study period an increase in both numbers of reports and percentages of completely evaluated reports was noted. The decrease that was observed from 2020 was probably due to the COVID-19 pandemic which resulted in lower patient admissions. The increase of number of reports might be due to the fact that over time there was more knowledge about the value of [^{18}F]FDG-PET/LDCT in the diagnosis of infection. In 2011, the first report that met all criteria was observed. In this year, the Department of Nuclear Medicine at the UMCG implemented a systematic method of reporting according to body compartments. The increased percentage of completely evaluated reports over the years could be caused by developments in imaging modalities and/or due to the introduction of multidisciplinary consultation (including a vascular surgeon, a microbiologist, an infectiologist, a radiologist, and a nuclear medicine physician) of VGEI patients. Another explanation could be an increased knowledge on patterns that can be observed on [^{18}F]FDG-PET/LDCT. Despite the fact that there is a slight upward trend in reporting VGEI, <50% of the reports contained all criteria, while the report is often the only way of communication between the nuclear medicine physician and the clinician (in this case, the vascular surgeon).[26] This indicates that there is a strong need to improve the reporting, including a more systematic reporting approach with standardized interpretation criteria. As described earlier by the European Association of Nuclear Medicine and the European Association of Cardiovascular imaging, it is crucial that the referring clinician understands the report as intended by the nuclear medicine physician, as this approach is already more common in conventional nuclear cardiology[27], and in PET/CT applications in oncology.[8–10,28] Reporting of several [^{18}F]FDG-PET/CT-applications in cardiovascular diseases are less well addressed, as in the current situation with VGEI, but also in other infections and inflammatory diseases, such as (infective) endocarditis, infection of cardiac implantable electronic devices, large vessel vasculitis, and polymyalgia rheumatica.[29,30] Although interpretation for several inflammatory-, infective- infiltrative- and device related diseases is described, specific and user-friendly recommendations on reporting are often incomplete.[31] As highlighted now for VGEI, recommendations on reporting with standardized interpretation criteria should be compiled for these missing parts of [^{18}F]FDG-PET/CT-applications in cardiovascular diseases. An example of user-friendly, standardized reporting standards for nuclear imaging on cardiac amyloidosis are published by Dorbala et al.[32,33] It is recommended to write the report clearly and as simple as possible, with a limited number of abbreviations, with quantified data instead of qualitative (e.g. small, large, slightly) descriptions (if possible), and with less as possible defensive expressions (e.g. cannot be excluded).[27]

Hundred-twenty-three (80.9%) out of 152 patients were diagnosed with VGEI. This high proportion is due to the fact that CTA is still the gold standard imaging modality in suspected VGEI.[3] An [^{18}F]FDG-PET/LDCT scan was performed subsequently to confirm the diagnosis and/or to evaluate the extent of the infection. As a consequence, there is a selection bias with a high prevalence of VGEI in this suspected VGEI cohort. Almost three-quarter of the patients in our cohort got a graft infection after an open surgical procedure, most likely explained by an overall higher incidence after open surgical repair compared to endovascular repair. For open aortic repair the incidence is up to 4.5% versus 0.3-1.0% for endovascular aortic repair.[34] One of the reasons for this difference is the large, longer lasting surgical wound in open procedures.

Based on the results of the current study and according to available literature (VGEI specific and [^{18}F]FDG-PET/CT broad), we provide a first recommendation for a concise and complete [^{18}F]FDG-PET/LDCT report for VGEI (Figure 2).[7–9,12,31–33]

Figure 2. Recommendation for a concise and complete [^{18}F]FDG-PET/LDCT report for vascular graft and endograft infection

Clinical information/question: [*Lab (CRP, BSE), fever?, antibiotics & time period, type of vascular graft, when implanted, VGEI?*]

Imaging procedure:
[*[^{18}F]FDG-PET-scan, including Low Dose CT, performed according to standardized protocol after intravenous admission of radiopharmaceutical*]
Scanned area: […]
SUVmax according EARL and correction for glucose-levels.
Glucose (mmol/L):
Scanning time per bed position (min):
[*Date*] [*value*]

Administered medication:
F-18 fluorodeoxyglucose (FDG) injection [*x*] MBq, total administration: [*x*] MBq ([*x dosis*])

Result of the diagnostics:
Previous diagnostics: compared to [*previous diagnostic*]/ No previous (relevant) scan
Quality of scan: [*Good/moderate/low*]

Head/neck:
[*Any relevant findings*] Furthermore normal physiologic distribution, no indications for other pathology.

Thorax:
[*Any relevant findings*] Furthermore normal physiologic distribution, no indications for other pathology.

Abdomen/pelvis:
[*Any relevant findings*] Furthermore no indications for other pathology. Normal homogeneous uptake in the liver and spleen. Physiologic excretion via digestive tract. Physiologic excretion via kidneys, ureters and bladder.

Musculoskeletal:
[*Any relevant findings*] Furthermore normal physiologic distribution, no indications for other pathology.

Vascular:
Status after [*vascular graft type*], [*normal/mildly increased/moderately increased/strongly increased*] [*homogeneous/diffuse/linear/heterogeneous/focal/patchy*] FDG-uptake at [*location(s) on graft/entire graft/vessel*], starting on [*right/left/both side(s)*] from [*starting point*] till [*end point*]. Increased uptake is located [*in soft tissue/along graft*]. [*presence of soft tissue induration/lymph nodes/abscess/fistula + location*]. [*Any other relevant vascular findings*].

PET-scan conclusion:
[*Not suspected/suspected*] [*Graft type*] infection of [*location(s)*], with [*presence of soft tissue induration/lymph nodes/abscess/fistula + location*].
[*Any other relevant findings*]

Standardization of nuclear medicine reporting in the wide field of cardiovascular diseases should follow as well and this proposed reporting standard can serve as format for new reporting standards on other cardiovascular diseases, such as infective native aortic aneurysm, where there is a potential role of and value in performing a [^{18}F]FDG-PET/LDCT, but a lack of studies in the field.[35]

Limitations

This study has some limitations. The first limitation is the retrospective nature, which causes a lower level of evidence compared to other study designs. However, the original [^{18}F]FDG-PET/LDCT reports had been used, which were prospectively analysed by the nuclear medicine physician. Furthermore, a limitation of this study is the use of the MAGIC criteria, since these criteria are originally validated for aortic graft infection instead of peripheral graft infection.[13] The MAGIC criteria were later found to be useful as well for peripheral grafts.[36] However, the specificity was lower compared to central grafts.[36] Another limitation is the heterogeneity of the patients with different grades of infection, types of surgery, graft locations, and graft materials. Another limitation is that 27 (17.8%) patients had an early [^{18}F]FDG-PET/LDCT scan (<4 months), while a previously published study has shown that scans in the early postoperative phase may have a high false positive rate.[7] More than half of the patients used antibiotics during the time of their [^{18}F]FDG-PET/LDCT scan and in the false-negative group even 83.3% used antibiotics during the scan. This may have resulted in an underestimation of the prevalence of VGEI specific characteristics, because antibiotic therapy can induce a decrease in metabolic activity of the infection.[24] This decrease might have increased the number of false negative reports, which can lead to undertreatment of VGEI patients.

Conclusions

In this study, <50% of the [^{18}F]FDG-PET/LDCT reports of patients with a suspected VGEI met the predefined criteria for being complete. This led to a lower sensitivity and specificity in comparison with complete reports. Implementing a specific recommendation for VGEI reporting is therefore needed in a next VGEI guideline update.[7] Based on the results of the current study and accompanying literature, we provided a first recommendation for a concise and complete [^{18}F]FDG-PET/LDCT report for VGEI. Standardization of [^{18}F]FDG-PET/LDCT reporting is warranted to improve accuracy, and to reduce heterogeneity between different medical centres and to allow comparison between studies.

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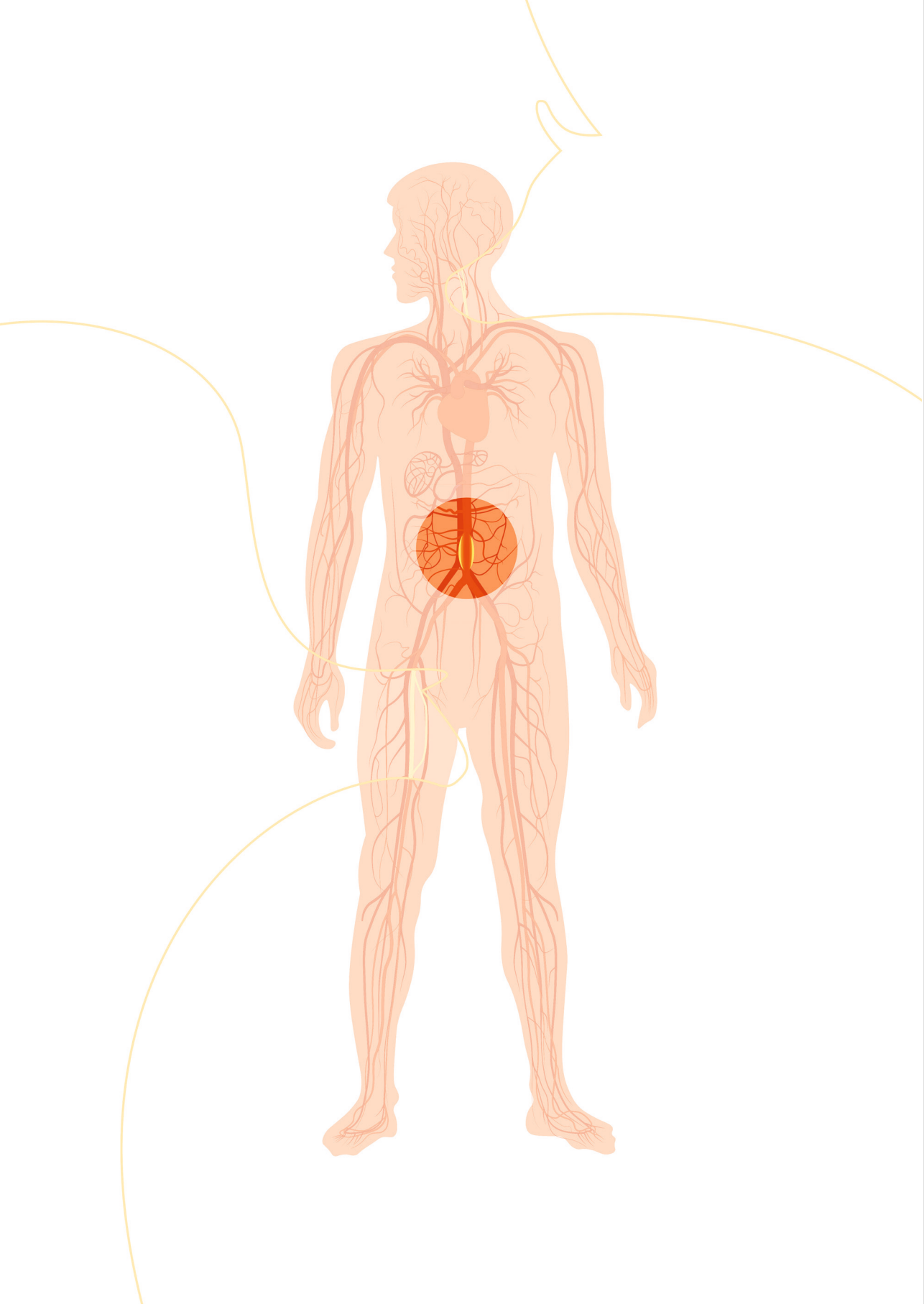

Chapter 4

Abdominal pain in a man with an endovascular aortic prosthesis

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ABSTRACT

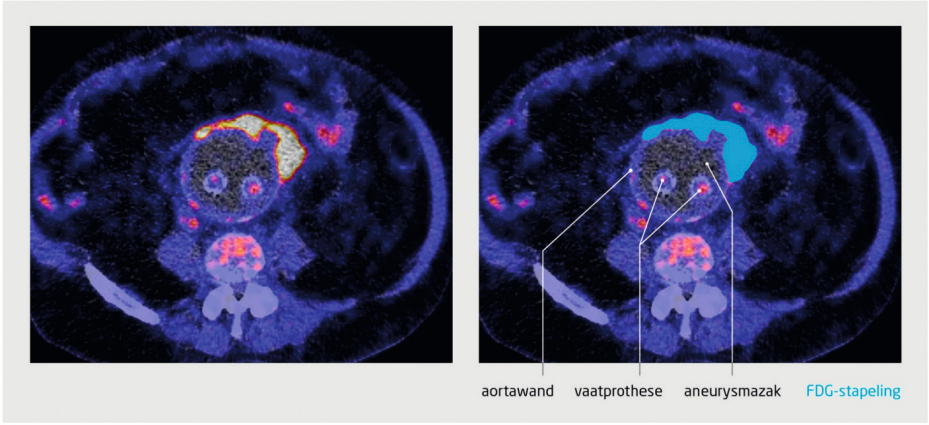
A 79-year-old man with an abdominal aorta aneurysm (AAA) with endovascular repair presented with abdominal pain and inflammation. Although the initial work-up was in favor of an idiopathic inflammatory AAA, FDG-PET imaging showed atypical irregular uptake. Per-operative assessment and culture of pus matter revealed infection by *Listeria monocytogenes*. Atypical findings on imaging of aortic wall inflammation should alarm the clinician of an infectious etiology.

CASUS (NEDERLANDS)

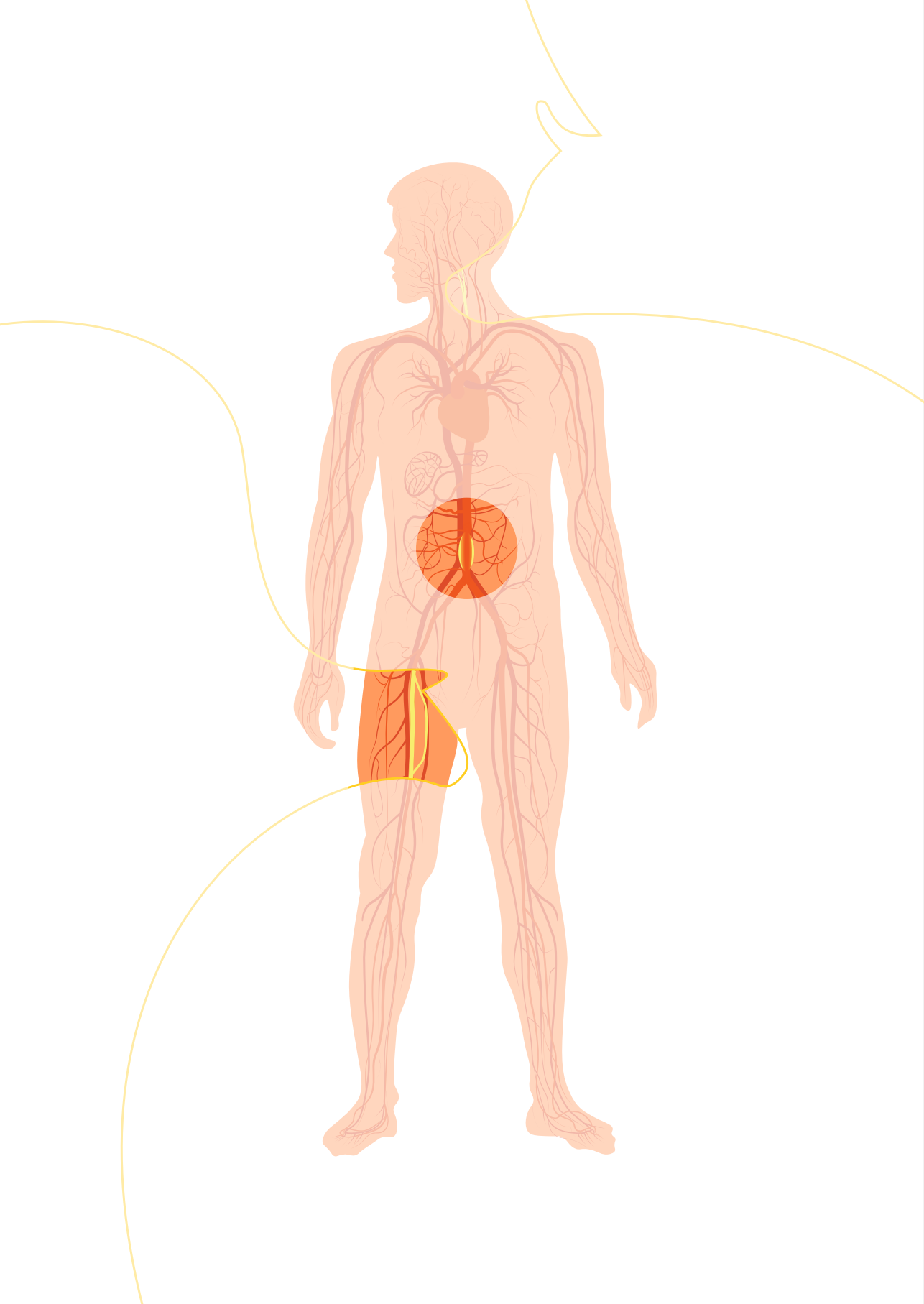
Een 79-jarige man die een endovasculaire behandeling had ondergaan wegens een aneurysma van de abdominale aorta (AAA), werd 3 jaar na deze operatie door de huisarts verwezen naar de internist, omdat hij buikpijn en verhoogde ontstekingswaarden had. De gebruikelijke diagnostiek bracht geen oorzaak aan het licht. Op een aanvullende FDG-PET-CT-scan werd inflammatie van de abdominale aortawand gezien. Uitgebreide diagnostiek, waaronder bloedkweken met een negatieve uitslag, maakte de diagnose 'infectie' niet aannemelijk. Punctie van de aneurysmazak was risicovol vanwege suboptimale aanhechting van de endoprothese en werd daarom achterwege gelaten. Met de werkdiagnose 'inflammatoir AAA' kreeg de patiënt prednisolon en later methotrexaat voorgeschreven, waarop hij een goede respons vertoonde. Na 2 jaar kreeg hij echter last van algehele malaise en steeg de CRP-waarde. De FDG-PET-CT-scan liet toen heterogene, intense FDG-stapelingen zien rond het AAA, met toename van de intensiteit aan de voorzijde van de aortawand ten opzichte van 2 jaar daarvoor (figuur). Ook CT-angiografie toonde een peri-aortale asymmetrische verdichting aan de voorzijde van de oorspronkelijke aortawand. Deze asymmetrische, irregulaire uitbreiding van peri-aortale inflammatie is atypisch voor een inflammatoir AAA en suggestief voor infectie. De prothese werd vervangen door een bioprothese; peroperatief werd pus in de aneurysmazak gezien, wat past bij een prothese-infectie. In puskweken werd *Listeria monocytogenes* aangetoond. Wij behandelden de patiënt met amoxicilline/gentamycine en 2 weken na de operatie werd hij naar huis ontslagen.

Inflammatie van de aortawand is meestal niet infectieus van aard. Als beeldvormend onderzoek na een vaatreconstructie echter kenmerken vertoont die atypisch zijn voor een inflammatoire AAA, moet een infectie overwogen worden, zelfs als de uitslag van de bloedkweken negatief is en er onvoldoende klinische argumenten zijn voor een infectie.

Figuur. **FDG-PET-CT-scan** (transversale coupe ter hoogte van de aortabifurcatie) van een patiënt met buikpijn bij wie 3 jaar geleden een endovasculaire prothese was geplaatst in een aneurysma van de abdominale aorta. Op deze scan zijn de poten van de vaatprothese te zien. De intensiteit van de FDG-stapelingen rond de aorta is toegenomen ten opzichte van een FDG-PET-CT-scan die 2 jaar eerder was gemaakt. Deze PET-kenmerken kunnen passen bij een infectie van de aortawand. Gezien de locatie zou ook de prothese geïnfecteerd kunnen zijn, al lijkt de FDG-activiteit rond de poten van de prothese laag.



Diagnose: infectie van een vaatprothese



Chapter 5

Use of Omniflow® II biosynthetic graft for the treatment of vascular graft and endograft infections

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ABSTRACT

Objectives

Vascular graft/endograft infection is a rare but life-threatening complication of cardiovascular surgery and remains a surgical challenge. Several different graft materials are available for the treatment of vascular graft/endograft infection, each having its own advantages and disadvantages. Biosynthetic vascular grafts have shown low reinfection rates and could be a potential second best after autologous veins in the treatment of vascular graft/endograft infection. Therefore, the aim of our study was to evaluate the efficacy and morbidity of Omniflow® II for the treatment of vascular graft/endograft infection.

Methods

A multicenter retrospective cohort study was performed to evaluate the use of Omniflow® II in the abdominal and peripheral region to treat vascular graft/endograft infection between January 2014 and December 2021. Primary outcome was recurrent vascular graft infection. Secondary outcomes included primary patency, primary assisted patency, secondary patency, all-cause mortality, and major amputation.

Results

Fifty-two patients were included with a median follow-up duration of 26.5 (10.8-54.8) months. Nine (17%) grafts were implanted in intracavitary position and 43 (83%) in peripheral position. Most grafts were used as femoral interposition (n=12, 23%), femoro-femoral crossover (n=10, 19%), femoro-popliteal (n=8, 15%), and aorto-bifemoral (n=8, 15%) graft. Fifteen (29%) grafts were implanted extra-anatomically and 37 (71%) in situ. Eight patients (15%) presented with reinfection during follow-up, most of these patients received an aorto-bifemoral graft (n=3, 38%). Intracavitary vascular grafting had a 33% (n=3) reinfection rate and peripheral grafting 12% (n=5; p=0.025). The estimated primary patencies at 1, 2, and 3 years were 75%, 72%, and 72% for peripherally located grafts and 58% (at all timepoints) for intracavitary grafts (p=0.815). Secondary patencies at 1, 2, and 3 years were 77% (at all timepoints) for peripherally located prostheses and 75% (at all timepoints) for intracavitary prostheses (p=0.731). A significantly higher mortality during follow-up was observed in patients who received a intracavitary graft compared to patients with a peripheral graft (p=0.003).

Conclusions

This study highlights the efficacy and safety of the Omniflow® II biosynthetic prosthesis for the treatment of vascular graft/endograft infection, in absence of suitable venous material, with acceptable reinfection, patency, and freedom of amputation prevalences, especially in replacing peripheral vascular graft/endograft infection. However, a control group with either venous reconstruction or another alternative graft is needed to make firmer conclusions.

INTRODUCTION

Vascular graft and endograft infection (VGEI) is a rare but life-threatening complication of cardiovascular surgery. It remains a surgical challenge due to a significant risk of recurrent infection with associated high morbidity and mortality.[1,2] Removal of the infected vascular graft material, extensive debridement, in situ reconstruction with infection resistant material, and (targeted) antibiotics is the first choice treatment of vascular graft infection.[1] Several graft materials are available for the treatment of VGEI including autologous veins, cryopreserved allografts, synthetic grafts, biological xenografts, and biosynthetic materials, such as Omniflow® II prosthesis. Each of these materials has its own set of advantages and disadvantages. Autologous veins are commonly used because of their moderate resistance to reinfection and desirable patency.[3,4] However, veins are not always of suitable size or quality, nor readily available in emergency setting. The main advantage of cryopreserved allografts is that they have a lower infection rate than synthetic prostheses. Nevertheless, long-term outcomes are suboptimal with allograft degeneration and high reintervention rates.[5,6] The major benefit of synthetic grafts is that they are readily available. The main drawback of these grafts is the presumed higher reinfection rates compared to venous material and cryopreserved allografts.[1] Biosynthetic grafts have shown good late graft patency and low postoperative infection rates when used as elective bypass material.[7–9] Low infection rates could make biosynthetic grafts a potential alternative in the treatment of VGEI in the absence of autologous material. However, literature on biosynthetic prostheses in the treatment of VGEI in the abdominal and peripheral region is scarce.[7,10,11] In 2012, Töpel et al. found that biosynthetic grafts seem to be a possible alternative to venous reconstruction to replace infected infrainguinal grafts.[10] This conclusion was based on seven patients only. More recently, in 2022, Caradu et al. published acceptable results of using Omniflow® II in a septic context (including VGEI) when autologous veins were unavailable.[11] Although the results were promising, their cohort only consisted of 29 patients. Therefore, the aim of this study was to evaluate the efficacy and morbidity of Omniflow® II as a treatment for VGEI in the absence of venous material in five high-volume vascular surgery centers in the Netherlands.

METHODS

Study design

All consecutive patients who underwent treatment for abdominal aortic and peripheral VGEI using an Omniflow® II graft between January 2014 and December 2021 at five hospitals in the Netherlands (University Medical Center Groningen, Leiden University Medical Center, Zuyderland Medical Center, Albert Schweitzer Hospital, and Meander Medical Center) were included in this study. VGEI was defined according the Management of Aortic Graft Infection Collaboration (MAGIC) criteria.[12]

The Institutional Review Board approved dispensation in accordance with Dutch law on patient-based medical research obligations (registration no. METc 2021/494). Therefore, informed consent was not required. Local approval at each medical center was obtained. All patient related data were processed anonymously and stored electronically in agreement with the Declaration of Helsinki – Ethical principles for medical research involving human subjects.[13]

Patient characteristics and definitions

Baseline characteristics were obtained from the electronic patient file including age at time of surgery, sex, body mass index (BMI), tobacco use, hypertension, dyslipidemia, diabetes mellitus (type I or II), and cardiac-, pulmonary-, and renal disease. Tobacco use was defined as current use or less than one year of abstinence. Hypertension, dyslipidemia, cardiac-, pulmonary-, and renal disease were classified by the Society for Vascular Surgery (SVS) system (class 0-3) according to the Ad Hoc Committee on Reporting Standard.[14] These comorbidities were scored positive if the status was ≥1. American Society of Anesthesiologists (ASA) scores were noted.[15] Furthermore, preoperative characteristics, intraoperative characteristics, and postoperative (short-term adverse events, <30 day) outcomes were collected. The short-term (<30 days postoperative) adverse events included graft occlusion, (all-cause) mortality, wound infection, transient ischemic attack or cerebrovascular accident, urinary tract infection, cardiac complications (defined as myocardial infarction, angina pectoris, arrhythmia, or congestive heart failure), delirium, and hematoma (requiring surgical evacuation or arterial repair).

Technical aspects

The Omniflow® II vascular prosthesis (LeMaitre Vascular, Inc., 63 Second Avenue Burlington, MA 01803 USA) is a denatured ovine collagen prosthesis.[16] It is made of a grown ovine collagen tube that is induced by subcutaneously implanting a polyester mesh endoskeleton into a sheep. Prior to usage, a specific rinsing procedure is performed, as prescribed by the manufacturer.[16] Manipulation of the graft was minimized. In case of intracavitary positioning (aortic, aorto-bifemoral, or aorto-biiliac), a (bifurcated) bypass was created by the surgeon by spatulating and anastomosing two 8-mm tubular Omniflow® II grafts (Figure 1). In case of large diameters the graft could be cut obliquely to prevent discrepancy.

Figure 1. A bifurcated bypass created by spatulating and anastomosing two 8-mm tubular Omniflow® II grafts.

