The life cycle of the vascular access: from creation to ligation

Voorzaat, B.M.

The life cycle of the vascular access
From creation to ligation

by

Bram Mattijs Voorzaat

The life cycle of the vascular access: From creation to ligation

ISBN: 978-94-6419-324-4

Layout: B.M. Voorzaat

Printing: Gildeprint B.V., Enschede

The life cycle of the vascular access

From creation to ligation

Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op dinsdag 26 oktober 2021

klokke 15:00 uur

door

Bram Mattijs Voorzaat

geboren te Nieuwegein

in 1984

Promotor	Prof. dr. A.J. Rabelink
Co-promotores	Dr. J.I. Rotmans
	Dr. K.E.A. van der Bogt
Promotiecommissie	Prof. dr. J.F. Hamming
	Prof. dr. C.E. Lok, University of Toronto
	Dr. M. Snoeijs, Universiteit Maastricht
	Prof. dr. C. van Kooten

The studies presented in this thesis were carried out at the Leiden University Medical Center, The Netherlands.

Table of contents

Chapter 1

General introduction

Treatment of end stage kidney disease patients

The kidneys are the organs responsible for the removal of waste products and excess fluid. Furthermore, they are part of the regulation of blood pressure, red blood cell formation and bone formation. The kidneys consist of an intricate network of blood vessels, tubules and associated cells. Diseases such as hypertension, diabetes or autoimmune diseases can reduce kidney function by damaging one or more of these compartments of the kidney. Some patients reach end stage kidney disease (ESKD), a state in which the kidney function has irreversibly deteriorated to the point where, if no action is taken, the patient will die due to the accumulation of waste products or fluid in the body, or a combination of both.

If a patient is expected to reach ESKD, treatment options are a conservative approach, renal replacement therapy or kidney transplantation. At the end of 2019, in the Netherlands a total of 17,933 ESKD patients received either renal replacement therapy (6,292) or were alive with a functioning kidney transplant (11,641) [1].

Vascular access for hemodialysis

In hemodialysis (HD), the blood passes a filter in close proximity to a clean fluid, the dialysate, allowing the waste products and excess fluid to be removed from the body and enter the dialysate. An artificial filter is used external to the body. To pass through this filter, the blood must flow from the body to the filter and then flow back into the body. To efficiently dialyze a patient in a reasonable amount of time, blood flow rates around 300 milliliters per minute are typically used. These flow rates cannot be provided by simply cannulating a vein with a needle repeatedly. A vascular access must be created specifically for this purpose. An ideal vascular access can be created quickly and used instantly, provides a high blood flow, can be reliably used repeatedly, has a low incidence of complications and required few maintenance procedures during its' lifetime.

Several types of vascular access are available. The central venous catheter (CVC) consists of a tube with two lumens approximately 3 to 3.5 mm in diameter and is typically placed in the jugular vein, although other sites can be used as well. Benefits of a CVC are that it be inserted quickly at the bedside, and insertion can be delayed until the patient actually starts HD. For maintenance HD, there are several disadvantages of CVCs. As CVCs are relatively long tubes with a relatively small diameter, they provide resistance to blood flow, limiting the blood flow which can be provided to the HD machine. By having a foreign body inserted into the body at all times, the

patient is exposed to a significant risk of infections. CVCs are also associated with thrombosis and occlusion of the veins they are inserted into.

Arteriovenous conduits, in which a high-pressure artery is connected to a low-pressure vein to create a high-flow conduit, tackle some of the problems of CVCs. In the 1940's Alwall pioneered the creation of glass arteriovenous conduits, and in 1960 Scribner created a vascular access consisting of a metal plate and a curved Teflon tube between the radial artery and a forearm vein, located outside the body [2,3]. The tube could be connected to the HD machine repeatedly. Currently, arteriovenous grafts (AVGs) consisting of a subcutaneously placed artificial tube are used. Although these conduits provide an adequate flow for HD, infections and thrombosis often occur.

In 1966, the Brescia, Cimino, et al pioneered the creation of the native arteriovenous fistula (AVF), in which the radial artery is directly connected to the cephalic vein in a small surgical procedure, without the use of artificial graft materials [4]. After creation of this radiocephalic AVF (RCAVF), the vein was observed to dilate and thicken and the blood flow increased. This vein could then be cannulated repeatedly during HD sessions. The AVF was shown to be reliable and because no artificial materials were introduced, infections were uncommon.

Maturation of arteriovenous access

Immediately after a high-pressure artery is connected to a low-pressure vein, blood flow through the newly created AVF increases and a process of maturation of the vein is initiated [5]. Due to active outward remodeling, the diameter of the lumen increases. Conversely, excessive intimal hyperplasia formation may decrease the lumen. If the balance between these processes is tilted towards outward remodeling, a vein with a proper diameter and blood flow may be obtained. If the balance is tilted towards more intimal hyperplasia, the AVF may be stenosed and fail. Typically, an AVF is considered mature and suitable for HD if it meets the 'rule of sixes': a diameter of 6 mm, a flow of 600 ml/min and a length of at least 6 cm suitable for cannulation at a depth of no more than 6 mm, at 6 weeks after surgery. Less strict criteria have also been shown to be clinically useful [6]. Unfortunately, a large proportion of AVFs does not mature successfully, with maturation rates at 6 months in literature ranging from only 26% to 40% [7,8]. These patients require additional procedures to assist maturation, or the AVF may be abandoned altogether and the patient will be burdened with creation of another VA. In **Chapter 2** the topic

of clinical nonmaturation will be discussed and in **Chapter 3** we will look into the long-term functional outcomes of vascular accesses.

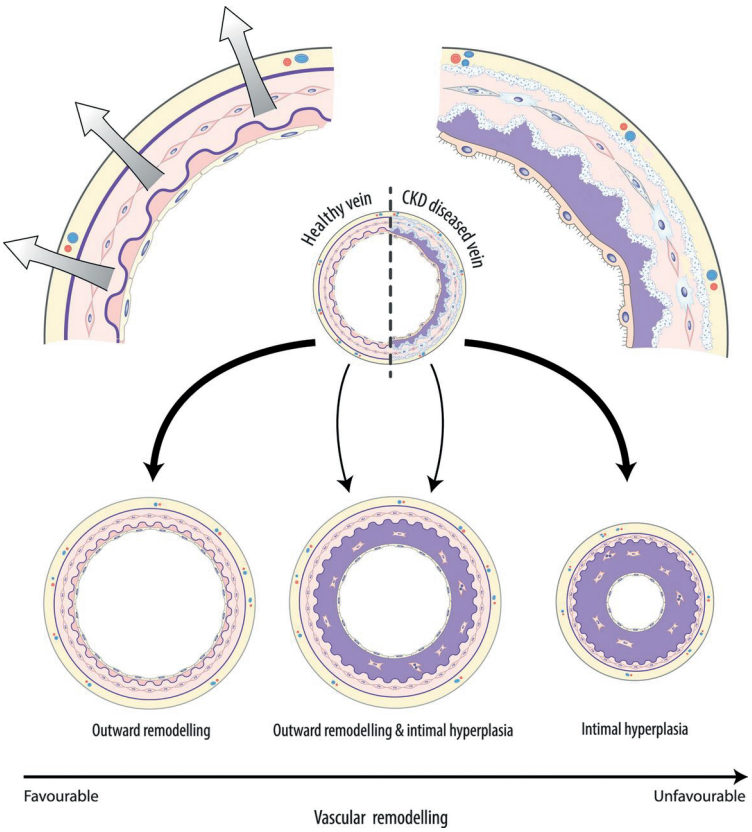


Figure 1 The balance between outward remodelling and intimal hyperplasia [5].

Pathophysiology of nonmaturation

The typical lesion of nonmaturation is that of a juxta-anastomotic stenosis, a narrowing of the vessel near the connection between the artery and vein, limiting the blood flow through the entire AVF and preventing further maturation. The formation of intimal hyperplasia responsible for this stenosis involves an inflammatory response which may be triggered by surgical trauma or the increased blood flow after AVF creation [9]. In human arterial disease, modulating inflammation with doxycycline increased aneurysm growth [10]. Prior work by our group demonstrated that in mice, AVF maturation could be improved by inhibiting inflammation using liposomal prednisolone, a locally-acting drug that targets sites of inflammation. In **Chapters 4**

and 5 the design and results of a clinical trial of liposomal prednisolone to improve AVF maturation in humans will be discussed.