Outcomes

The primary outcome of this study was recurrent vascular graft infection (based on the MAGIC-criteria). Secondary outcomes were primary patency, primary assisted patency, secondary patency, all-cause mortality, and major amputation during the total postoperative follow-up period (from surgery to long-term follow-up). Primary, primary assisted and secondary patency were defined according to the Reporting standards of the SVS.[14,17] Major amputation was defined as transtibial amputation, knee disarticulation, or transfemoral amputation.

Statistical analysis

Distribution of continuous data were checked visually and supplemented by the Shapiro-Wilk test. Non-normally distributed continuous variables were reported as median and interquartile range (first quartile-third quartile). Categorical data were reported in absolute numbers with according percentages. Kaplan-Meier survival curves were plotted to visualize the survival of primary and secondary outcomes. Subgroups were compared using the Log rank test. Statistical analysis was performed in R, version 4.0.5

(R Foundation for Statical Computing, Vienna, Austria), using the *survival*, *survminer-*, and *ggplot2*-packages. In all analyses, p<0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 52 patients were included in this study. The median age was 71.0 (62.0-75.0) years and 32 (62%) patients were male. The prevalence of comorbidities at baseline were as follows: 83% hypertension, 87% dyslipidemia, and 33% diabetes mellitus (type I or II). The majority of patients (64%) had an ASA-score of III. Other co-morbidities are shown in Table I.

Table I. Patient characteristics

Patient Characteristics	**N (%) or median (P25-P75)**
Number of patients	52
Age in years	71.0 (62.0-75.0)
Sex (males)	32 (62)
BMI in kg/m^2	25.5 (23.1-29.4)
Tobacco use	24 (46)
Hypertension	43 (83)
Dyslipidemia	45 (87)
Diabetes mellitus	17 (33)
Cerebrovascular disease	14 (27)
Cardiac disease	26 (50)
Pulmonary disease	19 (37)
Renal disease	12 (23)
ASA-score	
I	0 (0)
II	8 (15)
III	33 (64)
IV	10 (19)
V	1 (2)

Abbreviations: P25= first quartile, P75= third quartile, BMI= body mass index

Preoperative data

Sixty-four percent of patients were on preoperative antiplatelet therapy, 52% received anticoagulation (of which 22 patients [81%] used a vitamin K antagonist and 5 patients [19%] used a direct oral anticoagulant), and 65% received antibiotics (other than standard perioperative antibiotic prophylaxis) (Table II). Thirty-one percent of patients

underwent acute surgery, 42% underwent semi-elective surgery (<2 weeks), and 27% underwent elective surgery. Laboratory findings included a median hemoglobin level of 7.0 (6.3-8.2) mmol/L, a median white blood cell count of 8.8 x 10^9/L (7.4-12.1), and a median CRP level of 30.0 (9.8-107.8) mg/L.

Table II. Pre-, intra- and postoperative characteristics

Characteristic	**N (%) or median (P25-P75)**
Preoperative	
Antiplatelet therapy	34 (64)
Anticoagulation	27 (52)
Preoperative antibiotic therapy[a]	34 (65)
Blood cultures	
Cultures taken (yes)	35 (67)
- Negative	17 (49)
- Positive	18 (51)
Setting	
Acute (48 hours)	16 (31)
Semi-elective (<2 weeks)	22 (42)
Elective	14 (27)
Hemoglobin (mmol/l)	7.0 (6.3-8.2)
White blood cell count (10^9/L)	8.8 (7.4-12.1)
C-reactive protein (mg/L)	30.0 (9.8-107.8)
Intra-operative	
Intervention time (minutes)	297.5 (211.0-420.0)
Complete removal of (infected) prosthetic material	25 (48)
Intra-operative cultures	
Cultures taken (yes)	47 (90)
- Negative	12 (26)
- Positive	35 (74)
Position of reconstructive bypass	
Intracavitary	
Aorto-biiliac	1 (2)
Aorto-bifemoral	8 (15)
Peripheral	
Axillo-femoral	1 (2)
Ilio-femoral crossover	1 (2)
Ilio-femoral	6 (12)

Table II. Continued

Characteristic	N (%) or median (P25-P75)
Obturator bypass	3 (6)
Femoral interposition	12 (23)
Femoro-femoral crossover	10 (19)
Femoro-popliteal	8 (15)
- Below knee	7 (88)
- Above knee	1 (13)
Femoro-crural	2 (4)
Diameter	
6 mm	20 (39)
8 mm	25 (48)
Missing	7 (13)
Postoperative	
Antibiotic therapy	51 (98)
Length of hospital stay (days)	16 (10-27)
Median follow-up (months)	27 (11-55)

Abbreviations: P25= first quartile, P75= third quartile. [a] other than standard perioperative regime.

Intraoperative data

The median intervention time was 297.5 (211.0–420.0) min and infected prosthetic material was completely removed in 48% of the cases (Table II). Intraoperative cultures were taken in 90% of operations, of which 35 (74%) were positive. Nine (17%) prostheses were implanted in intracavitary position and 43 (83%) in peripheral position. In 3 patients with an intracavitary graft, an aorto-enteric fistula was repaired during index surgery. Partial removal of the infected graft was the case for 2 intracavitary and 24 peripheral grafts. Forty-five patients were treated for a graft infection, 5 patients for an endograft infection, and 2 patients for a combination of graft and endograft infection. The most common locations of the vascular reconstruction with Omniflow® II were aorto-bifemoral (*n* = 8, 15%), femoral interposition (*n* = 12, 23%), femoro-femoral crossover (*n* = 10, 19%), and femoro-popliteal (*n* = 8, 15%; 1 above knee and 7 below knee distal anastomosis). Other graft positions are shown in Table II.

Postoperative data

Ninety-eight percent of patients received postoperative antibiotic therapy. Twelve (23%) patients received (life-long) antibiotic suppression therapy until failure. The other patients received antibiotic therapy for median 42 (14–42) days. The median length of hospital stay was 16 (10–27) days. Median follow-up duration was 27 (11–55) months (Table II).

Short-term adverse events (<30 days)

The most common short-term adverse event was occlusion (10%) of which the following bypasses were affected: axillo-femoral (*n* = 1), aorto-bifemoral (*n* = 1), ilio-femoral (*n* = 1), femoro-femoral crossover bypass (*n* = 1), and femoro-popliteal (below the knee) (*n* = 1). Two patients underwent a thrombectomy, 1 patient underwent graft replacement surgery, and 1 patient underwent endarterectomy with patch angioplasty with a bovine patch. The last patient with an occluded reconstruction (femoropopliteal) did not undergo a surgical procedure, because this patient had too few symptoms compared to the risks of the surgical procedure.

The second most common 30-days adverse event was mortality (8%). In the 30-day mortality group, 1 patient died due to sepsis after receiving an axillo-femoral prosthesis. The other 3 patients in this group all got aorto-bifemoral reconstructions. The first patient with an infected aorto-bifemoral reconstruction presented with rectal blood loss caused by an aorto-enteric fistula. This patient underwent replacement surgery and repair of the fistula. However, postoperatively, the patient deteriorated clinically and biochemically and a hemorrhagic shock without further treatment options was diagnosed. The other 2 patients died due to intestinal ischemia. One patient underwent a relaparotomy with resection of an ischemic sigmoid 4 days postoperatively. An explorative relaparotomy was performed 2 days later because of deterioration. Free fluid was observed and rinsing and drainage was performed. However, the patient died, 2 days postoperatively. The other patient had abdominal pain 2 days postoperatively and underwent a sigmoidoscopy where transmural ischemia was seen on sigmoidoscopy. At relaparotomy there was ischemia of the entire sigmoid, from 60 cm after ligament of Treitz including the ileocecal angle, and multiple parts of the jejunum and ileum. A sigmoid resection was performed and 3 parts of small intestine were removed. Parts of the remaining small intestine were still ischemic. A relaparotomy was done 1 day later and the ischemia had increased. The patient died the same day. Wound infection was also observed in 8% of the patients. All wound infections were treated with antibiotic therapy, incision and drainage. One of these patients developed a recurrent vascular graft infection (Table III).

Table III. Post-operative short-term adverse outcomes (<30 days)

Characteristic	N (%)
Graft occlusion	5 (10)
Mortality	4 (8)
Wound infection	4 (8)
TIA or CVA	3 (6)
Urinary tract infection	3 (6)
Cardiac complication[a]	2 (4)
Delirium	2 (4)
Hematoma[b]	1 (2)

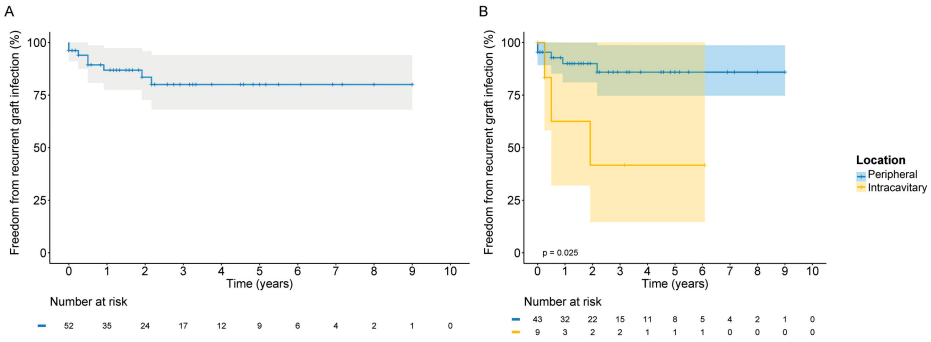
Abbreviations: TIA=transient ischemic attack, CVA=cerebrovascular accident. [a] defined as myocardial infarction, angina pectoris, arrhythmia, or congestive heart failure. [b] Society of Vascular Surgery (SVS) Reporting standards: hematoma class II-III.

Recurrent vascular graft infection

Eight patients (15%) got a reinfection of the vascular graft (Figure 2A and Supplemental Table I). In 4 (50%) of these patients, vascular graft material was not completely removed at time of index surgery (i.e. initial VGEI treatment with Omniflow® II). The estimated freedom of reinfection was 87%, 83%, and 80% at 1, 2, and 3 years, respectively. The grafts of these patients were located in the following positions: aorto-bifemoral (*n* = 3), ilio-femoral (*n* = 1), femoral interposition (*n* = 2), and femoro-femoral (*n* = 2). Thirty-three percent (*n* = 3) of grafts in intracavitary position and 12% (*n* = 5) of grafts in peripheral position got a reinfection (*P* = 0.025, Figure 2B). In the intracavitary group, the cause of initial VGEI (at index surgery) was an aorto-enteric fistula in 1 patient and unknown in the other patients. Blood cultures were taken in 7 cases, of which 2 were positive. The first culture contained *Enterococcus faecium*, *Bacteroides fragilis* and *Eikenella corrodens* and the second culture contained *Granulicatella adiacens* and *Fusobacterium nucleatum*. All patients were treated with antibiotic therapy. Five (63%) patients underwent a reintervention. Four patients got complete removal of the Omniflow® II and 1 patient got an aorto-enteric fistula removed. The last patient underwent partial replacement of the prosthesis (infected area based on imaging) and repair of the aorto-enteric fistula. One patient underwent removal without replacement of a new prosthesis, because of a pre-existent occlusion. The other patients underwent in situ repair with an Omniflow® II bypass, a venous (deep femoral vein) graft, and a bovine pericardial prosthesis (BioIntegral Surgical No-React), respectively. Infected material was obtained and cultured during all procedures. All cultures were positive. A mortality of 38% (*n* = 3) was observed in patients with a reinfection. Two of these patients were treated surgically and 1 patient with antibiotic therapy alone. The first patient died within 1 week after reintervention (partial graft replacement and aorto-enteric fistula removal), most likely because of a persistent bleed (hemodynamic instability

with a Hb decrease). The other patient died 7 months after replacement surgery (with a venous graft) in a palliative setting because of progression of peripheral arterial disease and infection. The conservatively treated patient died 3 years after the diagnosis of VGEI due to cardiopulmonary disease.

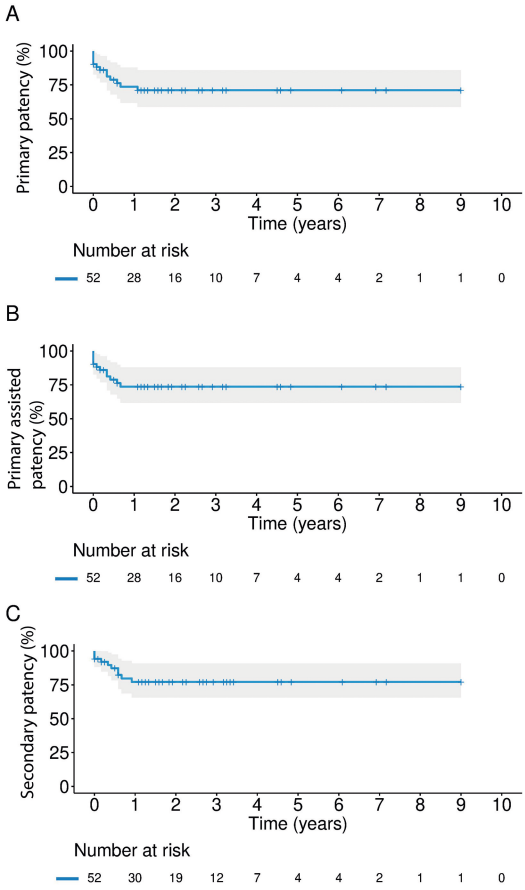
Figure 2. Occurrence of recurrent graft infection for patients treated with Omniflow® II (**A**) and recurrent graft infection stratified by position (intracavitary vs. peripheral) **(B)**



Primary (assisted) and secondary patency

The estimated primary patencies of the total group at 1, 2 and 3 years were 73%, 71%, and 71%, respectively (Figure 3A). Primary assisted patency at 1, 2, and 3 years were 73% (Figure 3B). The estimated secondary patencies at 1, 2, and 3 years were 77% (Figure 3C). The estimated primary patencies at 1, 2, and 3 years were 75%, 72%, and 72% for peripherally located grafts and 58% (at all timepoints) for intracavitary grafts, respectively. Primary assisted patencies at 1, 2, and 3 years were 75% (at all timepoints) for peripherally located prostheses and 58% (at all timepoints) for intracavitary prostheses. Secondary patencies at 1, 2, and 3 years were 77% (at all timepoints) for peripherally located prostheses and 75% (at all timepoints) for intracavitary prostheses. No significant differences were observed between intracavitary and peripheral Omniflow® II bypass grafts regarding primary patency ($P = 0.815$), primary assisted patency ($P = 0.763$), and secondary patency ($P = 0.731$).

Figure 3. Primary patency (**A**), primary assisted patency (**B**), and secondary patency (**C**) of Omniflow® II used for treatment of vascular graft and endograft infection.



Mortality and major amputation

Fourteen (27%) patients died during the follow-up period (Supplemental Figure 1A). The 1, 2, and 3 year estimated mortality rates in the total group were 82%, 79%, and 76%, respectively. The estimated mortality at 1, 2, and 3 years were 90%, 87%, and 82% for peripherally located grafts and 44% (at all timepoints) for intracavitary grafts, respectively. The most common reasons for mortality were malignancy (21%), intestinal ischemia (14%), bleeding from an aorto-enteric fistula (14%), and progression of peripheral arterial disease (14%). Six (43%) of the patients who died had an aorto-biiliac (n = 1) or an aorto-bifemoral prosthesis (n = 5). A significantly higher mortality was observed in patients who received an intracavitary Omniflow® II graft versus patients who received a graft peripherally (p= 0.003, Supplemental Figure 1B). The ASA-scores of patients who received an intracavitary Omniflow® II were significantly higher than the ASA-scores of patients with a peripheral Omniflow® II (P = 0.006). Five patients (55%) with an in-

tracavitary Omniflow® II and none of the patients with a peripheral Omniflow® II had an ASA-score ≥ IV (Supplemental Table II). Overall, 6 (12%) major amputations were required, of which 4 were transfemoral and 2 were transtibial. None of the patients with an intracavitary Omniflow® II underwent an amputation. The 1 and 3 year estimated freedom of amputation were 89% and 87%, respectively (Supplemental Figure 2).

DISCUSSION

This multicenter cohort study includes the largest cohort of patients treated with Omniflow® II biosynthetic bypass for VGEI. It shows the efficacy and safety of the Omniflow® construct when an autologous venous reconstruction is unfeasible.

In the current study, the reinfection-free survival (87% and 80% at 1 and 3 years, respectively) was comparable to a recently published French multicenter study about the use of Omniflow® II in a septic field.[11] Caradu et al. found a reinfection-free survival of 86% at 1 and 3 years. Reinfections were most common in intracavitary prostheses, followed by peripherally located prostheses in our cohort. Interestingly, no reinfections were observed in femoro-popliteal reconstruction. Another study focusing on replacement surgery for infected peripheral grafts also found no reinfections.[18] These lower reinfection occurrence could possibly be related to the rapid graft incorporation after implantation in the host.[19] A study performed by Matic et al. examined infected femoropopliteal grafts that were replaced with silver-coated prostheses and found a reinfection occurrence of 19%.[20] Though cryopreserved allografts have shown lower reinfection rates than prosthetic or biosynthetic grafts, degeneration of the allograft can occur, leading to devastating complications (i.e. aneurysm formation and rupture).[21–23] Another disadvantage of cryopreserved allografts is their limited availability. Previous studies on various graft materials used for aortic graft infection have shown lower reinfection than we observed.[1,24–26] These studies found reinfection occurrences of 9%, 11%, and up to 16% for cryopreserved allografts, silver coated grafts, and bovine pericardial grafts, respectively.[1,24] El Beyrouti et al. found a reinfection prevalence of 6.3% using Omniflow® II in patients with intracavitary reconstruction with a mean follow-up of 29 ± 17 months. However, their study included patients with a high risk of vascular graft infection, in addition to patients with an already diagnosed VGEI.[25] Our group included a large amount of patients being critically ill, with 55% of the patients having an ASA-score ≥ IV, which may be an explanation for the higher reinfection occurrence.

The primary patency we observed was in line with prior studies on Omniflow® II and alternative grafts. One study described a primary patency prevalence of 66% at 3 years in peripherally placed Omniflow® II grafts that were used in septic context.[11] Another study found a primary patency prevalence of 57% in cryopreserved allografts in a peripheral position 3 years postsurgery.[22] In addition to the patency observed in our cohort, freedom of (major) amputation prevalences were excellent: 89% at 1 year and

87% at 3 years. Our results are comparable to existing literature referred to above, with freedom of major amputation prevalences of 84% and 87%.[11,22]

Limitations

This study has its limitations. First, the retrospective design of our study limits the conclusions to be hypothesis generating. Another limitation is the heterogeneity of our cohort, including differences in medical (i.e., antibiotic therapies) and surgical treatment (i.e., different anatomical positions). Furthermore, the lack of a control group reduces the power of the conclusions on this graft. However, literature on the use of Omniflow® II bypass for the treatment of VGEI is scarce and to our knowledge, to date, this multi-center study represents the largest study of its kind.

Conclusion

This study highlights the efficacy of the Omniflow® II biosynthetic prosthesis for the treatment of VGEI as an "off-the-shelf" prosthesis, in absence of a suitable vein. It has shown acceptable reinfection-, patency-, and freedom of amputation prevalences, especially for treatment of peripheral VGEI. More research is needed to evaluate the use of Omniflow® II for intracavitary VGEI and to evaluate the outcomes of Omniflow® II compared to other materials (i.e., autologous veins, cryopreserved allografts, or synthetic prostheses).

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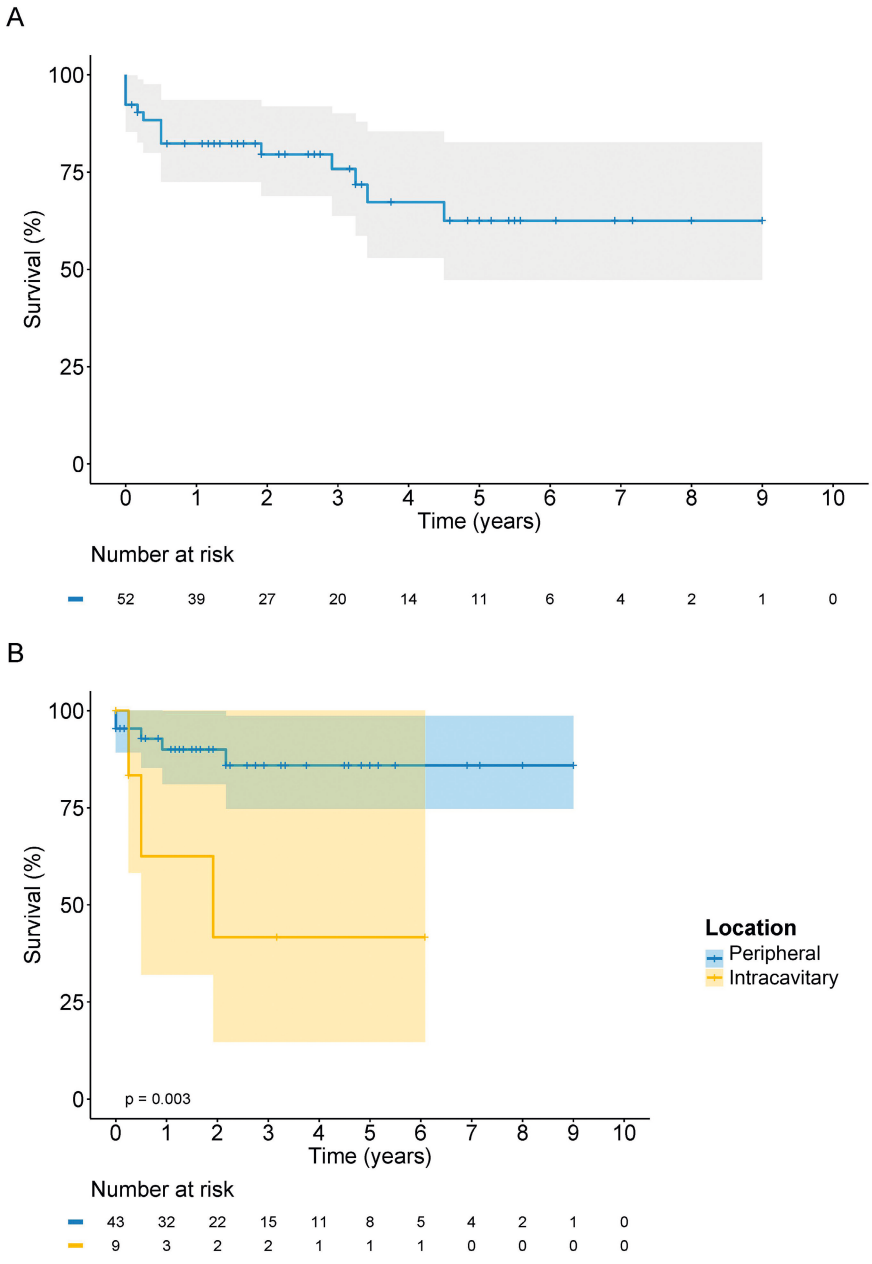
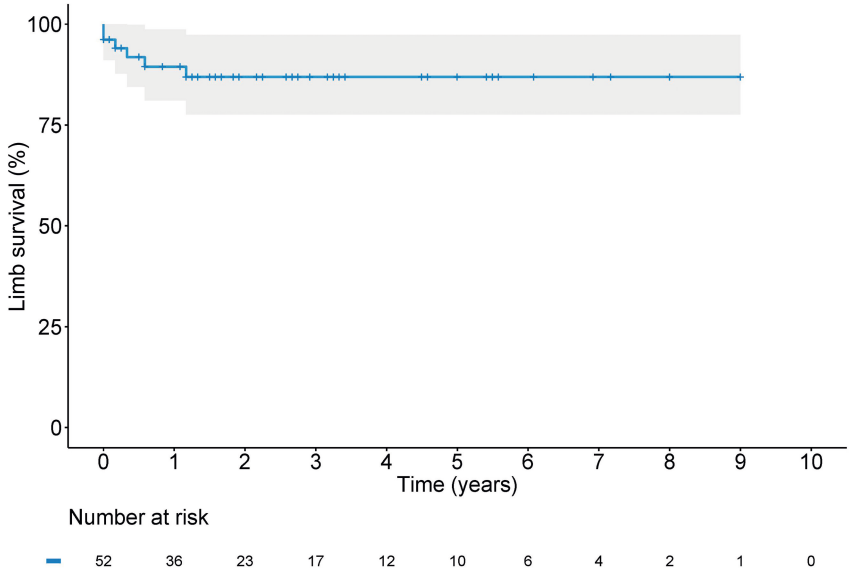
SUPPLEMENTARY DATA

Supplemental Figure 1. Survival curves (all-cause mortality) of patients treated with Omniflow® II (**A**) and survival stratified by position (intracavitary vs. peripheral) (**B**).



Supplemental Figure 2. Limb survival curve for patients treated with Omniflow® II.