Cardiac effects of an arteriovenous access conduit

The presence of an arteriovenous conduit poses a burden to the cardiovascular system due to the additional blood flow which gets 'added' to the systemic circulation, increasing the cardiac output. In the vulnerable HD population, this may have unfavorable effects on cardiac structure and function had been dubbed 'AVF toxicity' in literature [11]. In **chapter 6** we performed a review of literature on the cardiac effects of arteriovenous conduits and in **chapter 7** we performed a survey to investigate physicians' opinions on how to act if an access remains patent after kidney transplantation.

Scope of this thesis

Our group previously investigated the pathophysiology of AVF maturation failure and developed an animal model in which to test pharmacological interventions aimed at improving maturation. This thesis focuses on the clinical aspects of the life cycle of the AVF. The first part, chapters 2 and 3, describe the current outcomes of vascular accesses in a retrospective study. In the second part, chapters 4 and 5, outcomes of a novel intervention aimed at improving AVF maturation are presented. In the third part, chapters 6 and 7, a side-effect of a well-functioning AVF is described and we investigate opinions in the field on how this should be approached.

In **Chapter 2** we investigate the outcomes of maturation of AVFs and initial functional outcomes of AVGs in the Netherlands in a multi-center retrospective cohort from 8 hospitals, and we aimed to create a model predicting nonmaturation. **Chapter 3** focuses on the patency outcomes and long-term side-effects and maintenance of the vascular accesses in this cohort.

Chapter 4 presents the rationale and design for the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study, a randomized controlled trial in which we investigated if liposomal prednisolone improves RCAVF maturation in humans. **Chapter 5** presents the results of this trial.

Chapter 6 introduces the problem of AVF toxicity and provides a review of literature investigating the effect AVF creation and closure have on on cardiac parameters. In **Chapter 7** we aimed to measure the opinions of physicians on how to approach an AVF after kidney transplantation.

Finally, in **Chapters 8 and 9** we discuss and summarize the findings from this thesis.

References

1. Nefrovisie. Nefrodata [Internet]. 2020 [cited 2020 Jul 31]. Available from: http://www.renine.nl
2. ALWALL N. On the artificial kidney; apparatus for dialysis of the blood in vivo. Acta Med Scand. 1947; 128(4):317–25.
3. Quinton W, Dillard D, Scribner BH. Cannulation of blood vessels for prolonged hemodialysis. Hemodial Int 2004; 8(1):6–9.
4. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. N Engl J Med. 1966; 275(20):1089–92.
5. Rothuizen TC, Wong C, Quax PHA, van Zonneveld AJ, Rabelink TJ, Rotmans JI. Arteriovenous access failure: more than just intimal hyperplasia? Nephrol Dial Transplant. 2013; 28(5): 1085–92.
6. Robbin ML, Chamberlain NE, Lockhart ME, Gallichio MH, Young CJ, Deierhoi MH, et al. Hemodialysis arteriovenous fistula maturity: US evaluation. Radiology. 2002; 225(1): 59–64.
7. Bylsma LC, Gage SM, Reichert H, Dahl SLM, Lawson JH. Arteriovenous Fistulae for Haemodialysis: A Systematic Review and Meta-analysis of Efficacy and Safety Outcomes. Eur J Vasc Endovasc Surg. 2017; 54(4):513–22.
8. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA. 2008; 299(18):2164–71.
9. Mitra AK, Gangahar DM, Agrawal DK. Cellular, molecular and immunological mechanisms in the pathophysiology of vein graft intimal hyperplasia. Immunol Cell Biol; 2006. p. 115–24.
10. Arnoud Meijer C, Stijnen T, Wasser MNJM, Hamming JF, Van Bockel JH, Lindeman JHN. Doxycycline for stabilization of abdominal aortic aneurysms: A randomized trial. Ann Intern Med. 2013; 159(12): 815–23.
11. Amerling R, Ronco C, Kuhlman M, Winchester JF. Arteriovenous fistula toxicity. Blood Purif. 2011; 31(1–3):113–20.