Supplemental Table I. Characteristics reinfection

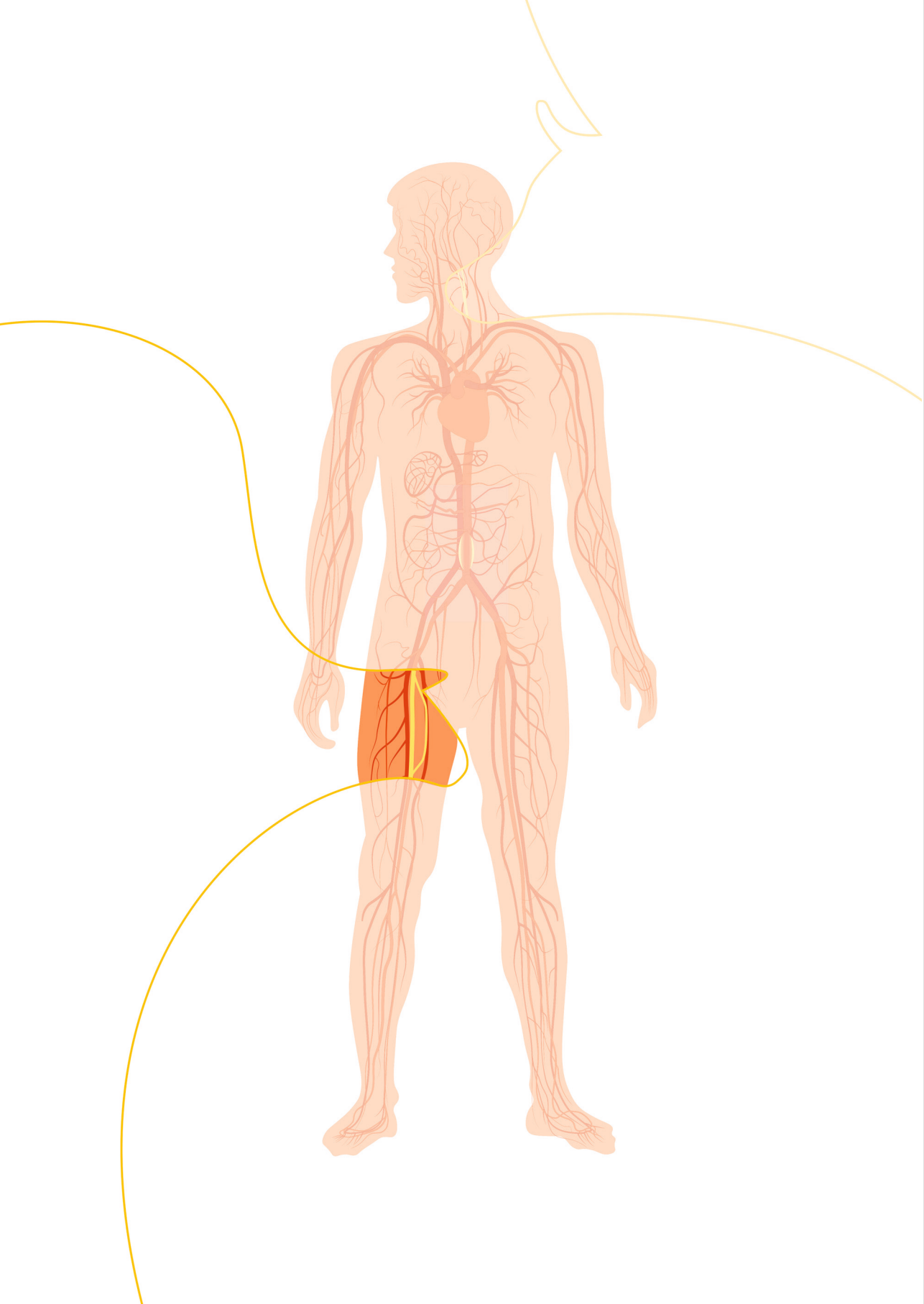
No.	Location Omniflow	Blood cultures	Antibiotic therapy	Re-intervention	Time (months) to reinfection[a]	Intra-operative cultures
1	Aortobifemoral	No	Yes	No	3	-
2	Aortobifemoral	*Enterococcus faecium, Bacteroides fragilis, Eikenella corrodens*	Yes	Surgical removal aorto-enteric fistula	6	*Enterococcus faecium, Enterococcus faecalis, Escherichia coli, Bacteroides thetaiotaomicron*
3	Aortobifemoral	*Granulicatella adiacens and Fusobacterium nucleatum*	Yes	No	23	-
4	Femorofemoral crossover	Negative	Yes	Omniflow ® II obturator bypass	1	*Staphylococcus aureus*
5	Femorofemoral crossover	Negative	Yes	Venous graft	0.5	*Bacteroides fragilis, Enterococcus faecium, Enterococcus faecalis, Staphylococcus lugdunensis*
6	Iliofemoral	Negative	Yes	No	6	-
7	Femoral interposition	Negative	Yes	Biointegral (because of a history of an aortobifemoral graft)	11	*Candida albicans*
8	Femoral interposition	Negative	Yes	Removal (preexistent occlusion)	26	*Streptococcus agalactiae (group B streptococcus)*

Abbreviation: No.= number. [a] Time (months) from Omniflow® II implantation to reinfection

Supplemental Table II. American Society of Anesthesiologists score: Central vs. peripheral

	Peripheral	**Central**	**p-value**
ASA-score			**0.006**
I	0 (0)	0 (0)	
II	6 (14)	2 (22)	
III	31 (72)	2 (22)	
IV	0 (0)	4 (44)	
V	0 (0)	1 (11)	

Abbreviations: ASA= American Society of Anesthesiologists.



Chapter 6

Outcomes of Omniflow® II prosthesis used for revascularization in the femoral tract both in infected and non-infected setting

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ABSTRACT

Background

Evidence regarding the outcomes of Omniflow® II prosthesis in peripheral arterial revascularization at different anatomical sites and for different indications is scarce. Therefore, the aim of this study was to evaluate the outcomes of the Omniflow® II used at various positions within the femoral tract both in infected and non-infected setting.

Methods

Patients who underwent reconstructive lower leg vascular surgery with implantation of an Omniflow® II from 2014 until 2021 at five medical centers were retrospectively included (n=142). Patients were subdivided into the following categories: femoro-femoral crossover (n=19), femoral interposition (n=18), femoro-popliteal (above-the-knee [n=25; AK] or below-the-knee [n=47; BK]), and femoro-crural bypass grafts (n=33). Primary outcome was primary patency and secondary outcomes included primary assisted patency, secondary patency, major amputation, vascular graft infection, and mortality. Outcomes were compared according to different subgroups and the surgical setting (infected vs. non-infected).

Results

The median follow-up was 35.0 (17.5-54.3) months. Three years primary patency of 58% was observed for femoro-femoral crossover bypass, 75% for femoral interposition graft, 44% for femoro-popliteal above-the-knee bypass, 42% for femoro-popliteal below-the-knee bypass, and 27% in the femoro-crural position (p=0.006). Freedom from major amputation at three years were 84% for femoro-femoral crossover bypass, 88% for femoral interposition bypass, 90% for femoro-popliteal AK bypass, 83% for femoro-popliteal BK bypass, and 50% for femoro-crural bypass (p<0.001).

Conclusions

This study demonstrates the safety and feasibility of the use of Omniflow® II for femoro-femoral crossover-, femoral interposition-, and femoro-popliteal (AK and BK) bypass. Omniflow® II seems to be less suitable for femoro-crural bypass with a significantly lower patency compared to other positions.

INTRODUCTION

Peripheral arterial disease (PAD) is a severe condition that is associated with amputation, cardiovascular disease, and all-cause mortality.[1–3] Apart from life-style interventions (i.e., supervised exercise training) and medical therapy, surgical or endovascular revascularization may be indicated to treat PAD.[4,5] Various graft materials can be used for surgical revascularization depending on the anatomical location of PAD. For femoro-popliteal bypass surgery, in-situ reconstruction and the use of the great saphenous vein is recommended.[2] According to the European Society for Vascular Surgery guidelines, a prosthetic graft should be considered for above-the-knee surgery in the absence of a suitable vein.[2] In this case, the Omniflow® II (LeMaitre Vascular, Inc, Burlington, MA, USA) could be an effective, biological alternative. Initially, this prosthesis was used for hemodialysis. However, its use is slowly gaining attention in other locations, and meanwhile it has also been used to treat PAD and to replace vascular grafts and infected endografts.[6]One of the reasons for the increase in popularity of Omniflow® II is the growing evidence of its infection resistant properties.[7–10] One example is the study of Caradu et al. where they found an acceptable freedom from amputation and reinfection in patients (n=29) treated with an Omniflow® II in lower extremity arterial revascularization in a septic context.[11] However, the outcomes of Omniflow® II for different indications at various anatomical positions are yet to be investigated. Therefore, the aim of this multi-center study was to evaluate the outcomes of the Omniflow® II prosthesis used at various anatomical positions within the femoral tract primary and or as a replacement for graft infection.

MATERIAL AND METHODS

Study design

All patients who underwent reconstructive lower leg vascular surgery with implantation of an Omniflow® II (LeMaitre Vascular, Burlington, MA, USA) prosthesis from January 2014 until December 2021 in the following positions were included: femoro-femoral crossover, femoral interposition, femoro-popliteal above-the-knee (AK), femoro-popliteal below-the-knee (BK), and femoro-crural. Patient data were retrieved from five medical centers in the Netherlands (Albert Schweitzer Hospital, Leiden University Medical Center, Meander Medical Center, University Medical Center Groningen, and Zuyderland Medical Center). There were no exclusion criteria regarding the indication for surgery. In total, 142 patients were included in this study. Nineteen (13.4%) grafts were implanted in the femoro-femoral crossover position, 18 (12.7%) as femoral interposition bypass, 25 (17.6%) as femoro-popliteal AK bypass, 47 (33.1%) as femoro-popliteal BK bypass, and 33 (23.2%) in the femoro-crural position. The Omniflow® II biosynthetic graft is made from a polyester mesh endoskeleton covered with cross linked ovine collagen.

The Medical Ethical Institutional Review Board granted dispensation for Medical Research Involving Human Subjects Act (WMO) obligation (registration no. METC 2021/494). Local approval was obtained at each of the participating hospitals. Patient data were processed and electronically stored in agreement with the Declaration of Helsinki – Ethical principles for medical research involving human subjects.[12] Patients were identified by searching for intervention codes. Data were extracted from the electronic patient files at each hospital.

Pre-operative patient characteristics

Baseline characteristics were collected, including age at time of surgery, sex, and body mass index (BMI). Furthermore, comorbidities were scored using the Society for Vascular Surgery (SVS) system (class 0–3) according to the Ad Hoc Committee on Reporting Standards.[13] Tobacco use was defined as current use, or less than one year of abstinence (SVS-class II-III). Hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular disease, cardiac disease, pulmonary disease, and renal disease were scored positive if SVS-class ≥1.[13] In addition, American Society of Anesthesiologists (ASA) scores were collected.[14] Preoperative antiplatelet therapy, anticoagulation, reason for surgery, and setting (elective and urgent within 24 hours) were noted. Reasons for surgery were categorized into four groups: primary Omniflow without infection risk (i.e., primary bypass surgery for PAD), primary Omniflow with high infection risk (i.e., positioned in an area with an active infection, such as a mycotic aneurysm), graft replacement without infection (i.e., replacement surgery for PAD), and graft replacement with infection (graft infection based on the Management of Aortic Graft Infection Collaboration (MAGIC) criteria).[15] Patients received an Omniflow® II if there was no adequate superficial vein in the upper or lower extremities (e.g., greater saphenous vein) available. Furthermore, patients were classified according the Rutherford Classification scheme and the presence of chronic limb-threatening ischemia (CLTI) was noted.[16] CLTI included rest pain, an ulcer, or gangrene attributable to PAD for duration of >2 weeks. The number of previous ipsilateral procedures were noted (both endovascular and surgical procedures). Preoperative hemoglobin level, leukocyte count, and C-reactive protein were collected.

Intra-operative and postoperative (<30 days)

Information regarding prosthesis size (6 or 8 mm), the use of postoperative antiplatelet therapy and the use of anticoagulation therapy were collected. Any complications (during the surgical procedure or in the first 24 hours post-surgery), postoperative length of hospital stays (days), and follow-up duration (months) were noted. Short-term (<30 days) adverse events included (all-cause) mortality, occlusion (confirmed by imaging), wound infection, cardiac complications (arrhythmia, angina pectoris, myocardial infarction, or congestive heart failure), delirium, and urinary tract infection. Standard follow-up was performed at four or six weeks postoperatively, followed once a year thereafter.

Outcomes

The primary outcome was primary patency. Secondary outcomes were primary assisted patency, secondary patency, major amputation, vascular graft infection (MAGIC criteria), and all-cause mortality. Patency was defined according to the Reporting standards of the SVS.[13,17] Major amputation was defined as transtibial amputation, knee disarticulation, or transfemoral amputation. Outcomes were compared according to different subgroups (i.e., anatomical positions) and different surgical settings (i.e., graft or endograft infection vs. no infection).

Statistical analysis

The distribution of continuous variables was determined visually and assessed with the Shapiro-Wilk test. Normally distributed continuous variables are displayed as mean and standard deviation (SD). Skewed variables are presented as median and interquartile range (IQR, written as: 25th percentile – 75th percentile). Continuous variables of the different anatomical locations were compared using one-way ANOVA (normal distribution) or the Kruskal Wallis test (skewed distribution). Categorical variables were reported as numbers with accompanying percentages and compared between groups using the Fisher's exact tests. Kaplan-Meier survival curves were plotted to visualize the effect of anatomical positions of Omniflow® II on the primary and secondary outcome(s). Cox proportional hazard models with stepwise backward elimination calculating hazard ratio (HR) with the 95% confidence interval were made. Univariable Cox regression was performed to investigate the crude effect of the anatomical position of the Omniflow® II on the primary and secondary outcome(s). Furthermore, multivariable Cox regression analyses were performed. Baseline and preoperative characteristics with $p<0.10$ in the univariable analyses were selected for the adjusted models. If the regression coefficient of the anatomical position changed with >10%, a variable was defined as confounder. All confounders remained in the final multivariable models. The models showed the estimated regression coefficient (β) with a hazard ratio and 95% confidence interval. The Cox regression model assumptions were tested and fulfilled. In the multivariable models, Rutherford classification was not included in the multivariable models because collinearity between the Rutherford classification and CLTI. In the multivariable analyses, effect modification by graft location and confounders was tested by including interaction terms (e.g. graft location * CLTI). Univariable and multivariable Cox regression analyses were also performed to compare the surgical setting (VGEI replacement vs. graft replacement in the non-infected setting). Statistical analyses were performed in R, version 4.0.5 (R Foundation for Statical Computing, Vienna, Austria), using the survival, survminer-, and ggplot2-packages. A p-value of <0.05 was considered statistically significant.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

RESULTS

Baseline characteristics

Patients had a mean age of 70.6 ± 10.2 years and 76 (53.5%) were male. Forty-nine percent of patients used tobacco, 76.8% had hypertension, and 31.0% had diabetes mellitus. Most patients had an ASA-score of III (65.5%) (Table I). No significant differences in baseline characteristics were found between the various bypass locations.

Table I. Patient characteristics of patients who have received an Omniflow® II stratified by bypass position.

Patient Characteristics	Femoro-femoral	Femoral interposition	Femoro-popliteal AK	Femoro-popliteal BK	Femoro-crural	Total	*P*-value
Number of patients	19 (13.4)	18 (12.7)	25 (17.6)	47 (33.1)	33 (23.2)	142 (100.0)	
Age (years)	67.3 ± 12.1	70.0 ± 10.4	69.1 ± 10.8	72.2 ± 8.4	71.5 ± 10.7	70.6 ± 10.2	0.401
Sex (males)	9 (47.4)	10 (55.6)	13 (52.0)	24 (51.1)	20 (60.6)	76 (53.5)	0.896
BMI (kg/m^2)	24.9 ± 4.1	24.5 ± 6.9	26.0 ± 5.5	25.6 ± 5.6	27.2 ± 6.4	25.8 ± 5.7	0.485
Tobacco use	10 (52.6)	12 (66.7)	14 (56.0)	24 (51.1)	9 (27.3)	69 (49.3)	0.055
Hypertension	15 (78.9)	16 (88.9)	20 (80.0)	36 (76.6)	22 (66.7)	109 (76.8)	0.506
Hyperlipidemia	17 (89.5)	15 (83.3)	24 (96.0)	40 (85.1)	27 (81.8)	123 (86.6)	0.545
Diabetes mellitus	5 (26.3)	4 (22.2)	12 (48.0)	13 (27.7)	10 (30.3)	44 (31.0)	0.384
Cerebrovascular disease	5 (26.3)	4 (22.2)	8 (32.0)	5 (10.6)	4 (12.1)	26 (18.3)	0.135
Cardiac disease	11 (57.9)	6 (33.3)	12 (48.0)	28 (59.6)	16 (48.5)	73 (51.4)	0.391
Pulmonary disease	4 (21.1)	10 (55.6)	10 (40.0)	17 (36.2)	9 (27.3)	50 (35.2)	0.204
Renal disease	7 (36.8)	4 (22.2)	9 (36.0)	10 (21.3)	6 (18.2)	36 (25.4)	0.380
ASA-score							0.965
I	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
II	4 (21.1)	5 (27.8)	6 (24.0)	11 (23.4)	9 (27.3)	35 (24.6)	
III	12 (63.2)	11 (61.1)	17 (68.0)	33 (70.2)	20 (60.6)	93 (65.5)	
IV	3 (15.8)	2 (11.1)	2 (8.0)	3 (6.4)	4 (12.1)	14 (9.9)	
V	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

Abbreviations: -. Data is presented as n (%) or mean ± standard deviation.

Preoperative patient characteristics

Preoperatively, no significant differences were observed regarding antiplatelet and anticoagulation use (Table II). In total, 50 (35.2%) patients who had low infection risk got a primary Omniflow® II, three (2.1%) patients with a high risk of infection got a primary Omniflow® II, 53 (37.3%) patients underwent graft replacement without infection, and 36 (25.4%) patients underwent graft replacement due to infection. A significant difference ($p<0.001$) between the five anatomical positions was observed in the distribution of indication for surgery. The most common indication for femoro-femoral crossover (63.2%) and femoral interposition grafts (72.2%) was graft replacement in case of an infected graft/endograft infection. The most common indication for femoro-popliteal AK and BK located grafts (56.0% and 48.9%, respectively) was primary Omniflow® II without infection. The most common indication for femoro-crural positioned grafts (72.7%) was graft replacement without infection. In 41 patients (28.9%) surgery was performed in an emergency setting (within 24 hours) of which 10 (24.4%) primary Omniflow® II without infection, 18 (43.9%) graft replacement without infection, and 13 (31.7%) graft replacement for the treatment of VGEI Significant differences were found regarding the distribution of the Rutherford Classification ($p<0.001$) and the presence of CLTI ($p<0.001$). CLTI rates were highest in patients with a femoro-crural bypass (90.9%), followed by patients with a femoro-popliteal AK bypass (80.0%), femoro-popliteal BK (76.6%), femoro-femoral crossover bypass (42.1%), and femoral interposition graft (22.2%).

Table II. Pre-, intra-, and post-operative characteristics of patients who have received an Omniflow® II stratified by bypass position.

Patient Characteristics	**Femoro-femoral crossover** (n=19)	**Femoral interposition** (n=18)	**Femoro-poplitial AK** (n=25)	**Femoro-poplitial BK** (n=47)	**Femoro-crural** (n=33)	***P*-value**
Preoperative						
Antiplatelet therapy	13 (68.4)	12 (66.7)	15 (60.0)	29 (61.7)	23 (69.7)	0.928
Anticoagulation	8 (42.1)	9 (50.0)	10 (40.0)	20 (42.6)	13 (39.4)	0.963
Indication for surgery						**<0.001**
Primary Omniflow (no infection)	3 (15.8)	2 (11.1)	14 (56.0)	23 (48.9)	8 (24.2)	
Primary Omniflow (high infection risk)	1 (5.3)	1 (5.6)	0 (0)	1 (2.1)	0 (0)	
Graft replacement (no infection)	3 (15.8)	2 (11.1)	8 (32.0)	16 (34.0)	24 (72.7)	
Graft replacement (graft infection)	12 (63.2)	13 (72.2)	3 (12.0)	7 (14.9)	1 (3.0)	
Setting						0.441
Elective	12 (63.2)	11 (61.1)	16 (64.0)	37 (78.7)	25 (75.8)	
Emergent (<24h)	7 (36.8)	7 (38.9)	9 (36.0)	10 (21.3)	8 (24.2)	
Rutherford Classification						**<0.001**
0	8 (42.1)	9 (50.0)	3 (12.0)	2 (4.3)	1 (3.0)	
1	1 (5.3)	2 (11.1)	0 (0)	2 (4.3)	0 (0)	
2	1 (5.3)	3 (16.7)	1 (4.0)	3 (6.4)	2 (6.1)	
3	1 (5.3)	0 (0)	1 (4.0)	4 (8.5)	0 (0)	
4	4 (21.1)	0 (0)	8 (32.0)	11 (23.4)	12 (36.4)	
5	3 (15.8)	3 (16.7)	8 (32.0)	12 (25.5)	14 (42.4)	
6	1 (5.3)	1 (5.6)	4 (16.0)	13 (27.7)	4 (12.1)	
Chronic Limb-threatening ischemia	8 (42.1)	4 (22.2)	20 (80.0)	36 (76.6)	30 (90.9)	**<0.001**

Table II. Continued

Patient Characteristics	Femoro-femoral crossover (n=19)	Femoral interposition (n=18)	Femoro-poplitial AK (n=25)	Femoro-poplitial BK (n=47)	Femoro-crural (n=33)	*P*-value
Previous procedures (ipsilateral)	2.0 (1.0-3.0)	2.0 (2.0-4.0)	(0.0-2.0)	1.0 (0.0-2.0)	2.0 (0.5-2.5)	**0.001**
Hemoglobin level	7.4 (6.5-8.4)	7.0 (6.1-8.5)	7.6 (6.6-8.5)	8.0 (7.1-8.5)	7.8 (6.8-9.1)	0.251
Leukocyte count	8.3 (7.1-10.6)	8.8 (6.4-12.4)	8.7 (7.7-10.9)	8.8 (7.3-11.1)	9.6 (7.8-11.3)	0.932
C-reactive protein	13.0 (4.1-22.0)	30.0 (11.0-166.0)	9.0 (6.5-30.5)	22.0 (5.8-66.0)	17.0 (6.0-59.0)	0.342
Intra-operative						
Intervention time (minutes)	271.0 (190.0-312.0)	186.0 (153.5-217.5)	200.0 (154.0-224.0)	215.0 (155.0-270.0)	225.0 (170.5-310.8)	0.069
Size						**<0.001**
6 mm	6 (31.6)	7 (38.9)	18 (72.0)	26 (55.3)	25 (75.8)	
8 mm	8 (42.1)	7 (38.9)	1 (4.0)	3 (6.4)	2 (6.1)	
Missing	5 (26.3)	4 (22.2)	6 (24.0)	18 (38.3)	6 (18.2)	
Postoperative						
Antiplatelet therapy	10 (52.6)	11 (61.1)	17 (68.0)	29 (61.7)	14 (42.4)	0.318
Anticoagulation	10 (52.6)	12 (66.7)	9 (36.0)	22 (46.8)	20 (60.6)	0.240
Length of hospital stay (days)	10.0 (7.5-19.5)	11.5 (5.8-27.5)	6.0 (4.0-8.0)	6.0 (4.0-13.5)	7.0 (5.0-10.0)	**0.023**
Median follow-up (months)	26.0 (18.0-58.0)	29.0 (13.80-54.5)	34.0 (13.0-54.0)	43.0 (25.0-63.0)	34.0 (14.0-49.0)	0.441

Abbreviations: -. Data is presented as n (%) or median (interquartile range, written as: first quartile-third quartile).

Intraoperative characteristics

Median intervention time ranged from 186.0 (153.5-217.5) minutes (femoral interposition) to 271.0 (190.0-312.0) minutes (femoro-femoral crossover). See Table II.

Postoperative characteristics

No differences were found regarding postoperative antiplatelet therapy (p=0.318) or the use of anticoagulation (p=0.240). The median length of hospital stay was 10.0 (7.5-19.5), 11.5 (5.8-27.5), 6.0 (4.0-8.0), 6.0 (4.0-13.5), and 7.0 (5.0-10.0) days for femoro-femoral crossover-, femoral interposition-, femoro-popliteal AK-, femoro-popliteal BK-, and femoro-crural grafts, respectively (p=0.023; Table II).

Complications (during surgery or <24 hours post-surgery)

Four femoro-crural grafts got occluded within 24 hours after surgery. One patient underwent a transfemoral amputation one week postoperatively as there were no open surgery or endovascular treatment options left. The other three patients underwent a mechanical thrombectomy. However, this procedure was unsuccessful for all patients. One of these patients underwent replacement surgery and received a venous graft, with success. The other two patients underwent a transtibial amputation within 1 week and 2 months after the re-intervention, respectively. Another complication that occurred was postoperative bleeding in a patient who received a femoro-popliteal BK bypass. This patient underwent a successful re-exploration. However, two days postoperatively, the bypass got occluded and a successful thrombectomy was performed.

Post-operative short-term adverse outcomes (<30 days)

Four (21.1%) femoro-femoral crossover bypasses, none (0.0%) of the femoral interposition grafts, 1 (4.0%) femoro-popliteal AK bypass, 8 (17.0%) femoro-popliteal BK bypasses, and 12 (36.4%) femoro-crural bypasses (including 4 within 24 hours post-surgery, see above) got occluded within 30 days (p=0.003). No other differences were found between the anatomical positions regarding early adverse events (Table III).

Table III. Post-operative early adverse outcomes (<30 days) in patients who have received an Omniflow® II stratified by bypass position.

Characteristic	Femoro-femoral crossover (n=19)	Femoral interposition (n=18)	Femoro-poplitial AK (n=25)	Femoro-poplitial BK (n=47)	Femoro-Crural (n=33)	*P*-value
Mortality	0 (0)	0 (0)	0 (0)	3 (6.4)	0 (0)	0.428
Occlusion	4 (21.1)	0 (0)	1 (4.0)	8 (17.0)	12 (36.4)	**0.003**
Wound infection	2 (10.5)	2 (11.2)	3 (12.0)	4 (8.5)	2 (6.1)	0.901
Cardiac complication	0 (0)	1 (5.6)	0 (0)	1 (2.1)	0 (0)	0.531
Delirium	2 (10.5)	1 (5.6)	1 (4.0)	3 (6.4)	3 (9.1)	0.904
Urinary tract infection	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.0)	0.669

Abbreviations: -. Data is presented as n (%).

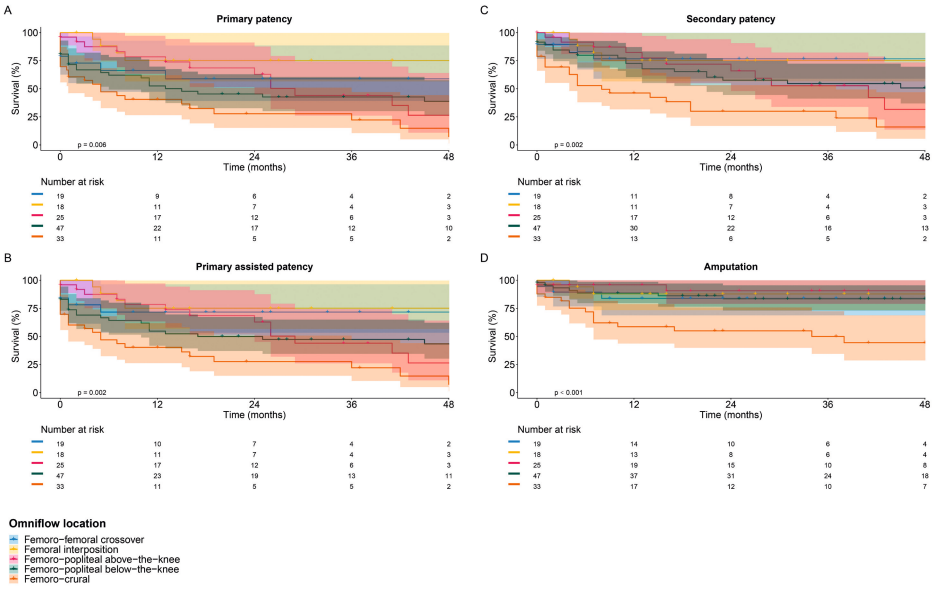
Follow-up

The median follow-up of the total cohort was 35.0 (17.5-54.3) months. The median follow-up varied between 26.0 months and 43.0 months across the five groups, but the differences in follow-up durations were not significant (p=0.441).

Primary patency, primary assisted patency, and secondary patency

Significant differences in primary patency (p=0.006), primary assisted patency (p=0.002), and secondary patency (p=0.002) were observed between the five anatomical positions, with the poorest outcomes for the femoro-crural location (Figures 1A, B, and C; Supplementary Table I; Table IV).

Figure 1. Primary patency (**1A**), primary assisted patency (**1B**), secondary patency (**1C**), and freedom of amputation (**1D**) of Omniflow® II stratified by bypass location.