Chapter 2

Arteriovenous fistula maturation failure in a large cohort of hemodialysis patients in the Netherlands

Bram M. Voorzaat, Koen E.A. van der Bogt, Cynthia J. Janmaat, Jan van Schaik, Friedo W. Dekker, Joris I. Rotmans, on behalf of the Dutch Vascular Access Study Group

World Journal of Surgery 2018: 42, 1895–1903. DOI: 10.1007/s00268-017-4382-z

Abstract

Objectives Radiocephalic arteriovenous fistulas (RCAVF) are the preferred vascular access (VA) for hemodialysis (HD). Cohort studies from North America revealed that nonmaturation is a significant disadvantage of RCAVFs compared to other VAs.

Design This present retrospective study describes the incidence of nonmaturation of AVFs and functional failure of arteriovenous grafts (AVG) in a multicentre cohort in the Netherlands and attempts to create a prediction model for nonmaturation of RCAVFs. Furthermore, the efficacy of interventions to promote maturation as well as the variability between hemodialysis centers was evaluated.

Materials Medical records from 8 hospitals from 1997 to 2016 were retrospectively evaluated for VA type, maturation/primary success and demographics and comorbidities.

Methods A prediction model was created for RCAVF nonmaturation using multivariate logistic regression analysis, selecting significant predictors using backward selection. Discrimination and calibration of the model were assessed.

Results 1383 AVFs and 273 AVGs were included in 1221 patients. Overall nonmaturation was 24% for RCAVFs, and 11% for upper arm AVFs. The functional failure rate for AVGs was 6%. The nonmaturation rate of contralateral RCAVFs after failure of an RCAVF was 22%. Procedures to improve RCAVF maturation were successful in 98/142 cases (69%). Predictors for nonmaturation were female gender, peripheral vascular disease, cerebrovascular disease and a cephalic vein diameter <2.5mm, but the prediction model lacked sensitivity and specificity predicting individual RCAVF nonmaturation (C-statistic 0.629).

Conclusion Nonmaturation rates are highest for RCAVFs, but nonmaturation could not be predicted with demographic parameters.

Introduction

The arteriovenous fistula (AVF) is the preferred type of permanent vascular access (VA) in maintenance hemodialysis (HD) patients. AVFs are associated with a lower incidence of patency-related procedures than arteriovenous grafts (AVGs) and less infectious complications than both AVGs and central venous catheters (CVC). As a consequence, healthcare costs are lowest for patients with an AVF, compared to patients with an AVG or CVC[1].

Both the NKF KDOQI and EBPG guidelines advocate the creation of AVFs distally in the upper extremity whenever possible [1,2]. Radiocephalic AVFs (RCAVFs) have the advantage of preservation of more proximal options for future VAs in case of access failure. In addition, RCAVFs are associated with a lower incidence of HD access-induced distal ischemia [3], when compared to upper arm AVFs. High flow also predisposes to increased cardiac output and impaired systemic blood flow in patients with impaired cardiac function, a phenomenon known as 'AVF cardiotoxicity' [4,5].

The main disadvantage of RCAVFs is nonmaturation, characterized by inadequate dimensions of the venous outflow tract or insufficient blood flow [6]. Although a uniform definition of nonmaturation is lacking, rates up to 65% are reported [7]. Forearm location and female gender are well-known risk factors for early failure [8]. A decade ago, Lok and co-workers [9] developed a scoring system to predict nonmaturation in a North-American cohort. Predictors were age over 65 years, female gender, non-white race, and coronary and peripheral arterial disease.

Most studies on AVF maturation are from the United States and Canada. As demonstrated in the DOPPS study, CVC preference is higher [10] and AVF cannulation is performed later [11] than in Europe. Other significant differences are ethnicity, BMI and cardiovascular comorbidities [12]. The aim of the current study was to evaluate the incidence of nonmaturation of RCAVFs and upper arm AVFs in a large cohort in the Netherlands and to create a prediction model for RCAVF nonmaturation. As a comparator group, functional failure of AVGs was also assessed. In addition, the efficacy of interventions to promote maturation as well as the variability between HD centers was assessed.

Methods

Patient selection

Adult patients who underwent creation of an AVF or AVG as a permanent VA for maintenance HD were retrospectively identified in 5 affiliated teaching hospitals and 3 academic hospitals in the Netherlands. To prevent survivorship bias, the time frame varied per hospital and was limited to years in which medical records were available for all consecutive AVF and AVG recipients in that year (Supplement, table 5). Overall, patients receiving their VA between 1997 and 2016 were included.