After adjusting for confounders in the multivariable analysis, femoro-popliteal AK grafts showed a lower hazard of losing primary patency (p=0.030), primary assisted patency (p=0.045), and secondary patency (p=0.047) compared to femoro-crural grafts (setting femoro-crural as reference). Femoro-popliteal BK grafts showed a lower hazard of losing secondary patency compared to femoro-crural grafts (p=0.017). No significant differences were observed on primary patency and primary assisted patency between femoro-popliteal BK and femoro-crural grafts. Femoro-femoral and femoral interposition grafts showed no significant differences regarding primary, primary assisted, and secondary patency compared to femoro-crural grafts in the multivariable analyses (Table V). There was no effect modification between graft location and any of the confounders. When comparing femoro-popliteal AK and femoro-popliteal BK (setting femoro-popliteal BK as reference) in the multivariable analyses, no significant differences were observed regarding primary (p=0.939), primary assisted (p=0.641), and secondary patency (p>0.999). The estimated primary, primary assisted, and secondary patencies at one, two, and three years are shown in Table IV.

Table IV. Patency, freedom of amputation, mortality and vascular graft infection rates of Omniflow® II stratified by bypass location

Characteristic	Femoro-femoral crossover	Femoral interposition	Femoro-poplitial			Femoro-crural
	(n=19)	(n=18)	*Total* (n=72)	*AK* (n=25)	*BK* (n=47)	(n=33)
Primary patency (%)						
1 y	65	75	61	78	52	40
2 y	58	75	53	68	45	27
3 y	58	75	43	44	42	27
Primary assisted patency (%)						
1 y	71	75	63	78	54	40
2 y	71	75	56	68	50	27
3 y	71	75	47	44	47	27
Secondary patency (%)						
1 y	76	75	76	82	72	46
2 y	76	75	62	71	57	30
3 y	76	75	54	52	54	30
Freedom of amputation (%)						
1 y	84	88	91	96	89	59
2 y	84	88	86	90	83	55
3 y	84	88	86	90	83	50
Survival (%)						
1 y	84	100	89	83	91	84
2 y	79	100	84	79	87	74
3 y	72	100	70	59	77	66
Vascular graft infection (%)						
1 y	89	93	97	100	96	94
2 y	89	93	95	94	96	94
3 y	89	85	93	94	93	94

Abbreviations: AK, above the knee; BK, below the knee; y, year.

Table V. Multivariable Cox regression analyses on the estimated effect of graft location on mid-term outcomes including patency, major amputation, mortality, and vascular graft infection.

Outcome	Predictor (Reference: femoro-crural)	β (95% CI)	HR (95% CI)	*P*-value
Primary patency[a]	Femoro-femoral	-0.20 (-1.09;0.69)	0.819 (0.34;1.99)	0.660
	Femoral interposition	-0.51 (-1,65;0.63)	0.601 (0.19;1.88)	0.383
	Femoro-popliteal AK	-0.79 (-1.46;-0.08)	0.454 (0.22;0.93)	**0.030**
	Femoro-popliteal BK	-0.47 (-1.06;0.12)	0.628 (0.35;1.13)	0.121
Primary assisted patency[b]	Femoro-femoral	-0.58 (-1.56;0.41)	0.562 (0.21;1.50)	0.251
	Femoral interposition	-0.55 (-1.71;0.62)	0.578 (0.18;1.85)	0.357
	Femoro-popliteal AK	-0.73 (-1.44;-0.02)	0.482 (0.24;0.98)	**0.045**
	Femoro-popliteal BK	-0.57 (-1.17;0.04)	0.566 (0.31;1.04)	0.066
Secondary patency[c]	Femoro-femoral	-0.84 (-0.83;0.22)	0.43 (0.15;1.25)	0.123
	Femoral interposition	-0.55 (-1.77;0.65)	0.58 (0.17;1.92)	0.369
	Femoro-popliteal AK	-0.77 (-1.51;-0.01)	0.46 (0.22;0.99)	**0.047**
	Femoro-popliteal BK	-0.77 (-1.39;-0.14)	0.46 (0.25;0.87)	**0.017**
Amputation[d]	Femoro-femoral	-0.52 (-1.84;0.79)	0.59 (0.16;2.21)	0.437
	Femoral interposition	-0.20 (-2.00;1.60)	0.82 (0.14;4.97)	0.826
	Femoro-popliteal AK	-1.34 (-2.66;-0.02)	0.26 (0.07;0.98)	**0.047**
	Femoro-popliteal BK	-1.23 (-2.24;-0.22)	0.29 (0.11;0.80)	**0.017**
All-cause mortality[e]	Femoro-femoral	0.12 (-0.98;1.22)	1.13 (0.38;3.40)	0.827
	Femoral interposition	-1.65 (-3.86;0.58)	0.19 (0.02;1.79)	0.148
	Femoro-popliteal AK	0.09 (-0.76;0.94)	1.09 (0.47;2.56)	0.836
	Femoro-popliteal BK	-0.49 (-1.25;0.27)	0.62 (0.29;1.32)	0.210
Vascular graft infection[f]	Femoro-femoral	-0.23 (-2.75;2.29)	0.79 (0.06;9.84)	0.856
	Femoral interposition	-0.48 (-3.00;2.03)	0.62 (0.05;7.62)	0.707
	Femoro-popliteal AK	-0.82 (-3.35;1.71)	0.44 (0.04;5.52)	0.525
	Femoro-popliteal BK	-0.30 (-2.27;1.69)	0.74 (0.10;5.39)	0.770

Abbreviations: β, beta; CI, confidence interval.
[a] adjusted for indication for surgery, Chronic Limb-Threatening Ischemia, number of previous procedures (ipsilateral).
[b] adjusted for indication for surgery, Chronic Limb-Threatening Ischemia, number of previous procedures (ipsilateral).
[c] adjusted for indication for surgery, Chronic Limb-Threatening Ischemia.
[d] adjusted for tobacco use, indication for surgery, Chronic Limb-Threatening Ischemia, number of previous procedures (ipsilateral).
[e] adjusted for tobacco use, indication for surgery, Chronic Limb-Threatening Ischemia.
[f] adjusted for tobacco use, indication for surgery, Chronic Limb-Threatening Ischemia, number of previous procedures (ipsilateral).

Major amputation

In total, 35 major amputations were performed: 11 (7.7%) transtibial amputations, 3 (2.1%) knee disarticulations, and 21 (14.8%) transfemoral amputations. Freedom from major amputation at one, two, and three years is shown in Table IV. A significant difference was found between the different anatomical positions regarding freedom from major amputation (p<0.001) (Figure 1D; Supplementary Table I). In the multivariable analyses, both femoro-popliteal AK and femoro-popliteal BK grafts had a significant lower hazard (p=0.047 and p=0.017, respectively) from major amputation compared to femoro-crural grafts. Femoro-femoral (p=0.437) and femoral interposition (p=0.826) grafts showed no significant differences regarding amputation compared to femoro-crural grafts after adjusting for confounders (Table V). No effect modification was observed. When comparing femoro-popliteal AK and femoro-popliteal BK (setting femoro-popliteal BK as reference) in the multivariable analyses, no significant differences were observed (p=0.875).

All-cause mortality

In total, 51 (35.9%) patients died during follow-up. Overall, no significant differences were observed between the five groups regarding all-cause mortality (p=0.086; Supplementary Figure 1A). However, univariable Cox regression showed a significantly lower hazard (p=0.033) of all-cause mortality for patients with a femoral interposition graft compared to patients with a femoro-crural graft (Supplementary Table I). After adjusting for confounders, no significant differences regarding mortality were observed between the different groups (Table V). No effect modification was observed between graft location and any of the confounders. When comparing femoro-popliteal AK and femoro-popliteal BK (setting femoro-popliteal BK as reference) in the multivariable analyses, no significant differences were observed regarding mortality (p=0.150). Most common causes of mortality included: progression of PAD leading to gangrene and sepsis (15.7%), cardiac disease (13.7%), and malignant disease (13.7%). Estimated survival at one, two, and three years is shown in Table IV.

Vascular graft infection

The Omniflow® II got infected in 10 patients (7.0%). No significant differences regarding graft infection were found between the various anatomical positions (p=0.867; Supplementary Figure 1B, Supplementary Table I). Even after adjusting for confounders in the multivariable Cox regression analysis, no significant differences were found between the various anatomical positions (Table V). No effect modification was shown. When comparing femoro-popliteal AK and femoro-popliteal BK (setting femoro-popliteal BK as reference) in the multivariable analyses, no significant differences were observed (p=0.653). The estimated freedom of vascular graft infection at one, two, and three years is shown in Table IV. Blood cultures were taken in eight patients, of which 2 (25.0%) were positive for *Staphylococcus aureus*. One preoperative puncture was performed, which was positive for *Streptococcus dysgalactiae*. Intraoperative cultures were

performed in eight patients of which seven (87.5%) were positive. The cultures were monomicrobial in six patients: *Candida albicans*, *Streptococcus agalactiae*, *Escheria Coli*, *Staphylococcus lugdunensis* (in two patients), and *Staphylococcus aureus*, respectively. One patient had a positive, polymicrobial culture. This culture included *Bacteroides fragilis*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Staphylococcus lugdunensis*.

Omniflow® II used for replacement of infected grafts or endografts vs. Omniflow® II used for replacement of non-infected grafts

Thirty-six patients underwent VGEI replacement surgery and 53 patients underwent graft replacement for non-infected grafts. Univariable Cox regression analyses (with the VGEI replacement group as reference) showed significant differences between both groups in favour of the non-infected grafts group regarding primary patency (HR: 3.21 [1.56; 6.65]; p=0.002), primary assisted patency (HR: 3.63 [1.69; 7.80], p<0.001), secondary patency (HR: 2.78 [1.28; 6.03], p=0.010), freedom from major amputation (HR: 3.59 [1.23; 10.46], p=0.019), and freedom from all-cause mortality (HR: 3.24 [1.23; 8.51], p=0.017). No significant difference was observed regarding recurrent vascular graft infection (HR: 0.60 [0.15; 2.41], p=0.471). After correction for confounders in the multivariable Cox regression analyses, no significant differences between the two groups were observed regarding primary patency (HR: 2.34 [0.93; 5.88], p=0.070), primary assisted patency (HR: 2.47 [0.951; 6.44], p=0.063), secondary patency (HR: 1.86 [0.71; 4.86], p=0.204), freedom from major amputation (HR: 1.35 [0.37; 4.97], p=0.654), freedom from all-cause mortality (HR: 1.59 [0.45; 5.70], p=0.473), and freedom from graft infection (HR 1.45 [0.24;8.89], p=0.689). At 1 and 3 years in the group treated for VGEI, primary patencies were 81% and 70%, primary assisted patencies were 81% and 74%, and secondary patencies were 81% and 74%, respectively. The freedom from major amputation was 88%, freedom from all-cause mortality were 95% and 82%, and the freedom from reinfection were 91% and 85% at 1 and 3 years, respectively. In patients treated in a non-infected setting, primary patencies at 1 and 3 years were 49% and 32%, primary assisted patencies were 49% and 32%, and secondary patencies were 64% and 40%, respectively. Freedom of major amputation in the non-infected group were 75% and 63%, freedom from all-cause mortality were 89% and 69%, and the freedom from reinfection were 96% and 91% at 1 and 3 years, respectively.

DISCUSSION

This multi-center study showed the feasibility of the Omniflow® II in different anatomical positions. Femoro-femoral crossover, femoral interposition, and femoro-popliteal grafts (AK and BK) all showed acceptable graft patency and high freedom from major amputation. In femoro-crural bypasses, poor graft patency was observed. However, this group of patients had the highest rate of CLTI (90.9%) pre-operatively.

The use of Omniflow® II as a femoro-femoral crossover bypass has not yet been described in a large group of patients. One study investigated the use of synthetic femoro-femoral bypass grafts (n=133) for unilateral iliac artery occlusion and found slightly higher primary and secondary patencies compared to our results at three years.[18] However, in the current cohort, 50% of femoro-femoral crossover patients had CLTI compared to 17% in the cohort of Park et al. Furthermore, the indication for surgery was related to an infection in almost two-thirds of the patients (treatment of a vascular graft infection or primary Omniflow® II with a high infection risk) in the current cohort compared to 0% in the cohort of Park et al. The reason for the high number of infection-related operations performed with Omniflow® II was due to the available literature regarding acceptable outcomes in patients with a high risk for infection.[19,20] A possible explanation of this property could be that Omniflow ® II grafts allow for early neovascularization and graft incorporation.[21]

The use of Omniflow® II as a femoral interposition graft showed high primary, primary assisted, and secondary patencies (75% at all time points) in the current cohort. Though the most common indication was replacement of an infected graft, the freedom of graft infection was high at 3 years (85%), which is in line with previous research on the use of Omniflow® II for this indication.[10]

Our results regarding femoropopliteal bypasses are in line with existing literature. Evans et al. found a one year graft patency of 54% which is comparable to the primary patency of 61% (AK and BK) in our cohort. They observed a lower rate of limb survival compared to our study (75% vs 91% at one year and 71% vs 86% at three years, respectively).[22] Another study evaluated the use of Omniflow® II for femoro-popliteal bypass and found a lower primary patency compared to the current cohort (60% vs 78% at one year for AK bypasses and 47% vs 52% for BK bypasses).[23] A previously published multi-center study that evaluated Omniflow® II in femoro-popliteal position found higher primary, primary assisted, and secondary patencies (until five years) compared to our results.[8] A possible explanation for this contrast is the difference in indication for bypass surgery compared to our cohort. Eleven percent of the femoro-popliteal bypasses in our cohort were implanted to replace an infected vascular graft, compared to one (0.5%) patient in their study. In addition, in our cohort, CLTI was present in 77.8% (of which 66.1% were in Rutherford class 5-6) of the femoro-popliteal patients compared to 50.7% in their cohort. In the multivariable analyses of the current cohort, femoro-popliteal AK grafts showed a significantly lower hazard on losing primary patency compared to femoro-crural grafts, while no differences were observed between BK femoro-popliteal grafts and femoro-crural grafts. This is in line with the study of Socrate et al. where they found that the necessity of below-the-knee bypass surgery is a predictor of primary patency loss.[24] However, when comparing femoro-popliteal AK and BK in the multivariable analyses no significant differences were observed regarding the mid-term outcomes. The Cochrane review (2018) of Ambler et al. compared different graft types for fem-

oro-popliteal bypass surgery.[25] They found moderate-quality evidence of improved long-term primary patency of venous reconstruction compared to prosthetic materials for AK femoro-popliteal bypass surgery. For BK femoro-popliteal grafts, only low-quality data was available. However, Omniflow® II was not included in this Cochrane review. Further research should compare Omniflow® II with other graft materials.

Primary, primary assisted, and secondary patencies observed in femoro-crural position were lower compared to other positions. Even after adjusting for confounders in the multivariable regression analyes, a lower patency and higher prevalence of major amputation was observed in femoro-crural position compared to femoropopliteal grafts. A possible explanation for these poor outcomes is that the outflow is limited in femoro-crural position. Furthermore, it is known and established in literature that prosthetic grafts have worse outcomes in below-the-knee setting.[26] In this anatomical site, patients often have multilevel disease and morbidity and mortality remains high.[27] Dünschede et al. identified five year patencies in patients with CLTI who received a femoro-crural Omniflow® II bypass with and without distal arteriovenous (AV) fistula.[28] They found patency and amputation rates that are comparable to our cohort, consisting of patients without AV fistula. Three year patencies have been studied in patients who received other materials. One study on heparin-bonded expanded polytetrafluorethylene (HePTFE) femoro-crural bypasses found a primary patency of 70% at 3 years.[29] Another study found a higher primary graft patency for venous (69%) and prosthetic grafts (46%) in femoro-tibial position at three years, compared to our results.[30] Similarly, Bellosta et al. found a primary patency of 33% for heparin-bonded polytetrafluorothylene (propaten) and 47% for precuffed expanded polytetrafluoroethylene (PTFE, Distaflo) at two years follow-up, without significant differences between the two materials (p=0.793). Overall, other materials seem to be more suitable for femoro-crural bypass surgery due to higher patencies.

Interestingly, reinfection was not different when comparing patients treated for VGEI to patients who underwent graft replacement in a non-infected setting. In both groups acceptable low graft infection rates were observed. This is possibly due to the infection resistant properties of this material, which could be declared by a rapid incorporation of the prosthesis by host tissue after implantation.[21] Low infection rates are also shown by earlier studies.[11,20] In our cohort, these low infection rates were especially visible in the femoral interposition group (85% after three years), where the surgical indication was in 72.2% VGEI.

This study has some limitations. First, this cohort is heterogenous due to the inclusion of different surgical indications. However, this broad inclusion allows for generalizability of our results. Another limitation is the retrospective design which may result in a lower level of evidence due to biases compared to prospective cohort studies. However, since the outcomes assessed in this study are hard outcomes, information and detection

biases are less likely. In addition, to the best of our knowledge, this is the largest cohort studies evaluating Omniflow® II used in different anatomical positions with a mid-term follow-up. This study gave the first broad overview on the applicability and efficacy of Omniflow® II. However, future studies should compare revascularizations with Omniflow® II with alternative materials (e.g., autologous vein and prosthetic grafts) in same indications and tracts to draw conclusions regarding superiority of different materials.

Conclusions

This multi-center cohort study shows that it is feasible to use an Omniflow® II in femoro-femoral crossover, femoral interposition, and (AK and BK) femoro-popliteal positions for revascularization. Grafts at these locations showed an acceptable patency with high freedom from major amputation. Omniflow® II at the femoro-crural position showed poorer outcomes making it a less suitable option for this position.

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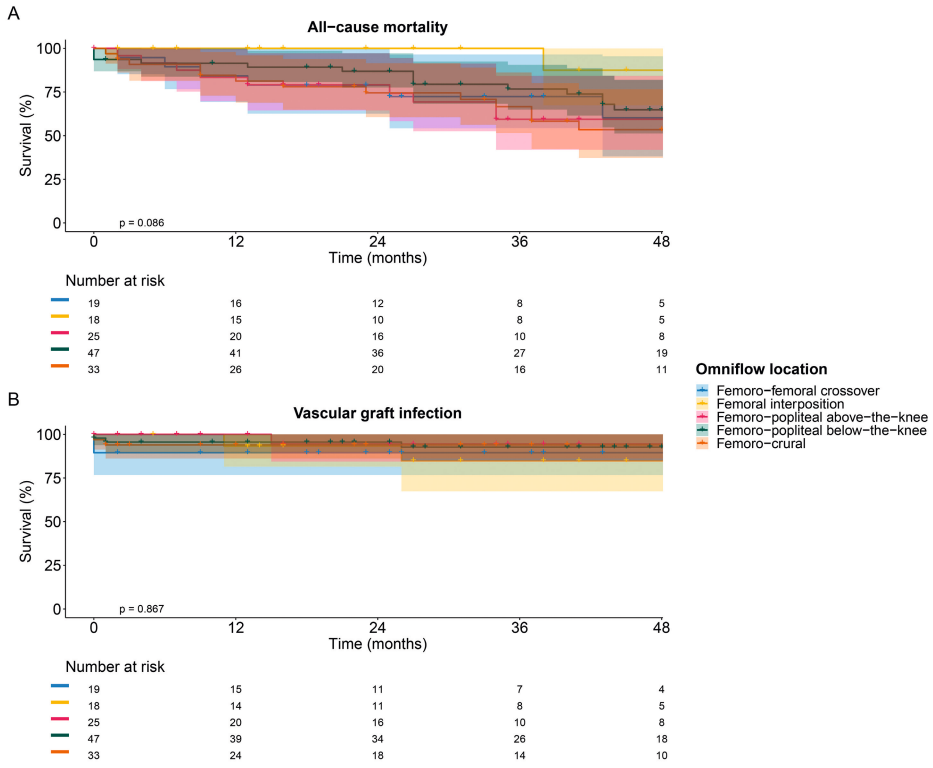
SUPPLEMENTARY DATA

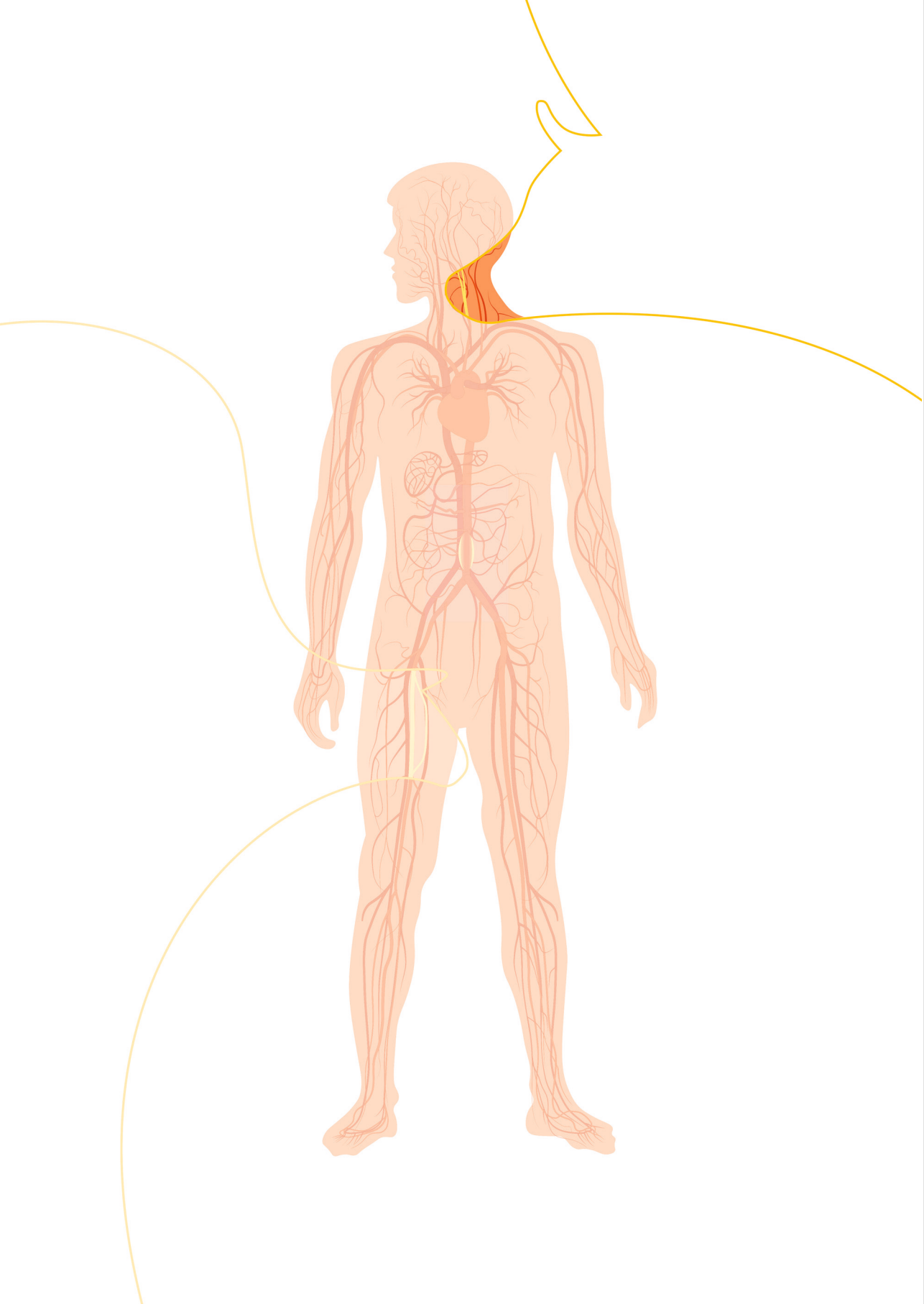
Supplemental Table I. Univariable Cox regression analyses on the estimated effect of graft location on mid-term outcomes including patency, major amputation, mortality, and vascular graft infection.

Outcome	Predictor (Reference: femoro-crural	β (95% CI)	HR (95% CI)	*P*-value
Primary patency	Femoro-femoral	-0.78 (-1.58;0.02)	0.46 (0.21;1.02)	0.057
	Femoral interposition	-1.44 (-2.41;-0.48)	0.24 (0.09;0.62)	**0.003**
	Femoro-popliteal AK	-0.78 (-1.46;-0.11)	0.46 (0.23;0.90)	**0.023**
	Femoro-popliteal BK	-0.59 (-1.14;-0.04)	0.56 (0.32;0.96)	**0.036**
Primary assisted patency	Femoro-femoral	-1.12 (-2.02;-0.23)	0.33 (0.13;0.79)	**0.014**
	Femoral interposition	-1.44 (-2.41;-0.48)	0.24 (0.09;0.62)	**0.003**
	Femoro-popliteal AK	-0.78 (-1.46;-0.11)	0.46 (0.23;0.90)	**0.023**
	Femoro-popliteal BK	-0.71 (-1.28;-0.15)	0.49 (0.28;0.86)	**0.013**
Secondary patency	Femoro-femoral	-1.23 (-2.21;-0.26)	0.29 (0.11;0.77)	**0.013**
	Femoral interposition	-1.28 (-2.21;-0.31)	0.28 (0.11;0.73)	**0.010**
	Femoro-popliteal AK	-0.83 (-1.56;-0.11)	0.44 (0.21;0.90)	**0.024**
	Femoro-popliteal BK	-0.92 (-1.51;-0.31)	0.40 (0.22;0.73)	**0.003**
Amputation	Femoro-femoral	-1.30 (-2.54;-0.07)	0.27 (0.08;0.94)	**0.039**
	Femoral interposition	-1.23 (-2.47;0.00)	0.29 (0.09;1.00)	0.051
	Femoro-popliteal AK	-1.61 (-2.85;-0.38)	0.20 (0.06;0.69)	**0.011**
	Femoro-popliteal BK	-1.43 (-2.32;-0.53)	0.24 (0.10;0.59)	**0.002**
Mortality	Femoro-femoral	-0.47 (-1.42;0.47)	0.62 (0.24;1.61)	0.329
	Femoral interposition	-2.19 (-4.20;-0.17)	0.11 (0.02;0.84)	**0.033**
	Femoro-popliteal AK	-0.11 (-0.88;0.66)	0.89 (0.41;1.93)	0.774
	Femoro-popliteal BK	-0.55 (-1.23;0.15)	0.58 (0.29;1.17)	0.121
Vascular graft infection	Femoro-femoral	0.58 (-1.38;2.54)	1.79 (0.25;12.69)	0.562
	Femoral interposition	0.57 (-1.39;2.53)	1.77 (0.25;12.54)	0.570
	Femoro-popliteal AK	-0.44 (-2.85;1.96)	0.64 (0.06;7.07)	0.717
	Femoro-popliteal BK	-0.02 (-1.81;1.77)	0.99 (0.16;5.89)	0.985

Abbreviations: β, beta; CI, confidence interval.

Supplemental Figure 1. All-cause mortality (A) and vascular graft infection (B) of Omniflow® II stratified by bypass location.





Chapter 7

Patch angioplasty during carotid endarterectomy using different materials has similar clinical outcomes

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ABSTRACT

Objectives

Patch angioplasty during carotid endarterectomy (CEA) is commonly used to treat carotid artery stenosis. However, the choice of which patch to use remains a matter of debate. Autologous venous material has disadvantages such as wound-related problems at the harvest site and a prolonged intervention time. These limitations can be bypassed when synthetic or biological patches are used. Both materials have been associated with divergent advantages and disadvantages. Therefore, the aim of our study was to compare the long-term follow-up outcomes in patients who underwent CEA and closure with either a bovine pericardial patch (BPP) or polyester patch.

Methods

A retrospective cohort study was conducted including all patients who underwent primary CEA and closure with a BPP or a polyester patch between January 2010 and December 2020 at our tertiary referral center. In 2015, the BPP was introduced as an alternative for polyester. The primary outcome was the occurrence of transient ischemic attack (TIA) or cerebrovascular accident (CVA) during follow-up and secondary outcomes included restenosis, reintervention, all-cause mortality, and patch infection. Cox proportional hazard models were used and hazard ratios with 95% confidence intervals were used to predict these outcomes.

Results

We included 417 CEA patients; 254 patients (61%) received a BPP and 163 received (39%) a polyester patch. The mean age was 70.2 ± 8.7 years and 67% were male. The median follow-up time was 15 months (range, 12-27 months) for BPP and 42 months (range, 16-60 months) for polyester ($P < .001$). Postoperative hematoma (≤30 days) was significantly lower in the BPP cohort (2% BPP vs 6% polyester; $P = .047$). No other significant differences on short-term outcomes were found. Univariable Cox regression analyses showed no significant differences between the effect estimates of polyester and BPP on TIA or CVA ($P = .106$), restenosis ($P = .211$), reintervention ($P = .549$), or all-cause mortality ($P = .158$). No significant differences were found after adjusting for confounders in the multivariable analyses: TIA or CVA ($P = .939$), restenosis ($P = .057$), reintervention ($P = .193$) and all-cause mortality ($P = .742$). Three patients with a polyester patch had patch infection compared with none of the patients in the group who received a BPP.

Conclusions

This large retrospective study showed comparable safety and durability of both BPP and polyester suggesting that both patch types can be safely applied for CEA with patch angioplasty. Patch infection was rare and was absent in the BPP group.

INTRODUCTION

Stenosis of the internal carotid artery is one of the major causes of ischemic stroke.[1,2] To decrease the risk of stroke in both symptomatic and asymptomatic carotid stenosis carotid endarterectomy (CEA) with patch angioplasty may be performed. For patients undergoing CEA, routine patch closure is recommended, rather than primary closure.[3] A variety of materials are available, including autologous veins (e.g., the saphenous vein), synthetic patches (e.g., polytetrafluoroethylene or polyester), and biological patches (e.g., bovine pericardial patches [BPP]).[4–6] However, the choice of which patch to use remains a matter of debate.[3] Although saphenous vein patches are often used and deliver good results, many disadvantages exist, resulting in a prolonged intervention time. Further, an additional incision must be made, which in turn increases the risk of developing wound complications at the harvest site, especially in patients with vascular disease owing to poor wound healing and a higher risk of infection.[1,7] These limitations can be bypassed when synthetic or biological patches are used, which are usually readily available. However, synthetic patches may be more thrombogenic, carry a higher risk of infection, and have an increased risk of bleeding when compared with autologous venous patches.[8] In recent years, the use of BPP has become more popular. A recently published network meta-analysis did not find significant differences between BPP and polyester patch regarding 30-day stroke or death rate and late restenosis.[9] In 2021, a Cochrane review demonstrated that BPP material may decrease the incidence of fatal stroke, infection, and death when compared with other graft materials.[1] However, the quality of evidence was low owing to the small numbers of events. Although these studies showed promising short-term outcomes for BPP, long-term outcomes for most patch types are still unknown and there are insufficient high-quality data to make recommendations in guidelines. Therefore, the aim of our study was to evaluate the difference between BPP and polyester in long-term follow-up outcomes (i.e., transient ischemic attack [TIA] or cerebrovascular accident [CVA], restenosis, reintervention, all-cause mortality, or patch infection in patients who received a CEA with patch angioplasty).

METHODS

Study design

All consecutive patients who underwent primary CEA with patch closure using bovine pericardium or polyester between January 2010 and December 2020 at our tertiary referral center were included in this study. In 2015, BPP was introduced as an alternative for polyester. In 2016, BPP surpassed polyester as the most used patch for CEA in our center. Patients who underwent CEA with primary closure or closure with other patch types than BPP/polyester were excluded from the current study.

The institutional review board approved dispensation in accordance with Dutch law on patient-based medical research obligations (registration no. METc 2021/493). Conse-

quently, informed consent was not obtained. All patient-related data were processed anonymously and stored electronically in agreement with the Declaration of Helsinki – Ethical principles for medical research involving human subjects.[10]

Patient characteristics and definitions

Baseline characteristics that were obtained from the electronic patient file included age at surgery in years, sex, body mass index, tobacco use, hypertension, hyperlipidemia, diabetes mellitus, and cardiac, pulmonary, and renal disease. Tobacco use was defined as current use or less than 1 year of abstinence. Hypertension, hyperlipidemia, cardiac, pulmonary, and renal disease were classified by the Society for Vascular Surgery (SVS) system (classes 0-3) according to the Ad Hoc Committee on Reporting Standards.[11,12] These comorbidities were scored positive if the status was 1 or higher. Symptomatic carotid stenosis (>50% internal carotid artery stenosis) was defined as ipsilateral CVA, TIA, or ocular symptoms (amaurosis fugax) 6 or fewer months before surgery. Asymptomatic stenosis was defined as asymptomatic internal carotid artery stenosis of more than 50% or as symptomatic carotid stenosis more than 6 months earlier (following the reporting standards for carotid interventions from the SVS and the European Society for Vascular Surgery guidelines).[3,13] Furthermore, symptoms at presentation, antiplatelet therapy, anticoagulation use, and statin use were collected. Grade of preoperative ipsilateral stenosis as seen on the duplex ultrasonography was noted. We used the following peak systolic velocities for the internal carotid artery: less than 125 cm/s for a less than 50% stenosis, 125 cm/s or more for 50% to 69% stenosis, 230 cm/s or more for 70% to 89% stenosis, and 400 cm/s or more for more than 90% stenosis (but not near occlusion).[14] The presence of contralateral occlusion of the internal carotid artery, as shown on duplex ultrasound examination, was noted.

Surgical procedure

Details of surgical procedure have been published previously.[15,16] Before surgical treatment, patients received a statin and antiplatelet therapy (aspirin 100 mg/d and/or clopidogrel 75 mg/d) unless they were already using anticoagulants. Before clamping the carotid artery, patients received 5000 IU heparin intravenously. Intraoperative monitoring was performed using electroencephalography and transcranial Doppler imaging. Intraoperative shunting was performed if there were significant electroencephalography and/or transcranial Doppler changes. Longitudinal arteriotomy was closed using a patch made of bovine pericardium (XenoSure Biologic Vascular Patch; LeMaitre, Burlington, MA) or polyester (Hemagard Carotid Patch; Getinge, Göteborg, Sweden). Protamine was not administered routinely. Postoperative monoantiplatelet or anticoagulant therapy was continued.

The following intraoperative variables were collected: operation side (left/right), type of anesthesia (regional or total), blood loss (mL), clamping time (minutes), shunting (yes/no), and patch type (BPP or polyester).

Postoperative length of hospital stay was noted. Standard antiplatelet therapy was given after CEA and surveillance duplex was performed 6 weeks postoperatively, followed once a year thereafter.

Outcome

The primary outcome measure was the occurrence of ipsilateral TIA/CVA during follow-up. This was based on evaluation by a neurologist and confirmation with cerebral imaging. Secondary outcomes included ipsilateral restenosis, ipsilateral reintervention, all-cause mortality, and patch infection. A peak systolic velocity threshold of more than 213 cm/s was used for diagnosing a restenosis of more than 50%.[3] Restenosis was scored positive if greater than 50%. Reintervention was defined according to the reporting standards for carotid interventions from the SVS as any postprocedural adjunctive maneuvers (i.e., management of access site complications and management of postoperative stroke).[13] Patch infection was diagnosed according the Management of Aortic Graft Infection group classification (with at least one major criterion and one minor criterion from another category).[17]

In addition, short-term results within 30 days after CEA were also considered consisting of peripheral nerve damage, cardiac complication (myocardial infarction, angina pectoris, arrhythmia, or heart failure), delirium, urinary tract infection, wound infection, cervical hematoma (defined according to the SVS reporting standards for carotid interventions; SVS classes 1-3 were scored as positive), restenosis, TIA/CVA, and mortality.[13]

Statistical analysis

The distribution of continuous data was checked visually and supplemented by the Shapiro-Wilk test. The means and standard deviations of normal distributed continuous variables were calculated. Skewed distributed data were presented as median and interquartile range. The Student *t* test was used to compare normal distributed variables and Mann-Whitney *U* tests was used to compare variables with a skewed distribution between both patch types. Fisher's exact test was performed to compare categorical variables. Kaplan-Meier survival curves were plotted to visualize the effect of patch types on the primary and secondary outcome(s). Survival analysis was performed using Cox proportional hazard model with stepwise backward elimination calculating hazard ratio with the 95% confidence interval. Univariable Cox regression models were fitted to assess the crude effect of patch type on time to the occurrence of TIA/CVA, restenosis, reintervention, all-cause mortality, and patch infection. Subsequently, multivariable models were fitted for each outcome. The eligible variables for the adjusted models were selected whenever the univariable analyses between both patch types yielded a *P* value of less than .10. A variable was considered a confounder whenever the regression coefficient of the patch type changed by 10% or more. Confounders remained included in the multivariable models. Effect modification by diabetes mellitus and hypertension was also tested by including an interaction term (e.g., Patch type × Diabetes

mellitus and Patch type × Hypertension). All models yielded an estimated regression coefficient (β) with a corresponding hazard ratio and 95% confidence interval. The Cox regression model assumptions were tested and fulfilled. Statistical analysis was performed in R, version 4.0.5 (R Foundation for Statical Computing, Vienna, Austria), using the *survival*, *survminer-*, and *ggplot2*-packages. In all analyses, a *P* of less than .05 was considered statistically significant.

RESULTS

In total, 417 CEA patients were included. Two hundred fifty-four patients (61%) received a BPP and 163 received a polyester patch (39%). The mean age of the total group was 70.2 ± 8.7 and 67% were male. In Table I, baseline characteristics and comorbidities per patch type are listed. Patients with a polyester patch were more likely to have hypertension (*P* = .004), cardiac disease (*P* = .001), and renal disease (*P* = .003). No other differences between patch types were found.

Table I. Patient characteristics associated with type of patch

Patient Characteristics	Bovine N (%) or mean ± SD	Polyester N (%) or mean ± SD	*P*-value
No. of patients	254 (61)	163 (39)	-
Age in years	69.6 ± 8.6	71.2 ± 8.9	0.076
Sex (males)	169 (67)	111 (68)	0.740
BMI in kg/m^2	27.2 ± 4.1	27.5 ± 5.1	0.518
Tobacco use	115 (45)	63 (39)	0.199
Hypertension	168 (66)	129 (79)	**0.004**
Hyperlipidaemia	211 (83)	139 (85)	0.550
Diabetes mellitus	55 (21)	48 (29)	0.072
Cardiac disease	85 (33)	80 (49)	**0.001**
Pulmonary disease	37 (15)	30 (18)	0.298
Renal disease	45 (18)	49 (30)	**0.003**

Abbreviations: SD=standard deviation.

There is a significant difference in the distribution of preoperative presentation (ipsilateral symptoms) in both groups (*P* < .001). There were no statistically significant differences in preoperative medication (antiplatelet, anticoagulation, and statin use), grade of stenosis, or presence of contralateral occlusion of the internal carotid artery (Table II).

Table II. Pre-, intra- and postoperative characteristics

Characteristic	Bovine N (%) or mean ± SD or median (IQR)	Polyester N (%) or mean ± SD or median (IQR)	*P*-value
Preoperative			
Ipsilateral symptoms			**<0.001**
CVA	89 (35)	74 (45)	
TIA	101 (40)	51 (31)	
Ocular	57 (22)	22 (13)	
Asymptomatic	7 (3)	16 (10)	
Antiplatelet therapy	236 (93)	145 (89)	0.160
Anticoagulation	32 (14)	26 (19)	0.334
Statin use	219 (86)	137 (84)	0.540
Stenosis grade			0.680
<50%	1 (0)	0 (0)	
50-69%	56 (22)	34 (21)	
70-89%	176 (69)	119 (73)	
>90% (but not near-occlusion)	21 (8)	10 (6)	
Contralateral occlusion	13 (5)	12 (7)	0.400
Intra-operative			
Operation side (right)	112 (44)	70 (43)	0.817
Intervention time (min)	148 ± 35	184 ± 32	**<0.001**
Clamping time (min)	33 ± 8	34 ± 9	0.165
Shunt use	31 (12)	15 (9)	0.333
Postoperative			
Length of hospital stay (days)	3(3-4)	3 (3-4)	0.580
Antiplatelet therapy	244 (96)	152 (93)	0.252
Use of anticoagulation	33 (13)	24 (15)	0.662

Abbreviations: SD=standard deviation, IQR= interquartile range (IQR is written as: first quartile-third quartile), min=minutes, TIA= transient ischemic attack, CVA= Cerebrovascular accident.

Intraoperative variables are shown in Table II Clamping time was 33 ± 8 minutes in BPP patients and 34 ± 9 in patients with a polyester patch (*P* = .165). Operation time was significantly longer in the group with CEA with polyester compared with BPP, at 184 ± 32 compared with 148 ± 35 minutes (*P* < .001). Thirty-one BPP patients (12%) underwent shunting compared with 15 polyester patients (9%) (*P* = .333).

The median postoperative length of hospital stay was 3 days (3-4 days) for both patch types. The median follow-up time was 15 months (12-27 months) for BPP and 42 months

(16-60 months) for polyester (*P* < .001). Other postoperative characteristics are shown in Table II.

Short-term complications (≤30 days post-procedure)

Short-term (≤30 days) postoperative complications are summarized in Table III Peripheral nerve damage occurred in 15 patients (6%) with BPP and 16 patients (10%) with a polyester patch (*P* = .136). Three patients (1%) with a BPP and 2 (1%) with a polyester patch developed a wound infection (*P* > .999). Clinical symptoms that were observed were fever, redness, localized pain, and swelling. All patients got antibiotic therapy (oral or intravenous) and three patients (2 BPP and 1 polyester) were treated with incision and drainage. None of the patients developed a patch infection. There were significantly fewer BPP patients with a postoperative cervical hematoma compared with polyester patients (5 [2%] vs 9 [6%]; *P* = .047). There were no significant differences on short-term (ipsilateral) restenosis, TIA/CVA, and mortality between in BPP and polyester patients. Two patients (1%) versus 2 patients (1%) had a restenosis (*P* > .999), 7 (3%) versus 10 (6%) had a TIA or CVA (*P* = .088), and 0 (0%) versus 2 (1%) patients died within 30 days postoperative (*P* = .152).

Table III. Post-operative short-term adverse outcomes

Characteristic	Bovine N (%)	Polyester N (%)	*P*-value
Peripheral nerve damage	15 (6)	16 (10)	0.136
Cardiac complication[a]	4 (2)	6 (4)	0.198
Delirium	4 (2)	4 (2)	0.717
Urinary tract infection	3 (1)	2 (1)	1.000
Wound infection	3 (1)	2 (1)	1.000
Cervical hematoma (Class 1-3[b])	5 (2)	9 (6)	**0.047**
Restenosis	3 (1)	2 (1)	1.000
TIA or CVA	7 (3)	10 (6)	0.088
Mortality	0 (0)	2 (1)	0.152

Abbreviations: TIA= transient ischemic attack, CVA= Cerebrovascular accident.
[a] defined as: myocardial infarction, angina pectoris, arrhythmia, or heart failure.
[b] according to the Society of Vascular Surgery Reporting standards for carotid interventions

Long-term outcomes

An overview of the number of adverse events per patch type is shown in Fig 1. The univariable Cox regression analyses showed no significant differences between the effect estimates of polyester and BPP on TIA/CVA (*P* = .106), restenosis (*P* = .211), re-intervention (*P* = .549), and all-cause mortality (*P* = .158) (Table IV and Fig 2). After adjusting for confounders in the multivariable Cox regression analyses, no significant

differences were found between patch types on TIA/CVA (*P* = .939), restenosis (*P* = .057), reintervention (*P* = .193), and all-cause mortality (*P* = .742) (Table IV). Effect modification by diabetes mellitus and hypertension was not observed in any model (all *P* > .073).

Figure 1. Total number of adverse events in patients with bovine pericardial patch (BPP) and polyester patch.

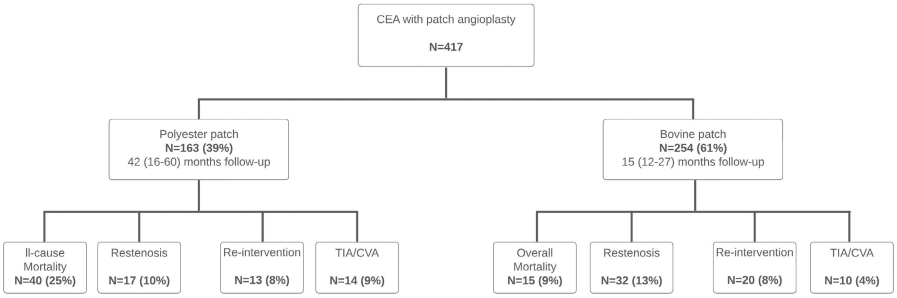
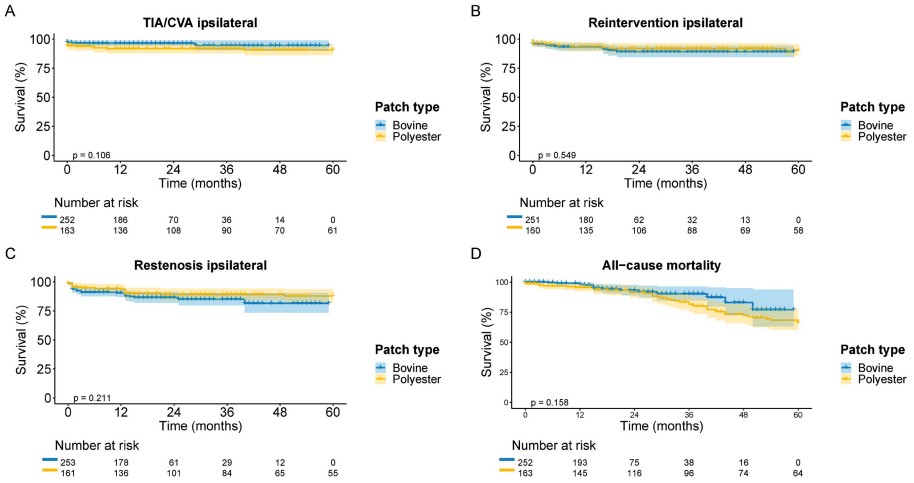


Table IV. Uni- and multivariable Cox regression analyses of the effect of patch type on TIA/CVA, restenosis, re-intervention, and all-cause mortality after 5-year follow-up.

Outcome	Predictor	β (95% CI)	HR (95% CI)	*P*
TIA or CVA (ipsilateral)	Polyester (ref: Bovine)	0.68 (-0.14-1.50)	1.97 (0.87-4.47)	0.106
	Polyester (ref: Bovine)[1]	-0.03 (-1.05-0.97)	0.96 (0.35-2.63)	0.939
Restenosis (ipsilateral)	Polyester (ref: Bovine)	-0.38 (-0.98-0.22)	0.68 (0.37-1.24)	0.211
	Polyester (ref: Bovine)[2]	-0.74 (-1.50-0.02)	0.48 (0.22-1.02)	0.057
Re-intervention (ipsilateral)	Polyester (ref: Bovine)	-0.22 (-0.94-0.50)	0.80 (0.39-1.65)	0.549
	Polyester (ref: Bovine)[3]	-0.62 (-1.56-0.32)	0.54 (0.21-1.37)	0.193
All-cause mortality	Polyester (ref: Bovine)	0.45 (-0.17-1.07)	1.57 (0.84-2.93)	0.158
	Polyester (ref: Bovine)[4]	0.13 (-0.62-0.88)	1.13 (0.54-2.40)	0.742

[1]adjusted for age, hypertension, renal disease, cardiac disease, symptoms ipsilateral, intervention time, shunt use.
[2] adjusted for intervention time.
[3]adjusted for intervention time, shunt use.
[4]adjusted for age, diabetes mellitus, renal disease, intervention time, shunt use, symptoms ipsilateral.
(tested: age, sex, hypertension, diabetes mellitus, cardiac disease, renal disease, intervention time, symptoms ipsilateral, shunt use).

Figure 2. Survival curves per patch type for different outcomes. **A,** Transient ischemic attack (TIA)/cerebrovascular accident (CVA) ipsilateral. **B,** Reintervention ipsilateral. **C,** Restenosis ipsilateral. **D,** All-cause mortality.



Peripheral nerve damage

One (7%) of the 15 BPP patients and 3 of the 16 polyester patch patients (19%) with (short-term) peripheral nerve damage had persistent symptoms at 1 year of follow-up (P = .600).

Patch infection

Three patients had a suspected graft infection in the total follow-up period. Two patients with a polyester patch presented with a pseudoaneurysm (after 57 and 37 months). The first patient underwent replacement surgery with an autologous venous patch and the second patient was treated conservatively. This patient was not fit enough for surgery and was treated with antibiotics alone. Diagnosis was based on clinical characteristics, intraoperative view, and imaging. Materials cultured during surgery were negative, however probably owing to long antibiotic use before surgery. The third patient presented (6 months postoperatively) with a fistula that extended from the (polyester) patch to the skin (Supplementary Figure). This infected graft was also replaced by an autologous venous patch. Intraoperative cultures were positive for *Staphylococcus aureus.*

DISCUSSION

In this retrospective study, we investigated the short- and long-term outcomes between BPP and polyester for CEA. With 417 CEA patients, of which 254 (61%) BPP, this is one of the largest retrospective studies comparing BPP with a synthetic alternative.[18] Our results showed that there were no statistically significant differences between the patch types regarding TIA/CVA, restenosis, reintervention, and all-cause mortality on multi-

variable analyses. These long-term outcomes without significant differences between both patch materials are comparable with previous published studies.[4,7,18,19]

Graft infection was rare and occurred in three patients with a polyester patch only; none of the BPP patients was affected. A similar lower infection rate (0.59%) of BPP compared with synthetic patches was found previously.[19] The hypothesis is that BPP is an acellular xenograft, making it less susceptible to infection compared with synthetic patches.[1] This acellular material of collagen may provide a natural environment for host cell migration and proliferation, which causes reendothelialization.[20] The possible infection resistant property was also demonstrated by several reports on BPP used in cardiovascular (graft) infection.[21–24]

Our study demonstrated that significantly fewer BPP patients has short-term (≤30 days) cervical hematoma compared with polyester patch patients (P = .047). A possible explanation for this difference may be the fact that the total suture line bleeding is significantly less with BPP compared with polyester patches (after adjustment for activated clotting time).[25] In this previously published study, bleeding at 3 and 4 minutes after carotid cross-clamp removal was observed. Furthermore, blood loss was quantified by weighing the sponge used to tamponade the bleeding. Suture line bleeding may be an explanation for the longer operation time that we found in the polyester patch group.

A previously published study did not show differences in 30-day hematoma (which required reintervention) between BPP and other materials (polyester, venous, primary closure, and other techniques).[18]

This study has limitations. First, the retrospective design of the study causes a lower level of evidence compared with prospective studies and causes a heterogenous sample with variety of follow-up periods. Because BPP was introduced in 2015, this type of patch had a shorter median follow-up time compared with polyester patch in our study. However, the medical management, diagnostic criteria, and surgical procedure remained the same throughout the study period (2010-2020). Because this study compares one type of BPP and one type of polyester patch, the results may differ when compared with patches from other manufacturers. Furthermore, the number of adverse events (longer term outcomes) were scarce, so comparison between two groups requires a large amount of patients to decrease type II error. In particular, the trends observed on the differences of short-term TIA/CVA (P = .088) and restenosis (P = .057) in the multivariable analysis deserve to be further investigated using a larger sample size. However, this is one of the largest retrospective studies comparing BPP with polyester patches on longer term outcomes.

Conclusion

This study showed comparable safety and durability of both BPP and polyester, making both options acceptable for CEA with patch angioplasty. Patch infection was rare and only three patients with a polyester patch were affected, while absent in the BPP group. In the short term, there were significantly fewer BPP patients with a postoperative hematoma compared with polyester patients. The choice between patch types remains depending on the experience of the surgical team.[3] Future studies with a larger sample will have to determine if there is a difference in the risk of getting (graft) infection between BPP and polyester.

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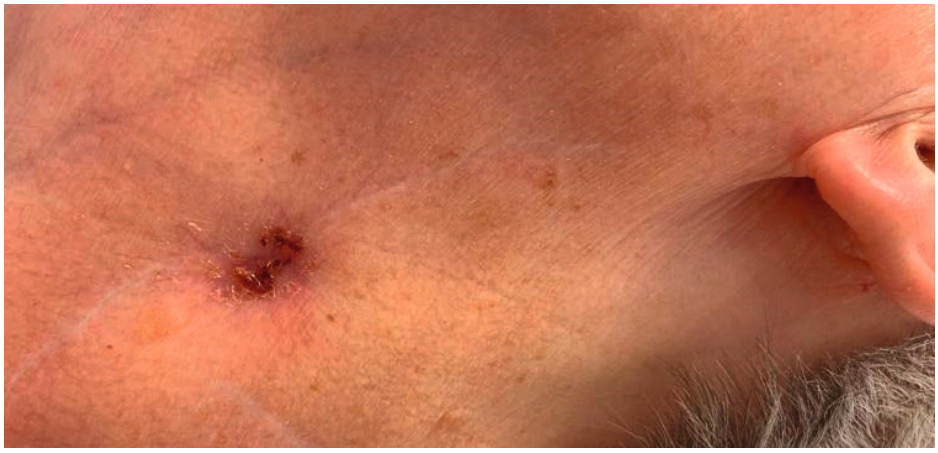
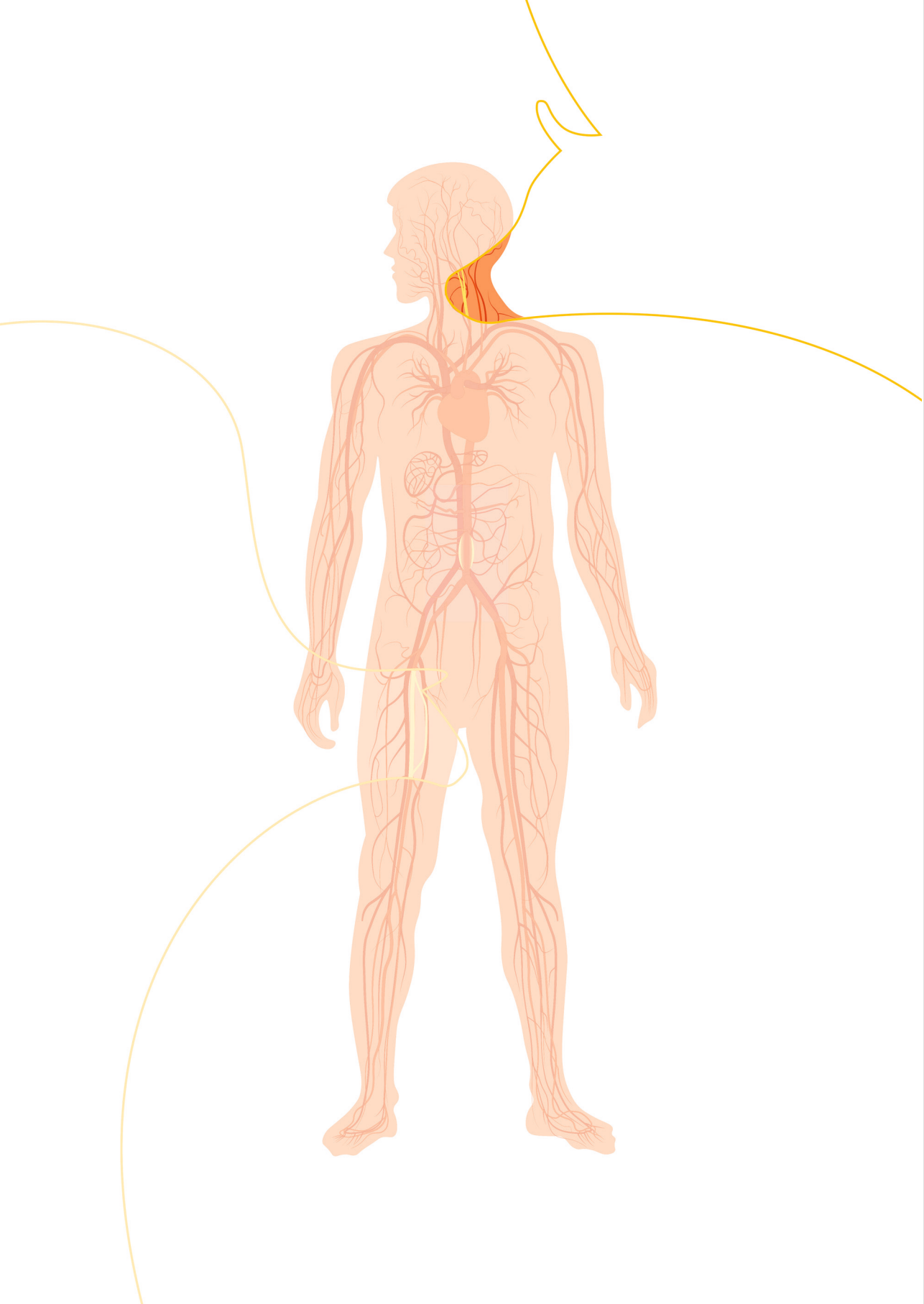
SUPPLEMENTARY DATA

Supplemental Figure. Fistula that extended to the skin of the patient.





Chapter 7a

Letter to the editor: “Autologous pericardium could be a good option as patch material for sensitive patients undergoing carotid endarterectomy surgery to avoid legal consequences”

Journal of Vascular Surgery, 2023

Emre Kubat
Veysel Başar
Ferit Çiçekçioğlu

We recently read the article titled “Patch angioplasty during carotid endarterectomy using different materials has similar clinical outcomes” by Liesker et al.[1] We congratulate them for their largescale study results. Their results are consistent with a recently reported Cochrane database analysis.[2] We know that no consensus has been reached regarding the best patch material to use for such patients. As a biologic patch material, bovine pericardial patches were found to be comparable in cost with the cost of other patch materials owing to their low risk of infection and advantages in terms of postoperative bleeding. The main reason for these advantages is that this patch material is an acellular xenograft. However, the patient population in general will not be homogeneous. The number of individuals who could be concerned about the use of ingredients of animal origin has been increasing and is an issue that we, as healthcare professionals, should no longer ignore. We should not forget that it is unethical to use a product when we know that its use is against the patient’s wishes. Thus, the use of biologic xenografts could result in legal consequences, and it will become necessary to obtain the consent of the patient for the use of these materials.[3] Therefore, the use of bovine pericardial patches could be a disadvantage for ethnic groups who are particularly sensitive about the use of additional biologic xenograft materials. We believe autologous pericardium might be a good alternative as a biologic patch material for patients sensitive about the use of bovine pericardial patches who require simultaneous carotid endarterectomy and coronary artery bypass grafting surgery. Recently, our retrospective results were reported (titled “Autologous pericardium may be an alternative carotid patch material in patient with undergoing simultaneous carotid endarterectomy and coronary artery bypass grafting”).[4] To the best of our knowledge, our study was the first study of the use of autologous pericardium as an alternative patch material during carotid endarterectomy surgery. Our study results revealed no statistically significant differences between the Dacron and autologous pericardial patch group, except for bleeding. Although our study had some limitations such as the retrospective design and small sample size, the use of autologous pericardium could be good option for sensitive patients as a biologic carotid patch owing to low postoperative bleeding profile, absence of immunoreactivity, its biocompatibility and resistance to infection, easy availability, and low cost.

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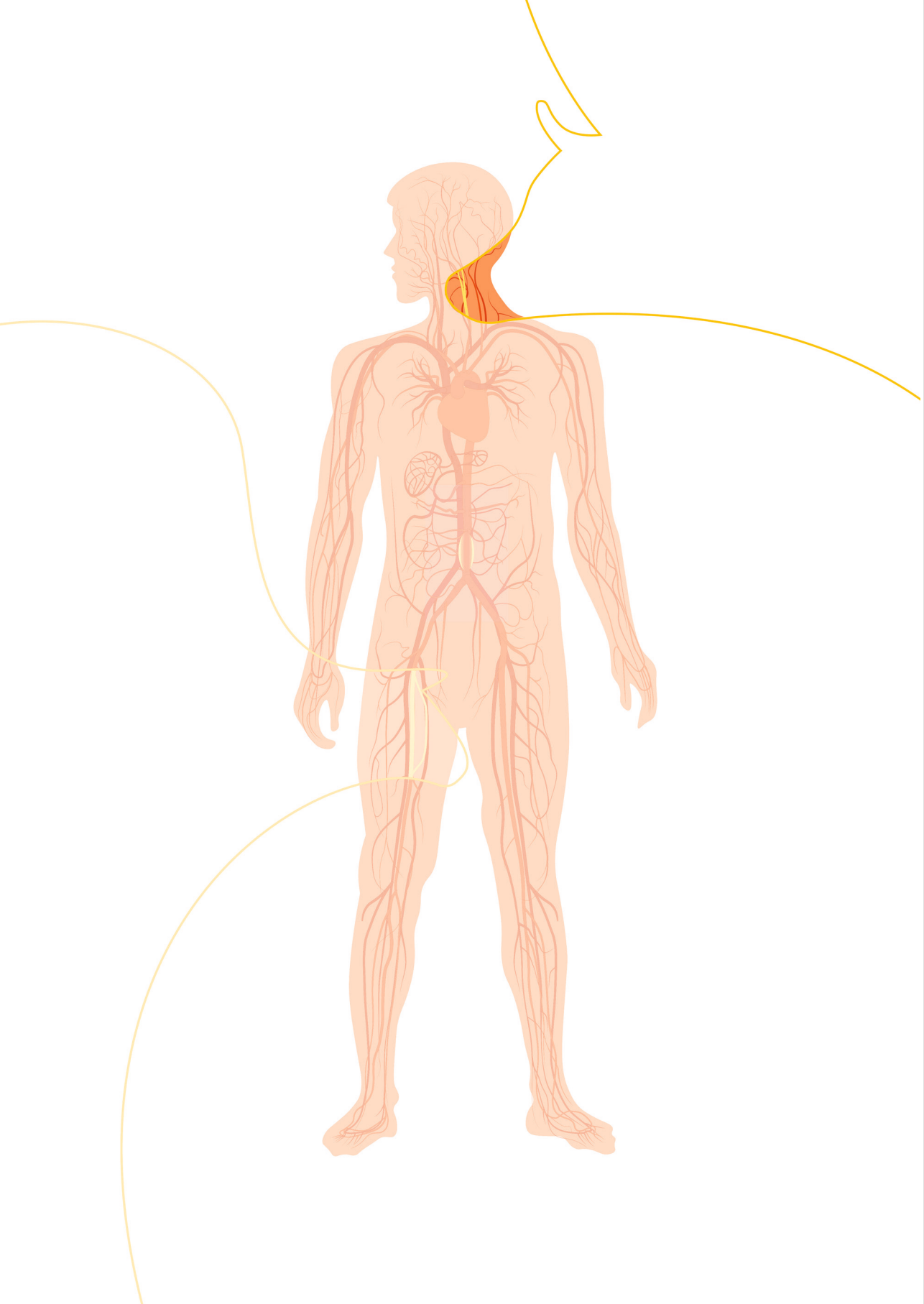

Chapter 7b

Reply

Journal of Vascular Surgery, 2023

David J. Liesker
Barzi Gareb
Rick S. Looman
Clark J. Zeebregts
Ben R. Saleem

With great interest, we read the comments by Kubat et al. regarding our study comparing bovine pericardial and polyester patches for carotid endarterectomy (CEA).[1] We agree that it is necessary to discuss the use of animal-derived materials with patients owing to the potential aversion they might have to these graft materials.[2] At our center, we disclose this information (including the use of bovine pericardial patches) to ensure the patient is able to make an informed decision before CEA.[3]

Although we agree that autologous pericardium could be an option, high-quality evidence to fully support this suggested alternative is unavailable. Başar et al.[4] examined patients who had undergone concomitant CEA and coronary artery bypass grafting (CABG). They showed promising results in favor of the autologous pericardial patch (n = 13). However, the sample size was too small to draw firm conclusions.[4] The Society for Vascular Surgery and European Society for Vascular Surgery guidelines have stated that CEA should be considered before or concurrent with CABG for patients with symptomatic carotid stenosis (50%-99%), bilateral asymptomatic stenosis (70%-99%), or unilateral stenosis (70%-99%) with contralateral occlusion who require both procedures.[5,6] For CABG patients with unilateral asymptomatic stenosis, staged or concomitant carotid intervention has not been recommended.[6] No specific recommendations on sequencing have been provided. Few patients have undergone concomitant CEA and CABG. Therefore, autologous pericardium is not often available.

When comparing the safety and durability of bovine and polyester patches, our results were basically similar to those found in a Cochrane review.[7] Minor differences were observed regarding the incidence of patch infection and postoperative hematoma. This had most probably resulted from the nature of the bovine pericardial patch, because it is an acellular xenograft of collagen that might provide a natural environment for host cell migration and proliferation. This, in turn, causes re-endothelialization.[8] However, at present, reported data are lacking to support the use of a biologic patch instead of a polyester patch. Therefore, with only minor differences between the two patches, we would advise the use of a polyester patch for CEA with patch angioplasty for patients who choose not to receive xenograft material.

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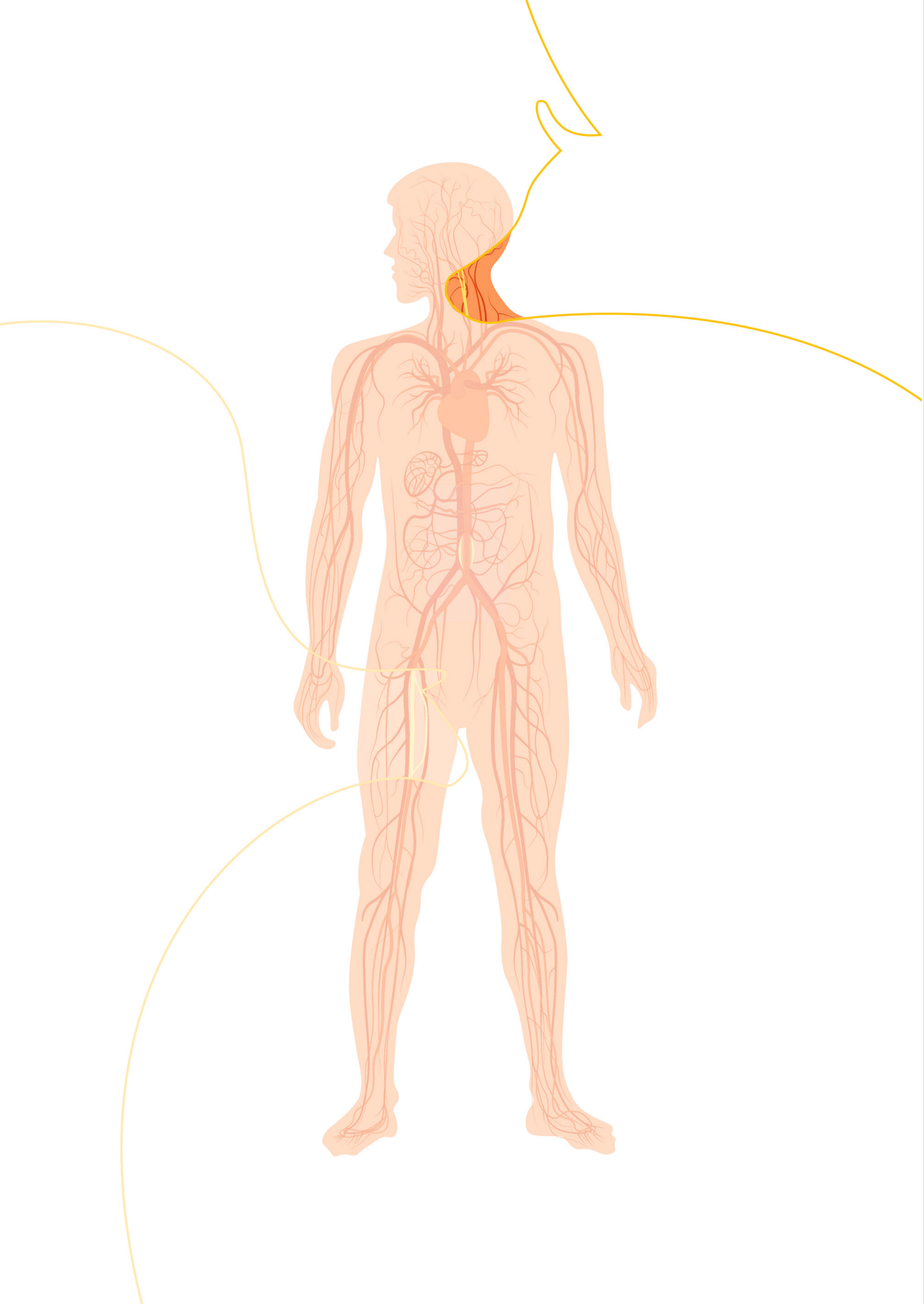

Chapter 8

Similar long-term outcomes for venous, bovine pericardial, and polyester patches for primary carotid endarterectomy in standard risk patients

American Journal of Surgery, 2023 (submitted)

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ABSTRACT

Background

Currently, the type of patch used for carotid endarterectomy (CEA) closure depends on the preference of the surgeon. Various patch materials are available. The purpose of this study was to compare the long-term outcomes of these patches.

Methods

Patients who underwent primary CEA with patch angioplasty using a venous patch, bovine pericardial patch (BPP), or polyester patch between 2010-2020 at two university medical centers were included. Study endpoints included long-term ipsilateral transient ischemic attack, cerebrovascular accident, ipsilateral restenosis, ipsilateral reintervention, and all-cause mortality.

Results

In total, 1481 CEAs were performed with a median follow-up of 32 (13-65) months. Venous patch was used in 309 patients (20.9%), BPP in 1000 patients (67.5%), and polyester patch in 172 patients (11.6%). Multivariable analyses showed no significant differences between the three materials regarding the long-term outcomes.

Conclusions

In standard risk patients undergoing primary CEA, the use of venous, BPP, or polyester patches seems equally safe and durable.

INTRODUCTION

Carotid endarterectomy (CEA) with standard or selective patch angioplasty may reduce the risk of perioperative occlusion and long-term restenosis and is therefore recommended over standard primary closure.[1,2] Various materials are currently available for patch angioplasty, including autologous vein, synthetic materials (e.g., polyester or polytetrafluoroethylene [PTFE]), or biological xenografts (e.g., bovine pericardial patch [BPP]). However, no specific recommendations are available with regard to which patch type to use. Currently, the choice depends on the preference of the operating surgeon.[1] Autologous venous patches (most commonly the great saphenous vein) show good results, with easy handling characteristics and resistance to infection.[3] However, a suitable vein is not always available. Furthermore, harvesting the vein prolongs intervention time and it carries the risk of developing wound complications at the harvesting site such as infection.[2,4] An advantage of using synthetic, 'off the shelf", patches such as synthetic or biological xenograft patches, is that the vein is left intact for future coronary or peripheral bypass surgery. A systematic review and meta-analysis that included CEA with either venous or synthetic patches showed similar outcomes for venous and synthetic patches in terms of reducing the risk of stroke, death, and restenosis during the perioperative period and long-term follow-up.[5] However, this meta-analysis included only one randomized controlled trial (RCT) comparing BPP (n=51) to synthetic patches (n=44) with a follow-up until 1 year, and redo CEA was not described as exclusion criterium. For intraoperative comparison, the RCT showed that BPP had significantly shorter suture-line bleeding time compared to polyester. Another group conducted a network meta-analysis and found that patching with BPP or PTFE was associated with a lower rate of short-term and long-term adverse outcomes compared to other techniques such as autologous vein and Dacron patching.[6] Our recent single center study compared BPP and polyester patches in 416 patients. Both patch types showed comparable safety and durability.[7] These comparable results are confirmed by a recently published registry-based study which included n=413 patients with a BPP and n=3921 patients with a polyester patch.[8] However, no venous patches were included in both studies. The aim of this multicenter study was to compare short- and long-term outcomes of primary CEA using autologous venous, BPP, and polyester patches.

METHODS

Study design

All consecutive patients who underwent primary CEA with patch angioplasty using venous patch, BPP, or polyester between January 2010 and December 2020 at the University Medical Center Utrecht (UMCU) or the University Medical Center Groningen (UMCG) were included in this study. In 2010, BPP was introduced as patch option at the UMCU and five years later, in 2015, it was introduced at the UMCG. Patients who

underwent redo carotid surgery, or CEA with primary closure or patch angioplasty using materials other than venous tissue, BPP, or polyester, were excluded.

The Medical Ethical Institutional Review boards of both centers granted dispensation for the study from the Medical Research Involving Human Subjects Act (WMO) obligation in accordance with Dutch law on patient-based medical research obligations (registration numbers UMCU 2022/896 and UMCG 2021/493). Patient data were processed and electronically stored in agreement with the declaration of Helsinki – Ethical principles for medical research involving human subjects.[9] Data were stored and analyzed anonymously. UMCU-data were retrieved from an ongoing prospective study: the Athero-Express Biobank (AE) study (www.atheroexpress.nl). An outline of the objectives of the AE has been published previously.[10] Data from the AE was supplemented with retrospectively retrieved data from the UMCU electronic patient file (HiX). Data from UMCG patients were collected retrospectively from the electronic patient file (EPIC) and were found using intervention codes.[7]

Patient characteristics and preoperative definitions

Patient characteristics included age at time of CEA, sex (assigned at birth: male/female), body mass index (BMI), and tobacco use (current use or ≤ 1 year of abstinence). The following comorbidities were collected according to the Society for Vascular Surgery system (class 0-3; positive if score ≥ 1) in accordance with the Ad Hoc Committee on Reporting Standards: hypertension, hyperlipidemia, and diabetes mellitus.[11,12] Furthermore, history of coronary artery disease (CAD) was based on the presence of angina pectoris, myocardial infarction, percutaneous coronary interventions, and/or coronary artery bypass grafting.

Carotid stenosis was defined as 'symptomatic' if an internal carotid artery stenosis of > 50% was present, in addition to one or more of the following preoperative ipsilateral symptoms in the past six months: ocular symptoms (amaurosis fugax), transient ischemic attack (TIA), or cerebrovascular accident (CVA). If none of these events occurred in the past six months, the carotid stenosis was labeled 'asymptomatic'.[1,13] Data on preoperative antiplatelet therapy and the use of anticoagulation were collected. The following peak systolic velocities (PSV) cut-off values were used to grade the pre- and post-operative internal carotid artery ipsilateral stenosis: < 125 cm/s for < 50% stenosis, ≥ 125 cm/s for 50-69% stenosis, ≥ 230 cm/s for 70-99% stenosis (but not near occlusion).[14] Contralateral occlusion (confirmed with duplex ultrasound) was also noted.

Technical aspects and follow-up

The technical aspects of the procedure have been published previously.[15] If patients were not already on anticoagulation therapy, they received antiplatelet therapy. Furthermore, they received a statin. Pre-operatively, 2 grams cefazolin intravenous was given. Five-thousand IU heparin intravenous was administered before the carotid artery

was clamped. Electro-encephalography (EEG) and transcranial doppler (TCD) were used to monitor patients during surgery. A shunt was utilized on indication depending on EEG and TCD changes. The arteriotomy was closed using a patch containing autologous vein (distal great saphenous vein), BPP (XenoSure Biologic Vascular Patch; LeMaitre, USA or Vascu-Guard Peripheral Vascular Patch; Baxter, USA), or polyester (Hemagard Carotid Patch; Getinge, Sweden). The choice of patch material was based on the preference of the operating surgeon. There were no specific indications to prefer one patch over another. Protamine was given in a standard fashion but only on indication. Antiplatelet (monotherapy) or anticoagulation therapy was prescribed post-operatively. Patients underwent standard surveillance duplex ultrasound examination at three months, at one year, and yearly thereafter. Perioperative variables that were collected, included side of CEA, shunt use, and postoperative length of hospital stay (days).

Short-term (< 30 days) adverse events

Short-term adverse events (within 30 days), including mortality, TIA or CVA, CAD, restenosis, wound infection (including infection of the cervical wound and the harvesting site in case of a venous patch), cranial nerve palsy (CNP), and cervical hematoma (according the SVS Reporting standard; class 1-3 were scored positive and re-explorations were noted) were collected.[13]

Primary and secondary outcomes

The primary outcome was ipsilateral TIA or CVA (i.e., diagnosed by a neurologist based on clinical presentation and cerebral imaging) during follow-up. Secondary outcomes were ipsilateral restenosis of >50% (defined as PSV-threshold >213 cm/s)[1], ipsilateral re-intervention (i.e., defined according the SVS reporting standards: management of access site complications and management of postoperative stroke)[13], and all-cause mortality. Graft infection was defined following the Management of Aortic Graft Infection group (MAGIC) criteria, with the presence of at least one major and one minor criterium from another category.[16]

Statistical analysis

Continuous data were described as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution. Distribution was checked visually and using the Shapiro-Wilk test. One-way ANOVA was used to compare normally distributed variables and Kruskal Wallis was used to compare variables with a skewed distribution between the three patches. Kaplan-Meier survival curves were used to visualize the effect of each patch type on the outcomes. Both uni- and multivariable Cox proportional hazard models were fitted to assess the effect of patch type to each outcome during follow-up. Multivariable Cox regression models were fitted using a stepwise backward elimination approach. Variables with an univariable *P*-value of <.10 were eligible to be confounders for the multivariable model. A variable was considered a confounder if the regression coefficient of the intervention changed ≥10%. All models

consisted of an estimated regression coefficient (β) with a corresponding hazard ratio (HR) and 95% confidence interval (CI). The Cox regression model assumptions were tested and fulfilled. *P*<0.05 was considered the threshold of statistical significance. *P*-values were adjusted for multiple testing using the Bonferroni correction. Statistical analyses were performed in R, version 4.0.5 (R Foundation for Statical Computing, Vienna, Austria), using the survival, survminer-, and ggplot2-packages.

RESULTS

In total, 1481 patients who underwent primary CEA with patch angioplasty were included in this study. Three hundred nine (20.9%) patients received a venous patch, 1000 (67.5%) patients received a BPP, and 172 (11.6%) patients received a polyester patch.

In both centers, after introduction of BPP, mainly BPP was used instead of venous or polyester patches. Baseline characteristics, divided per patch type, are shown in Table I. Patients with a venous patch had a mean age of 67.4 ± 9.5 years, those with a BPP were 70.4 ± 8.8 years, and those with a polyester patch were 71.5 ± 9.0 years. Patients with a BPP and patients with a polyester patch were significantly older than patients with a venous patch (p<0.001). No difference in age was found between BPP and polyester (p=0.420). Patients with a venous patch were more often male (76.4%), compared to BPP (68.9%) and polyester (67.4%) (p=0.027). Tobacco use (p=0.002), hypertension (p=0.039), diabetes mellitus (p<0.001), and CAD (p=0.002) differed significantly between the three intervention groups.

Table I. Baseline characteristics of patients who underwent carotid endarterectomy with patch angioplasty, divided per patch type.

Patient characteristics	Venous (n=309)	BPP (n=1000)	Polyester (n=172)	*P*-value
Age - years	67.4 ± 9.5	70.4 ± 8.8	71.5 ± 9.0	<0.001
Sex - males	236 (76.4)	689 (68.9)	116 (67.4)	0.027
Body mass index - kg/m^2	26.6 ± 3.8	26.8 ± 4.4	27.4 ± 5.0	0.123
Tobacco use	141 (45.6)	345 (34.5)	65 (37.8)	0.002
Hypertension	210 (68.0)	728 (72.8)	135 (78.5)	0.039
Hyperlipidaemia	256 (82.8)	828 (82.8)	147 (85.5)	0.571
Diabetes mellitus	45 (14.6)	261 (26.1)	49 (28.5)	<0.001
Coronary artery disease	64 (20.7)	302 (30.2)	56 (32.6)	0.002

Data are represented as n (%) or mean ± standard deviation.

Distribution of preoperative ipsilateral symptomatology was significantly different between patch types (p=0.002). Patients with a venous patch or polyester patch presented with a CVA most often (40.8% and 45.3%, respectively), while most patients with a BPP

presented with a TIA (36.6%). Furthermore, the use of anticoagulation was significantly lower in the venous patch group (8.1%), compared to BPP (11.6%) and polyester (16.9%; p=0.017). A significant difference was found in ipsilateral stenosis grades between the three groups. Seventy-nine percent of patients with a polyester patch had a severe stenosis (70-99%) compared to 83.5% and 86.8% of patients with venous and BPP grafts, respectively. The occurrence of a contralateral occlusion did not differ between the three groups. No significant differences in intra-operative characteristics were found between the patches (Table II).

Table II. Pre-, intra-, and postoperative characteristics of patients who underwent carotid endarterectomy with patch angioplasty, divided per patch type.

Characteristic	Venous (n=309)	BPP (n=1000)	Polyester (n=172)	*P*-value
Preoperative				
Ipsilateral symptoms				0.002
Cerebrovascular accident	126 (40.8)	318 (31.8)	78 (45.3)	
Transient ischemic attack	99 (32.0)	366 (36.6)	54 (31.4)	
Ocular	59 (19.1)	237 (23.7)	24 (14.0)	
Asymptomatic	25 (8.1)	79 (7.9)	16 (9.3)	
Antiplatelet therapy	290 (93.9)	909 (90.9)	152 (88.4)	0.098
Anticoagulation	25 (8.1)	116 (11.6)	29 (16.9)	0.017
Stenosis grade				0.020
<50%	4 (1.3)	6 (0.6)	0 (0.0)	
50-69%	47 (15.2)	126 (12.6)	36 (20.9)	
70-99%	258 (83.5)	868 (86.8)	136 (79.1)	
Contralateral occlusion	26 (8.4)	111 (11.1)	13 (7.6)	0.216
Intra-operative				
Operation side - right	156 (50.5)	466 (46.6)	73 (42.4)	0.224
Shunt use	44 (14.2)	119 (11.9)	18 (10.5)	0.410
Postoperative				
Length of hospital stay - days	3 (3-3)	3 (2-4)	3 (3-4)	<0.001

Data are represented as n (%), mean ± standard deviation, or median and interquartile range.

Short-term adverse events (<30 days)

In the 30 day postoperative period, no significant differences were observed in terms of mortality, TIA or CVA, CAD, restenosis, wound infection, and cervical hematoma (Table III). A significant difference in the occurrence of cranial nerve palsy was found (p<0.001). This was the lowest in the BPP group (3.6%), compared to venous (11.3%), and polyester (9.9%).

Table III. Post-operative short-term adverse outcomes (<30 days) of patients who underwent carotid endarterectomy with patch angioplasty, divided per patch type.

Characteristic	Venous (n=309)	BPP (n=1000)	Polyester (n=172)	*P*-value
Mortality	2 (0.6)	10 (1.0)	2 (1.2)	0.770
Transient ischemic attack or cerebrovascular accident	12 (3.9)	34 (3.4)	9 (5.2)	0.450
Coronary artery disease	3 (1.0)	20 (2.0)	3 (1.7)	0.559
Restenosis	5 (1.6)	8 (0.8)	2 (1.2)	0.373
Wound infection[a]	7 (2.3)	14 (1.4)	3 (1.7)	0.481
Cranial nerve palsy	35 (11.3)	36 (3.6)	17 (9.9)	<0.001
Cervical hematoma	14 (4.5)	45 (4.5)	10 (5.8)	0.687
Requiring re-exploration	9 (2.9)	35 (3.5)	6 (3.3)	0.173

Data are represented as n (%).
[a] including cervical wound (n=4) and harvesting site (n=3) of the venous graft.

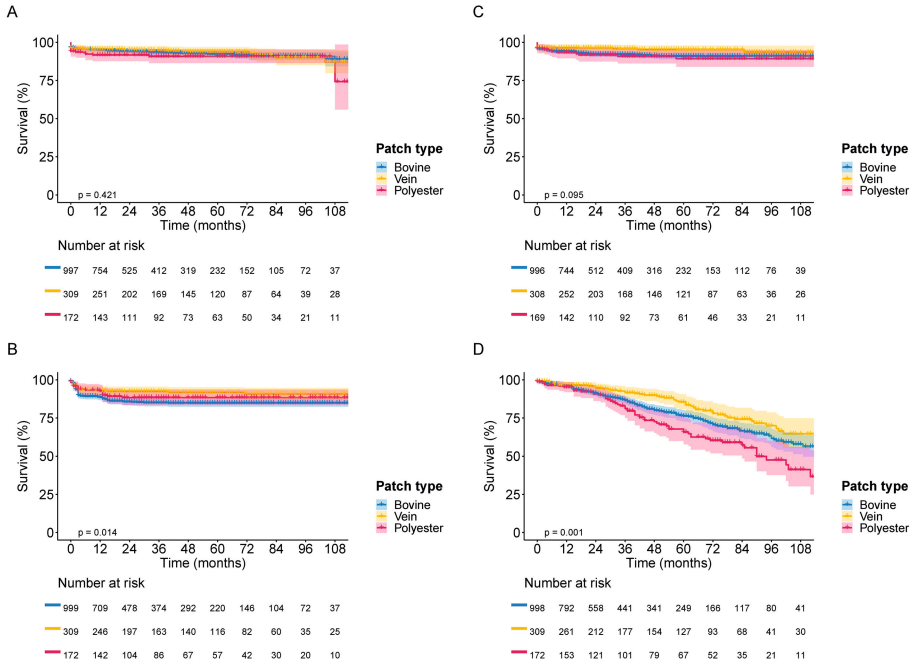
Follow-up

The median follow-up time was 32 (13-65) months for the total group, 47 (14-77) months for patients with a venous patch, 28 (13-59) months for BPP patients, and 42 (15-77) months for patients with a polyester patch (p<0.001).

Primary and secondary long-term outcomes

No significant differences were observed between venous, BPP, or polyester patches with univariable Cox regression analyses on TIA/CVA and re-intervention. (Supplementary Table I, and Figure 1). Restenosis occurred significantly less using venous patches (HR: 0.56 [0.36;0.86], p=0.008) compared to BPP (reference category). There was no difference between polyester and BPP regarding restenosis (HR: 0.76 [0.46;1.24], p=0.273). In the univariable Cox regression analysis, venous patch types (reference category) showed the lowest all-cause mortality compared to BPP (HR: 1.42 [1.08;2.01], p=0.014) and polyester patches (HR: 2.20 [1.52;3.20], p<0.001). Polyester patches were associated with higher all-cause mortality (HR: 1.49 [1.11-2.00]; p= 0.007) compared to BPP.

Figure 1. Survival curves per patch type for different outcomes (**1A**: transient ischemic attack or cerebrovascular accident (ipsilateral), **1B**: restenosis (ipsilateral), **1C**: reintervention (ipsilateral), **1D**: all-cause mortality).



Variables that were eligible as confounders for the multivariable model included age, sex, tobacco use, hypertension, diabetes mellitus, CAD, ipsilateral symptoms, antiplatelet therapy, anticoagulation, stenosis grade, and hospital where CEA was performed. After adjusting for confounders in the multivariable Cox regression analyses, no significant differences were observed between the patch materials regarding the four main outcomes, including ipsilateral TIA/CVA (venous: p=0.490, polyester: p=0.152, reference category=BPP), ipsilateral restenosis (venous: p=0.137, polyester: p=0.938, reference category=BPP), ipsilateral re-intervention (venous: p=0.095, polyester: p=0.938, reference category=BPP), and all-cause mortality (venous: p=0.124, polyester: p=0.562, reference category=BPP) (Table IV).

Table IV. Multivariable Cox regression analyses of the effect of patch type on TIA/CVA, restenosis, re-intervention, and all-cause mortality.

Outcome	Predictor (reference: BPP)	β (95% CI)	HR (95% CI)	*P*-value
Transient ischemic attack or cerebrovascular accident (ipsilateral)[a]	Venous	0.19 (-0.35;0.73)	1.21 (0.70;2.08)	0.490
	Polyester	0.49 (-0.35;1.15)	1.63 (0.84;3.16)	0.152
Restenosis (ipsilateral)[b]	Venous	-0.36 (-0.83;0.11)	0.70 (0.44;1.12)	0.137
	Polyester	-0.00 (-0.58;0.57)	1.00 (0.56;1.78)	0.989
Re-intervention (ipsilateral)[c]	Venous	-0.53 (-1.15;0.09)	0.59 (0.32;1.10)	0.095
	Polyester	0.03 (-0.64;0.70)	1.03 (0.53;2.01)	0.938
All-cause mortality[d]	Venous	-0.29 (-0.65;0.08)	0.75 (0.52;1.08)	0.124
	Polyester	0.13 (-0.30;0.55)	1.13 (0.74;1.73)	0.562

[a] adjusted for age, sex, hypertension, anticoagulation, hospital.
[b] adjusted for age, sex, tobacco use, hypertension, diabetes mellitus, ipsilateral symptoms, anticoagulation, stenosis grade, hospital.
[c] adjusted for age, hypertension, diabetes mellitus, ipsilateral symptoms, antiplatelet therapy, hospital.
[d] adjusted for age, tobacco use, hypertension, coronary artery disease, anticoagulation, hospital. (tested: age, sex, tobacco use, hypertension, diabetes mellitus, coronary artery disease, ipsilateral symptoms, antiplatelet therapy, anticoagulation, stenosis grade, hospital).

Cranial nerve palsy

After 1 year of follow-up, persistent symptoms of CNP were observed in two of the 35 (5.7%) patients with a venous patch, one of the 36 (2.8%) patients with a BPP, and three of the 17 (17.6%) patients with a polyester patch who had a short-term (<30 days) CNP. No significant differences were observed between the three patch types (p=0.158).

Patch infection

One (0.1%) patient with a BPP, and three (1.8%) patients with a polyester patch developed a graft infection (p=0.011) while patch infection was not scored in the venous patch group. The BPP patient presented with septic bleeding (two weeks postoperatively). Replacement surgery was performed using a venous patch and intraoperative cultures showed *Klebsiella oxytoca.* Graft infection in patients with a polyester patch was diagnosed at 6, 37, and 57 months, respectively. Two of the three patients with an infected polyester patch also underwent venous reconstruction. Intra-operative cultures were positive for *Staphylococcus aureus* in one patient and the other patients' cultures were negative (possibly due to long-term preoperative antibiotic therapy). The third patient was treated conservatively because he/she was physically unable to undergo surgical treatment.

DISCUSSION

Our analysis revealed no significant differences between autologous venous patch, BPP, or polyester patch for primary CEA regarding the occurrence of TIA/CVA, restenosis, re-intervention, and all-cause mortality after adjusting for confounders.

Our observations are largely confirmative with existing literature.[8,17] In a registry study, comparing different closure techniques, BPP revealed the lowest re-intervention and restenosis rate. However, these outcomes were only compared at one-year follow-up.[2] Another study, a meta-analysis of RCTs, compared BPP to other materials (including Dacron and venous patches) and also found no superior patch type with regard to short-term TIA, CVA, or mortality.[18] A recently published Cochrane review found little to no differences between venous and synthetic material regarding long-term adverse outcomes such as TIA/CVA. Although the authors stated that more trial data was necessary to draw conclusions, they found that BPP may lower the risk of perioperative fatal TIA/CVA and mortality compared to synthetic grafts.[19] However, the evidence was inconclusive due to the low number of events. Furthermore, none of the studies compared BPP to venous patches, and only two studies compared BPP to synthetic patches. Therefore, the strength of the current study is the comparison of all three of them with a large number of patients and long-term follow-up.

Our study highlights the rarity of patch infection across all patch types with the highest prevalence among patients with a polyester patch (venous: 0%, BPP: 0.1%, polyester: 1.8%, p=0.011). This corresponds with earlier published literature.[20] Biological materials (autologous vein or xenograft) seem to be more resistant to infection compared to synthetic material. The infection resistant property of BPP is possibly due to the fact that it is made of acellular material causing reendothelialization.[7] Due to these properties, the use of bovine pericardium is gaining popularity in other vascular surgical procedures when an infection is present in the surgical field.[21–23] In carotid surgery, autologous material is still the primary choice of treatment when a patient is diagnosed with a graft infection in a non-acute setting. This is underlined by the results of our study (0% patch infection).[24] Larger studies on the treatment of carotid patch infection should be performed to draw conclusions on the use of BPP as an alternative to venous reconstruction, if no suitable vein is available. However, the 0.1% patch infection of BPP seems promising compared to the 1% reported in the literature.[1]

The only statistically significant difference that we observed was on CNP, with the lowest prevalence among BPP patients. However, after one year follow-up, persistent symptoms were rare and no differences were observed between the three groups. In contrast to our previously published single-center study, no significant differences in short-term cervical hematoma were found between BPP (4.5%) and polyester (5.8%)[7]. These results are similar to another large study that compared BPP to other CEA techniques which

also showed no significant differences between groups regarding short-term presentation of a hematoma requiring surgical re-exploration.[3] A previous published prospective study found a prolonged suture line bleeding in polyester compared to BPP.[25] However, a longer hemostasis time does not necessarily lead to more hematoma explorations.[26]

Limitations

Although this is one of the largest cohorts comparing the long-term follow-up of different kinds of patches for CEA, limitations of this study exist, including the retrospective nature of the analysis and the heterogeneity of the patient population. The patients included in this study were operated in two different centers. However, the procedures were similar at both hospitals and patient data were kept prospectively. Additionally, we corrected for 'hospital location' in the multivariable analyses. Furthermore, including patients from two centers increases the generalizability of the conclusions.

Conclusion

Within standard risk patients undergoing primary CEA, long-term follow-up showed that venous, bovine, and polyester patches are safe options for closure and were comparable in terms of rate of CVA, restenosis, re-intervention, and all-cause mortality. Vascular graft infection was rare in all groups. This study confirms that the choice of patch material used for CEA remains in the hands of the operating team and local hospital preferences.

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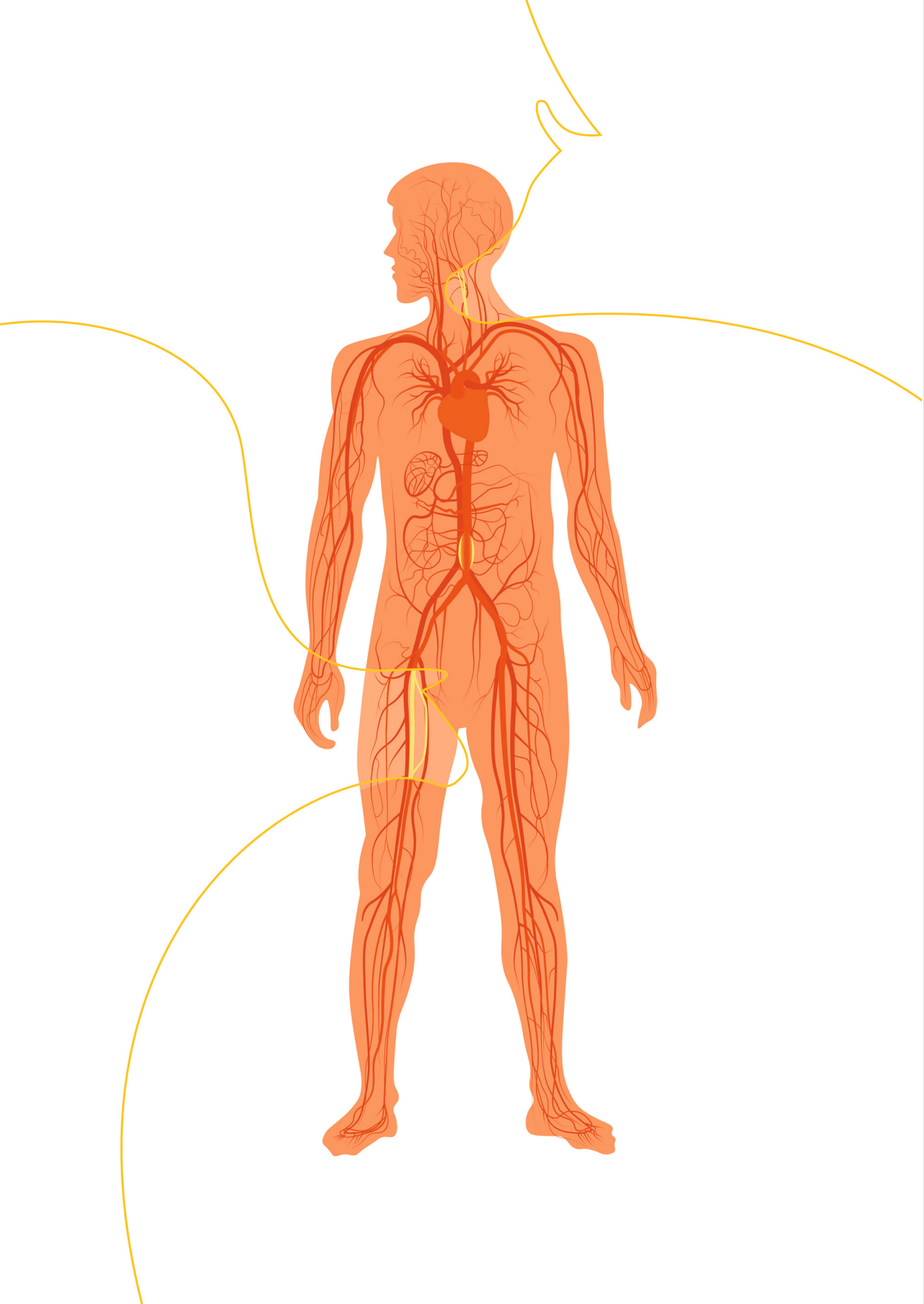
SUPPLEMENTARY DATA

Supplemental Table I. Univariable Cox regression analyses of the effect of patch type on TIA/CVA, restenosis, re-intervention, and all-cause mortality.

Outcome	Predictor (reference: BPP)	β (95% CI)	HR (95% CI)	*P*-value
Transient ischemic attack or cerebrovascular accident (ipsilateral)	Venous	-0.08 (-0.58;0.41)	0.92 (0.56;1.51)	0.746
	Polyester	0.33 (-0.21;0.86)	1.38 (0.81;2.36)	0.234
Restenosis (ipsilateral)	Venous	-0.59 (-1.02;-0.15)	0.56 (0.36;0.86)	0.008
	Polyester	-0.28 (-0.77;0.22)	0.76 (0.46;1.24)	0.273
Re-intervention (ipsilateral)	Venous	-0.55 (-1.12;0.02)	0.58 (0.33;1.02)	0.060
	Polyester	0.13 (-0.43;0.68)	1.13 (0.65;1.98)	0.659
All-cause mortality	Venous	-0.39 (-0.70;-0.07)	0.68 (0.50;0.93)	0.014
	Polyester	0.40 (0.11;0.69)	1.49 (1.11;2.00)	0.007



Chapter 9

Summary, discussion, and future perspectives

SUMMARY

This thesis includes various aspects of the diagnosis and treatment of infective native aortic aneurysm (INAA) and vascular graft and endograft infection (VGEI). **Part I** (Chapter 2-4) primarily focusses on diagnostic considerations, while **part II** (Chapter 5-8) elucidates the utilization of different biological materials, providing further insights. The findings from these studies are summarized and discussed below, and the future perspectives pertaining to the aforementioned subjects are described as well.

The first part of this thesis contains a study that centers on infective native aortic aneurysm (INAA) as well as a study that focusses on ^{18}F-fluoro-D-deoxyglucose positron emission tomography with computed tomography ([^{18}F]FDG-PET/CT) reporting of VGEI. Furthermore, it contains a case study, in which we illustrated the importance of a systematic diagnostic work-up for VGEI.

In **chapter 2**, patients with an INAA, admitted to the University Medical Center Groningen, were evaluated from initial presentation until last follow-up. Patients often had a symptomatic presentation with pain and/or fever and a (contained or full-blown) rupture was present in more than one quarter of the cohort. All patients underwent computed tomography angiography (CTA) and one quarter of the patients underwent [^{18}F]FDG-PET/CT scanning during the diagnostic work-up. The FDG-uptake was heterogeneous in all patients and the median maximum standardized uptake value (SUVmax) was 5.9. The most cultivated causative microorganism was *Streptococcus pneumoniae* followed by *Staphylococcus aureus* and *Escherichia coli*. Subsequently, our results unveiled a heterogenous treatment strategy, including varying types and durations of antibiotic and surgical treatments. Patients were treated with either endografts or various types of materials used during open surgery, such as autologous venous grafts, synthetic grafts, and biological xenografts. During a median follow-up of 20 months, a high mortality rate (42%) was observed. In conclusion, this study showed a highly heterogenous cohort. Therefore, it is anticipated that management should be individually based and discussed in a multidisciplinary setting.

Chapter 3 focused on the diagnostics of another infectious entity in vascular surgery, namely VGEI. Reporting [^{18}F]FDG-PET/CT-scans of suspected VGEI is challenging and established standards are still lacking. Within this chapter, the completeness of [^{18}F]FDG-PET/CT-scan reports for suspected VGEI was investigated. Reports were scored based on pre-selected criteria that were devised by experts in the field and informed by existing literature. The evaluation consisted of 10 criteria, and less than half of the reports met the criterion of completeness. The most frequently missing criterion was FDG-uptake pattern. Compared to the gold standard (diagnosis based on the MAGIC criteria), a sensitivity of 91%, a specificity of 72%, and an accuracy of 88% were observed. Furthermore, less complete (≤8 criteria) reports showed a lower sensitivity

and specificity compared to more complete reports (83% and 50% vs. 92% and 77%, respectively). The implementation of reporting standards that incorporate preselected criteria may increase the accuracy of this imaging modality in diagnosing VGEI.

In **chapter 4**, a case study is presented of a man with atypical findings in the abdominal aortic wall on [^{18}F]FDG-PET/CT. Initially, the suspected diagnosis was sterile inflammation of the aorta; however, it turned out to be an endograft infection caused by *Listeria monocytogenes*. The challenges associated with diagnosing VGEI are reflected in chapter 3.

The rising popularity of biological materials in the field of vascular surgery is attributed to their theoretically infection resistant properties. The second part of this thesis focuses on the treatment of different vascular diseases (including VGEI) using biological materials. This part comprises two cohort studies investigating the use of the Omniflow® II biosynthetic graft in various anatomical locations (intracavitary and peripheral) and surgical settings (infection and non-infection), and two cohort studies comparing the use of bovine pericardial patch (BPP) for carotid endarterectomy (CEA) to alternative materials.

The Omniflow® II is a biosynthetic graft composed of cross-linked ovine collagen and a polyester mesh endoskeleton. In **chapter 5**, we aimed to evaluate the efficacy and morbidity of Omniflow® II for the treatment of VGEI in a multicenter cohort study. A total of fifty-two patients with either intra-cavitary or peripheral infection were included in this study. Notably, 15% of the patients presented with a reinfection, with a higher reinfection rate observed in intra-cavitary vascular grafting compared to peripheral grafts (33% vs. 12%, respectively; p=0.025). After three years, the estimated primary patency was 72% for peripheral grafts and 58% for intra-cavitary grafts. Furthermore, patients with an intra-cavitary graft had a significantly higher mortality compared to patients with a peripheral graft. Our findings demonstrate that using Omniflow® II for the treatment of VGEI is a safe and feasible alternative to venous material (e.g. no suitable vein available or in case of emergency surgery), especially for peripheral VGEI reconstruction.

In **chapter 6,** we conducted a multicenter cohort study in which we evaluated the use of Omniflow® II for revascularization within the femoral tract in both infected and non-infected settings. A total of142 patients were included in this study and the following anatomical locations were evaluated: femoro-femoral crossover-, femoral interposition-, femoro-popliteal (above- and below-the-knee), and femoro-crural position. Most common indication for femoro-femoral crossover (63%) and femoral interposition grafts (72%) was graft replacement in cases of VGEI. Femoro-popliteal (both above- and below-the-knee) were most often used for primary bypass surgery and femoro-crural grafts for graft replacement of which neither had an increased infection risk. Chronic limb-threatening ischemia was present in 80% of patients with an above-the-knee femoro-popliteal-, 77% of patients with a femoro-popliteal below-the-knee-, and 91%

of patients with a femoro-crural bypass, respectively. The three-year primary patency rates observed for Omniflow® II were as follows: 58% for femoro-femoral crossover bypass, 75% for femoral interposition graft, 44% for femoro-popliteal above-the-knee bypass, 42% for femoro-popliteal below-the-knee bypass, and 27% for femoro-crural positions, respectively (p=0.006). Freedom from major amputation at three years was 84% for patients with a femoro-femoral crossover bypass, 88% for patients with a femoral interposition bypass, 90% for patients with a femoro-popliteal bypass above-the-knee, 83% for patients with a femoro-popliteal bypass below-the-knee, and 50% for patients with a femoro-crural bypass, respectively (p<0.001). Comparing patients treated for VGEI to patients who underwent graft replacement in a non-infective setting, no significant differences were observed regarding reinfection (p=0.689). Overall, this study shows that the Omniflow® II can be safely used in various anatomical locations within the femoral tract, both in infected and non-infected settings, except for the femoro-crural position where poor outcomes were observed.

This thesis also examines another biological graft known as BPP. In **Chapter 7,** we aimed to compare the long-term outcomes of patients who underwent CEA and closure with either a BPP or polyester patch in a single center cohort study. A total of 417 patients were included, of which 254 received a BPP and 163 received a polyester patch. After adjusting for confounders in the multivariable analyses, we found no significant differences regarding ipsilateral transient ischemic attack or cerebrovascular accident (TIA or CVA), ipsilateral restenosis, ipsilateral reintervention, and all-cause mortality at a follow-up until five years postoperative. Patch infection occurred in none of the patients who received a BPP, while three patients with a polyester patch experiences patch infection. Chapter 7 ends with a letter to the editor in which Kubat et al. states that the use of autologous pericardium could be a suitable option for sensitive patients requiring a biological carotid patch. This letter to the editor is followed by our reply stating that polyester can be a good alternative in patients who do not want to receive animal materials (such as BPP) due to religious reasons.

Chapter 8 builds upon chapter 7 by including venous patches, in addition to BPP and polyester, and through a multicenter collaboration with the University Medical Center Utrecht, resulting in an increase in sample size that reduces the risk of a type II error. A total of 1481 carotid endarterectomy patients were included this study of which 20.9% had a venous patch, 67.5% received a BPP, and 11.6% had polyester patch. A significant difference was observed in the occurrence of short-term (<30 days) cranial nerve palsy (p<0.001). The lowest rate was seen in the BPP group (3.6%), compared to the venous (11.3%), and polyester (9.9%) groups. However, after 12 months of follow-up, few patients experienced persistent symptoms, and no significant differences were observed between the three patch types regarding cranial nerve palsy. Overall, one patient with a BPP and three patients with a polyester patch developed a graft infection, while patch infection was not found in the venous patch group (p=0.011). Similar to the findings in

the single center study (chapter 7), the multivariable analyses showed no significant differences between the three patch types regarding long-term outcomes (ipsilateral TIA/CVA, ipsilateral restenosis, ipsilateral reintervention, and all-cause mortality). Based on the results of chapter 7 and 8, we can conclude that all three materials can be safely applied for CEA with patch angioplasty.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In **part I** of this thesis, it was shown that infective native aneurysms of the abdominal aorta have a high mortality rate. Moreover, the diagnosis of INAA remains challenging due to a non-specific presentation and large individual variation.[1] In addition, conducting studies with high statistical power has been difficult due to the rarity of the disease.[1,2] Until recently, there was no consensus regarding the terminology, classification, or diagnostic criteria for this disease. However, in early 2023, experts in the field published a Delphi consensus on these subjects.[3] An important aspect of this consensus document was agreement to replace the formerly proposed term "mycotic aortic aneurysm" with the new term "infective native aortic aneurysm." Furthermore, there was agreement on the potential role of nuclear medicine with [^{18}F]FDG-PET/CT as an additional diagnostic modality if there is uncertainty about the diagnosis. This statement aligns with the findings on INAA patients in **chapter 2**. Although a median SUVmax of 5.9 with [^{18}F]FDG-PET/CT was found, there are currently no validated cut-off points for diagnosing INAA. Also, cut-off points for infection in general remain debatable.[4,5] In VGEI, an SUVmax cutoff value of 8 yielded a positive predictive value of 80% and a negative predictive value of 54%.[6] In conclusion, studies are needed to answer questions regarding the diagnosis and treatment of INAA. For example, it is necessary to develop ^{18}F]FDG-PET/CT-criteria for the diagnosis of VGEI and to determine which specific patient group should receive which surgical treatment option (e.g. endovascular as possible bridge to open surgery in critically ill patients) in order to improve outcomes.

Currently, computed tomography angiography is the preferred imaging modality in patients with a suspected VGEI. However, in recent years, the use of [^{18}F]FDG-PET/CT for diagnosing VGEI has gained popularity.[7] Previous research has shown that [^{18}F]FDG-PET/CT has a high sensitivity, but a lower specificity compared to CTA.[7–9] There is currently no uniformity regarding standardization of scanning and interpretation of [^{18}F]FDG-PET/CT. Furthermore, there is a lack of reporting standards for [^{18}F]FDG-PET/CT to describe suspected VGEI. The implementation of specific protocols for patient preparation and imaging interpretation criteria have been shown to be crucial in achieving high diagnostic accuracy in for example infective endocarditis.[10,11] Apart from standardization in reporting, there is also a need for harmonization of scanning protocols. For instance, different grading scales (e.g. three-, four-, or five-point scale) exist for assessing [^{18}F]FDG-uptake intensity.[12] Without standardization of scanning protocols, comparison

between studies remains difficult. The importance of **chapter 3** is further underscored by the case description in **chapter 4**.

Chapter 5 demonstrated that the Omniflow® II may be a good alternative to venous reconstruction for the treatment of VGEI. The low reinfection rates were comparable to the findings of a study performed by Caradu et al. on the use of Omniflow® II biosynthetic grafts for the treatment of aortic graft infection and the study by Betz et al. on the use of Omniflow® II for aortic and peripheral graft infection.[13,14] The low occurrence of reinfection may be attributed to the rapid incorporation of the graft in the human body caused by the biocompatibility of the collagen structure.[15,16] In comparison, silver-coated femoro-popliteal grafts showed a higher reinfection rate than we observed in a comparable population.[17] However, in intracavitary position silver-coated grafts showed a lower reinfection rate compared Omniflow® II.[18] The higher reinfection rate for intracavitary located Omniflow® II could be attributed to the considerable manipulation that occurs when grafts are manually made by combining two grafts. However, this contradicts the manufacturer's recommendations regarding excessive handling (i.e. " do not pull, stretch, twist, squeeze or pinch the body of the prosthesis").[16] Cryopreserved allografts demonstrated lower reinfection rates; however, this material is associated with an increased risk of aneurysm formation and subsequent rupture due to degeneration that occurs over time.[19–21] Furthermore, the availability of cryopreserved allografts is limited in the Netherlands. Other evaluated endpoints, including patency and freedom of major amputation rate, showed acceptable results that were comparable with prior studies on Omniflow® II and studies on other graft material.[20,22] Future research should focus on comparing Omniflow® II to other materials. For instance, bovine pericardium has shown good short-term results after reconstruction for intracavitary or peripheral graft infection.[23] BPPs used for reconstruction following removal of infected arterial grafts exhibited a high reinfection free survival of 98%.[24] Until one year ago, an "off-the-shelf" bifurcated bovine pericardial xenograft (BioIntegral Surgical No-React®, bovine pericardial xenografts) was available. Terlecki et al. evaluated the BioIntegral in six patients treated for a VGEI and their preliminary results showed that these grafts may be a feasible alternative to other options for treatment of VGEI in the aorto-iliac region.[25] However, in April 2022, the producing company found *Mycobacteria chelonae* in two of their products and placed an immediate hold on all implantations and sales. Therefore, the BioIntegral bifurcated graft is no longer in use. An alternative approach could involve a self-made bovine pericardial prosthesis by combining BPP.[26,27] However, this option is mostly applies to aortic tube graft rather than bifurcated grafts such as the BioIntegral. A mechanically comparable alternative to bovine pericardium is porcine pericardium.[28] A previously published study on this material (surgeon-created tubes made of porcine pericardium patch) used for native aortic and aortic graft infection showed promising results, although the study only included 8 patients. Another potential alternative graft (Intergard Synergy graft) which has antimicrobial properties for intracavitary VGEI or INAA treatment was studied by

a French group (n=86).[29] This knitted polyester graft, coated with silver acetate and triclosan, has demonstrated promising early mortality and mid-term reinfection rates, suggesting it could be a safe alternative to other materials. However, larger studies with a longer follow-up period are needed to confirm these results.

A new bifurcated homograft developed by LeMaitre, Vascular Inc. is expected to be available in the upcoming months. LeMaitte has already obtained the "Human Tissue Licence" for the implantation of homografts in the United Kingdom and LeMaitre is currently applying for a German and Irish licence. Once these licenses are granted, tissue can be supplied to other European countries, including the Netherlands. Overall, there are different materials available for reconstruction of VGEI. However, current literature consists of small groups of patients and heterogenous cohorts. Therefore, future studies should aim to compare the aforementioned grafts as alternatives when venous reconstruction is not feasible for the treatment of VGEI. Given the rarity of these procedures, multicenter collaborations are crucial.

The use of Omniflow® II for revascularization in the femoral tract in both infected and non-infected surgical settings was assessed in **chapter 6.** These results showed acceptable graft patency and a high freedom from major amputation. However, we found that femoro-crural position showed poor patency compared to previously mentioned locations and to other graft materials.[30,31] A possible explanation for this result could be the high rate of pre-operative chronic limb-threatening ischemia in this group of patients. Notably, Omniflow® II was often used in cases of VGEI (i.e., it was the most common indication for femoro-femoral crossover and for femoral interposition grafts). Despite this indication, the occurrence of vascular graft reinfection was low, and there were no significant differences when comparing patients treated for VGEI to patients who underwent graft replacement in a non-infected setting. These findings reflect the low rate of reinfection in a previously published study on the use of Omniflow® II for aortic and peripheral VGEI, as stated above.[13] In the non-infective setting, it is important that future studies compare Omniflow® II to alternative graft materials (e.g. autologous vein or synthetic materials such as polyester), on different peripheral locations.

In **chapter 7,** we examined the short- and long-term outcomes of using BPP and polyester for CEA. In this single center study, no significant differences were observed in the multivariable analyses regarding the above-mentioned long-term outcomes. Similarly, no significant differences were observed in the study described in **chapter 8** (BPP vs. polyester vs. autologous vein). These findings in both studies were in line with the literature on the subject.[32–34] Patch infection was rare across all patch materials, but was the incidence was highest for polyester. A recently published, large, Swedish registry study by Jonsson et al., found a higher risk for ipsilateral TIA/CVA in patients who underwent primary closure compared to patch angioplasty, and there were no differences between different patch types (including polyester and BPP).[34] In addition, they found no

infection in the BPP group, which corresponds to above-mentioned studies on the use of bovine for VGEI. For patients undergoing primary carotid endarterectomy, all three investigated patch materials are deemed safe options for patch angioplasty. Therefore, the choice of closure material remains in hands of the operating team, as stated in the current European Society of Vascular Surgery guidelines.[35] Considerations specific to individual patients, such as the risk of infection and the presence of peripheral arterial disease, where harvesting the greater saphenous vein from the lower leg is not desired, should be taken into account during clinical decision making.

FUTURE PERSPECTIVES

This thesis, namely **chapter 3**, provides a recommendation for reporting [^{18}F]FDG-PET/CT scans in suspected VGEI patients. This recommendation should be incorporated into future VGEI guidelines as it may improve diagnostic accuracy and facilitates comparison between different centers for future studies.[9] According to the systematic review and meta-analysis by Reinders Folmer et al., FDG-uptake pattern is the most accurate assessment method for diagnosing VGEI using [^{18}F]FDG-PET/CT.[36] In addition to FDG-uptake pattern, FDG-uptake intensity, and SUVmax were evaluated in this meta-analysis. All three methods had a high pooled sensitivity but varied in terms of specificity. Since [^{18}F]FDG-PET/CT interpretation can be influenced by several factors, future prospective studies should utilize standardized methods (i.e., patient characteristics and scanning protocols) that assess which method (or methods combined) reveals the highest sensitivity and specificity in suspected VGEI. Textural analysis has shown promising results in characterizing heterogeneity in [^{18}F]FDG-uptake for diagnosing aortic graft infection.[37] Moreover, machine learning has become more developed and has received more attention in recent years. Therefore, machine learning, with or without radiomics, could be a helpful tool to improve the accuracy and standardization of [^{18}F]FDG-PET/CT interpretation. Radiomics, a quantitative approach that extracts large numbers of features from medical images using data-characterization algorithms, may provide insights using voxel intensity and spatial relationships that may not always be apparent to human observers.[38] Furthermore, integrating clinical biomarkers (e.g. C-reactive protein) and quantitative parameters (e.g. SUVmax or tissue-to-background ratio) to this tool could improve further enhance diagnostic accuracy. In research settings, radiomics commonly used in oncology, but its potential has also been shown in vascular PET imaging for diagnosing VGEI, for plaque characterization and in the diagnosis of aortic large vessel vasculitis.[37,39–42] Deep learning models, a subset of machine learning, can also be trained to diagnose VGEI. In oncology, this method has been shown to be more robust than radiomics.[43–45] However, training these models requires large amount of data, which is a challenge due to the rarity of VGEI . To address this challenge, a prospective multicenter cross-border study has been initiated in Groningen, aiming to investigate the diagnosis, treatment, and surgical outcomes of VGEI in the Ems-Dollard region (i.e., the three northern provinces of The Netherlands and an adjacent area in Germany). Another

aspect that needs further investigation is the use of new PET tracers for the diagnosis of VGEI. Currently, Fluorine-18 ([^{18}F]FDG), an analogue of glucose, is the most commonly used tracer. However, its diagnostic accuracy can be negatively influenced by antibiotic therapy.[46] Another disadvantage is that it is not specific for infection.[47] Furthermore, other diseases (e.g. cancer) and physiological processes (e.g. postoperative sterile inflammation) can induce an increased uptake as well. To overcome these limitations, VGEI-specific PET/CT tracers are needed, such as radiolabeled micro-organism specific components (e.g. antibody or radiolabeled antibiotics). Such studies have explored the use of such tracers, for example, one study linked Zirkonium-89 to a monoclonal antibody which targets *Staphylococcus aureus* (*in vivo* mouse model).[48] However, studies in humans are lacking.[47] Another example is 2-deoxy-2-[^{18}F]fluorosorbitol (^{18}F-FDS).[49] This is tracer can detect Enterobacterales (e.g. *Escherichia coli, Klebsiella pneumoniae,* and *Salmonella species*) by accumulating in the bacteria via a metabolic pathway.[50] This tracer has been successfully studied in humans and was able to distinguish infection from sterile conditions.[51] However the sample size was small (n=26). Another technique is the use of radiolabeled interleukin-2, which is secreted by activated T lymphocytes as seen in inflammatory diseases.[52,53] Most studies on this tracer have been performed in oncology.[54,55] Infection-specific tracers have limitations when the causative micro-organism is unknown, in low-grade infection, or when antibiotics are used during the scan. These disadvantages may potentially lead to false-negative findings. Therefore, larger comparative studies on the use of different infection-specific tracers are needed. An alternative to PET is white blood cell scintigraphy. However, this modality also has drawbacks. First, blood must be drawn to collect and label patients' own white blood cells. Next, the labeled cells must be injected again. Additionally, two different scans at two different time points are necessary to diagnose the patient which makes the process very time consuming. Another interesting technique is bacteria-targeted optical imaging (i.e. fluorescence) which can provide real-time information during surgery. The use of labeled vancomycin (vanco-800CW) has already been studied in fracture-related and prosthetic joint infection, and has the potential to provide accurate, real-time information (i.e. detection of a biofilm).[56,57] Future studies on the use of this technique during vascular surgical procedures are desirable.

Vascular graft material

In the coming decades, significant developments are expected in the field of biomaterials in vascular surgery, such as tissue-engineered blood vessels.[58] This approach involves the use of (human) cells to create blood vessels which are grown in a lab and subsequently implanted into the patient. An example of this technology is the human acellular vessel (HAV), which is made from human vascular smooth muscle cells, which are decellularized (i.e., human antigens were removed). The potential advantages of this technique are a reduced risk of infection and degeneration.[59–61] These benefits may arise from repopulation of autologous cells.[62] One of the main challenges of this method is growing these vessels at larger scale while maintaining an affordable price.

Furthermore, as this research is still in its early stages, more time is needed to gather knowledge on the long-term outcomes of these vessels. Ultimately, growing autologous blood vessels using patients' own (non-acellular) cells would be optimal.

Microorganisms are protected against both antibiotics and the host immune system once a mature biofilm is developed. Therefore, graft infection could be prevented if coatings inhibit bacterial adhesion and biofilm formation. Coatings can be divided into two categories: antifouling (i.e. preventing of biofilm formation) and antimicrobial.[63] Examples of antimicrobial coatings include antibiotic and silver coating and examples of antifouling coatings include polymer brush coating, polyethylene glycol (PEG)-based coatings, self-assembled monolayers (SAMs), and nanogels.[64–66] However, different coatings have different drawbacks such as bacterial resistance, cytotoxicity, or a decreased effectivity over time.[63] Furthermore, most coatings (especially the antifouling coatings) have been only studied *in vitro*. Therefore, clinical studies are needed to assess the safety and effectiveness of different, coatings (or combinations) that can be used for the prevention of vascular graft infection.

GENERAL CONCLUSION

In this thesis, we have outlined infectious diseases in vascular surgery, including INAA and VGEI. Due to a large individual variation in INAA, it is crucial that patients are discussed in a multidisciplinary setting involving a vascular surgeon, infectious disease specialist, and microbiologist. Regarding VGEI, we can conclude that applying reporting standards with preselected criteria for [^{18}F]FDG-PET/CT for suspected VGEI might lead to a higher diagnostic accuracy. Furthermore, we investigated the use of two biological materials for vascular surgical treatment. The Omniflow® II was shown to be a safe and feasible alternative to venous reconstruction for peripheral VGEI and for revascularization in both infective and non-infective settings in the femoral tract. Omniflow® II in femoro-crural position showed poorer outcomes, making it a less suitable option for this position. Next, we found that BPP is a safe and effective alternative to venous and synthetic patches for carotid endarterectomy with patch angioplasty. Future research on vascular (graft and endograft) infection should prioritize the exploration of novel diagnostic approaches such as the use of new tracers for PET/CT scans. Also, the use of various graft materials with enhanced antimicrobial properties should be investigated as an alternative to autologous venous material. Based on the findings presented in this thesis, biological (or biosynthetic) graft materials hold promise and should be incorporated into clinical practice.

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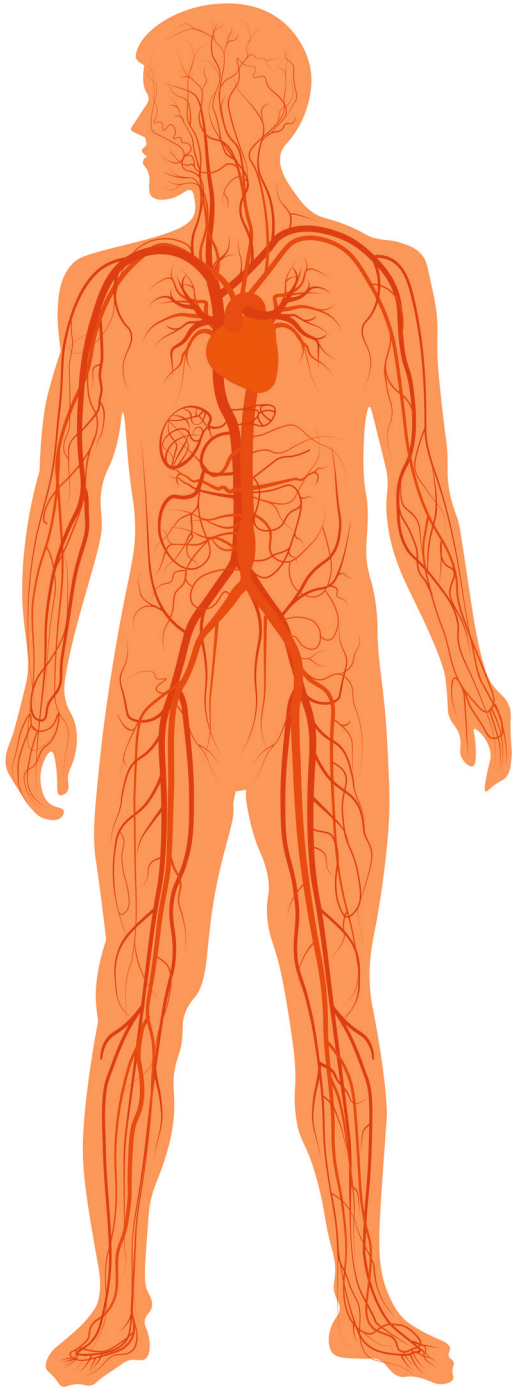

Appendices

SUMMARY IN DUTCH - NEDERLANDSE SAMENVATTING

In dit proefschrift worden verschillende aspecten onderzocht over de diagnose en behandeling van 'infectieuze natieve aorta aneurysma' (INAA) en vaatprothese en endoprothese infectie (VPEI). Deel I gaat met name over diagnostiek. Deel II geeft een beschrijving van verschillende biologische materialen die binnen de vaatchirurgie gebruikt worden. De resultaten van de studies in dit proefschrift worden hieronder beschreven.

Deel I bevat een studie, waarbij er aandacht is voor INAA en een andere studie waarbij de focus op de verslaglegging van [^{18}F]FDG PET/CT-scans voor de diagnose van VPEI ligt. Daarnaast wordt een casus beschreven, waarbij het belang van een systematische benadering bij de diagnostiek van VPEI wordt benadrukt.

Hoofdstuk 2 beschrijft het onderzoek van patiënten van het Universitair Medisch Centrum Groningen (UMCG) met een INAA vanaf hun eerste presentatie tot en met de lange termijn follow-up. Deze patiënten presenteerden zich vaak symptomatisch met pijn en/of koorts, bij meer dan een kwart zelfs met een ruptuur (inclusief rupturen die zich niet verder dan het retroperitoneum uitbreidden). Alle patiënten ondergingen een CT-scan met angiografie (CTA) en een kwart van de patiënten kreeg daarnaast een [^{18}F]FDG-PET/CT voor de diagnostiek. De FDG-opname was heterogeen verdeeld over alle patiënten. De mediane maximale opname ('maximum standardized uptake value', SUVmax) was 5.9. *Streptococcus pneumoniae* was de meest voorkomende verwekker die werd gekweekt. De gevonden behandelingen waren erg heterogeen. Er kwamen verschillen in type en duur van de antibiotica voor. Ook waren er verschillen in de chirurgische behandeling. Patiënten kregen een endovasculaire of open behandeling, waarbij er bij de open behandeling verschillende materialen werden gebruikt (autologe vene, synthetische materialen en dierlijke materialen). Gedurende de follow-up werd een hoge mortaliteit van 42% gezien. Wij concluderen dat deze studie een erg heterogene groep patiënten laat zien. Hierdoor moet de benadering patiëntgericht zijn en in een multidisciplinaire setting besproken worden.

Hoofdstuk 3 gaat over de andere infectieuze entiteit: VPEI. De volledigheid van de verslaglegging van [^{18}F]FDG-PET/CT-scans die gemaakt werden bij patiënten met verdenking op VPEI is onderzocht De verslagen zijn gescoord met behulp van door experts geformuleerde criteria gebaseerd op de huidige literatuur. Minder dan de helft van alle gescoorde verslagen voldeed aan alle tien criteria. In vergelijking met de gouden standaard voor de diagnose VPEI (volgens de MAGIC-criteria), werden een sensitiviteit van 91%, een specificiteit van 72% en een accuraatheid van 88% gevonden. Daarnaast bleek dat verslagen die voldeden aan minder criteria (≤8) een lagere sensitiviteit en specificiteit hadden vergeleken met complete verslagen. Hierbij was een beschrijving van het patroon van FDG-opname het meest afwezig in de verslaglegging. Het toepas-

sen van gestandaardiseerde verslaglegging zou kunnen bijdragen aan een verhoging van de accuratesse van de [^{18}F]FDG-PET/CT-scan wanneer gedacht wordt aan VPEI.

In **hoofdstuk 4** wordt een casus beschreven van een patiënt met atypische bevindingen op de abdominale aortawand op [^{18}F]FDG PET/CT. Initieel werd gedacht dat inflammatoire aortitis de onderliggende aandoening was. Later bleek dat een endoprothese infectie met als verwekker *Listeria monocytogenes* de oorzaak van dit beeld was. De moeizame diagnostiek bij VPEI benadrukt het belang van de conclusie in hoofdstuk 3.

Het tweede deel van dit proefschrift behandelt het gebruik van Omniflow® II op verschillende anatomische locaties bij zowel een infectieuze als niet-infectieuze setting. Tevens wordt het gebruik van de bovine pericardium patch (BPP) bij carotis endarterectomie (CEA) vergeleken met andere materialen.

De Omniflow® II is een bio-synthetische prothese die gemaakt is van een combinatie van schapencollageen en polyester. In **hoofdstuk 5** hebben wij het gebruik van deze prothese op het gebied van effectiviteit en morbiditeit bekeken bij de behandeling van VPEI. Tweeënvijftig patiënten die behandeld zijn voor een abdominaal of perifere VPEI werden geïncludeerd. In totaal kreeg 15% van de patiënten een re-infectie. Dit bleek vaker voor te komen bij abdominale reconstructies (33%) vergeleken met perifere reconstructies (12%). De primaire 'patency' na drie jaar was 72% voor perifere protheses en 58% voor centraal gelegen protheses. Daarnaast werd een significant hogere mortaliteit gevonden bij patiënten uit de centrale groep in vergelijking met de perifere groep. Op basis van de resultaten kan er gesteld worden dat het gebruik van Omniflow® II als alternatief voor een veneuze reconstructie bij de behandeling van VPEI veilig en toepasbaar is (bijvoorbeeld indien de vene niet geschikt is of in het geval van een acute operatie).

In de studie beschreven in **hoofdstuk 6** hebben we het gebruik van Omniflow® II voor re-vascularisatie in het femorale traject bekeken in een multicenter cohort bestaande uit 142 patiënten. De volgende posities werden meegenomen: femoro-femorale crossover, femorale interpositie, femoro-popliteaal (zowel tot boven als onder de knie) en femoro-cruraal. Bij de femoro-femorale crossover- (63%) en femorale interpostie-groep (72%) was de meest voorkomende indicatie reconstructie vanwege VPEI. Femoro-popliteale protheses (zowel boven als onder de knie) werden meestal gebruikt bij primaire bypasschirurgie. De femoro-crurale protheses werden het meest gebruikt in het geval van vervanging van een andere graft. Bij beide protheses betrof het een niet-infectieuze setting. Kritieke ischemie was aanwezig bij 80% van de personen met een femoro-popliteale bypass eindigend boven de knie, bij 77% van de patiënten met een femoro-popliteale bypass eindigend onder de knie en bij 91% van de patiënten met een femoro-crurale bypass. Na drie jaar werd een primaire 'patency' geconstateerd van 58% voor femoro-femorale crossover protheses, 75% voor femorale interpositie

protheses, 44% voor femoro-popliteale protheses eindigend boven de knie, 42% voor femoro-popliteale protheses eindigend onder de knie en 27% voor femoro-crurale protheses (p=0.006). Bij het vergelijken van patiënten die vervanging van een graft in een infectieuze versus een niet-infectieuze setting hebben ondergaan, werd er geen verschil aangetoond (p=0.689). Deze studie laat zien dat de Omniflow® II veilig gebruikt kan worden bij verschillende anatomische locaties in zowel de infectieuze als niet-infectieuze setting. Dit geldt niet voor de femoro-curale positie. Hierbij werden slechte resultaten gezien.

Hoofdstuk 7 beschrijft een onderzoek waarbij getracht wordt lange termijn uitkomsten van patiënten die een CEA gesloten met een BPP te vergelijken met patiënten met een polyester patch. Het betrof hier in totaal 417 patiënten, waarvan 254 met een BPP en 163 met een polyester patch. Na correctie voor mogelijke 'confounders' in de multivariabele analyses werden geen significante verschillen tussen beide materialen gevonden wat betreft ipsilaterale TIA of CVA, ipsilaterale restenose en mortaliteit (ongeacht de oorzaak). Infectie van de patch werd bij drie patiënten met een polyester patch en bij geen van de BPP-patiënten gevonden. Hoofdstuk 7 eindigt met een 'letter to the editor' geschreven door Kubat et al., waarin hij aangeeft dat het gebruik van autoloog pericard een goede optie is bij patiënten die vanwege hun religieuze overtuiging geen dierlijke materialen geïmplanteerd willen hebben. In een reactie hierop geven wij aan dat voor deze groep patiënten polyester een goed en veilig alternatief is.

Hoofdstuk 8 is een aanvulling op hoofdstuk 7 door de inclusie van de veneuze patch (naast BPP en polyester) en door de multicenter samenwerking met het Universitair Medisch Centrum Utrecht. Hierdoor zijn bij deze studie in totaal 1481 patiënten betrokken. Ook wordt door deze grotere groep de kans op een statistische type II fout verminderd. De veneuze patch werd bij 20,9% van de patiënten gebruikt, de BPP bij 67,5% van de patiënten en de polyester patch bij 11,6%. Het enige verschil dat bij de korte termijn (<30 dagen) uitkomsten werd gevonden, was dat er sprake was van craniale zenuwkneuzingen. Deze kwamen het minst voor in de BPP-groep (3,6%) vergeleken met veneus (11,3%) en polyester (9,9%). Wel bleek dat na 12 maanden follow-up nog maar weinig patiënten deze klachten ondervonden. Er bleek geen significant verschil meer te bestaan tussen de drie groepen. Eén patiënt met een BPP, drie patiënten met een polyester patch en géén van de patiënten met veneuze patches hadden een patch infectie (p=0.011). Net zoals bij de single-center studie (hoofdstuk 7) werden er geen significante verschillen gevonden tussen de verschillende materialen in de multivariabele analyses (ipsilaterale TIA of CVA, ipsilaterale restenose, ipsilaterale re-interventie en mortaliteit).

Op grond van de resultaten in hoofdstuk 7 en 8 kan geconcludeerd worden dat de besproken materialen veilig gebruikt kunnen worden bij CEA met patch angioplastiek.

LIST OF PUBLICATIONS

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CURRICULUM VITAE

David Jens Liesker werd geboren in Amstelveen op 14 september 1995. Hij groeide op in Ouderkerk aan de Amstel met zijn ouders en zus, Julia. In 2014 begon hij met de studie geneeskunde aan de Rijksuniversiteit in Groningen. Een van de hoogtepunten tijdens de master was het coschap in Suriname waarbij hij zijn voorliefde voor reizen, natuur en het ziekenhuis mooi kon combineren. Gedurende het laatste jaar van de geneeskundeopleiding heeft hij zijn stage wetenschap geschreven bij de vaatchirurgie in het Universitair Medisch Centrum Groningen (UMCG) waar hij toen al twee jaar werkzaam was als student-onderzoeker. Na het afstuderen in 2021 werd hij aangenomen als promovendus op dezelfde afdeling. Gedurende de tijd als PhD-kandidaat in het UMCG was David betrokken bij verschillende commissies (de organisatie van de chirurgencup in 2022 en de organisatie van het chirurgencabaret in 2023). Sinds augustus 2023 is David met veel plezier werkzaam als arts-assistent op de afdeling chirurgie in het St. Antonius Ziekenhuis.