The Medical Research Involving Human Subjects Act (WMO) was not applicable. Ethical approval was granted by the medical ethics committees of the Leiden University Medical Center. Data were collected and processed in accordance with the local research code of conduct.

Data collection

Data were collected from clinical records and included demographic variables, comorbidities, medication use, laboratory results, VA configuration and surgical details, initiation and abandonment of VA use, ultrasound results, surgical and endovascular interventions and clinical adverse events. Ethnicity of patients was not registered due to objections by the ethical committee.

Outcomes and candidate predictors

Pre-emptively created VAs were defined as VAs created in a patient who did not receive HD within two weeks after VA creation. The VA was considered mature if it was successfully used for at least three consecutive HD sessions or if the Robbin's ultrasound criteria for maturation were met[13]. The VA was considered nonmature if it was not cannulated in a patient on HD. If the patient has not started HD, a VA was considered nonmature if ultrasound or angiography demonstrated a failed VA using Robbin's criteria or another VA was created. If maturation could not be assessed due to death, kidney transplantation or loss to follow-up before VA cannulation or ultrasound, it was considered indeterminate.

For prevalent HD patients, maturation time was defined as the time until cannulation or ultrasound demonstrating maturation, whichever came first. Assisted maturation was defined as maturation with a procedure to improve patency.

A list of candidate predictors for nonmaturation was compiled: Patient age over 60 years, female gender, diabetes mellitus, a body mass index (BMI) over 25 kg/m^2, symptomatic coronary, cerebrovascular or peripheral arterial disease, an ipsilateral central venous catheter, hypertension, cystic kidney disease, whether the fistula was created pre-emptively and a pre-operative diameter of the artery or vein below 2.5mm.

Statistical analysis

Statistical analyses were performed for RCAVFs, upper arm AVFs and upper extremity AVGs. t- and ^{2}-tests were used where applicable. Baseline characteristics were summarized as mean with standard deviations for continuous variables and as count with percentages for categorical variables. Missing data were handled by multiple imputation methods using fully conditional specification with 10 repetitions [14,15]. Candidate predictors, VA sidedness and maturation outcome were entered. For age, BMI, mean arterial pressure and artery and vein diameters, continuous values were entered into the multiple imputation. The imputed values were dichotomized to appropriate categories.

A prediction model for nonmaturation was created. Candidate predictors were entered in a multivariate logistic regression analysis, with nonmaturation as the dependent variable. Backward selection was used to identify the most significant independent predictors. In logistic regression analysis, candidate predictors were considered significant at a p-value < 0.30. P-value of 0.30 was applied as conservative selection criterion to limit chances of overfitting [16]. We used the majority method to select the predictors for the final prediction model [17]. Predictors significant in at least 7 out of 10 imputation sets were entered into the final logistic regression analysis. Subsequently, forward selection was used to check stability of the results.

Sensitivity analysis was performed by repeating the logistic regression analysis with a significance level of p-value<0.40, <0.25 and <0.20. The model's predictive performance was examined by estimating calibration and discrimination. A receiver operating characteristic analysis was performed for the model and C-statistics from all imputation sets were pooled [18]. Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY).

	RCAVF	Upper arm AVF	AVG	p-value RCAVF vs other	Upper arm AVF vs other	AVG vs other
Number of accesses n=1 605	663	699	243			
Gender						
Male	463 (69.8%)	363 (51.9%)	108 (44.4%)	<0.001	<0.001	<0.001
Female	200 (30.2%)	336 (48.1%)	135 (55.6%)			
Patient age	62.6 ± 15.3 yr	62.7 ± 14.6 yr	64.3 ± 14.9 yr	0.516	0.624	0.116
Body mass index (BMI)	27.1 ± 5.9 kg/m²	26.5 ± 6.2 kg/m²	27.6 ± 6.5 kg/m²	0.288	0.017	0.066
Mean arterial pressure at VA creation	103 ± 16.4 mmHg	96 ± 17.3 mmHg	96 ± 18.4 mmHg	<0.001	<0.001	0.003
First permanent vascular access for patient	596 (89.9%)	414 (59.2%)	113 (46.5%)	<0.001	<0.001	<0.001
Pre-emptively created	366 (55.2%)	274 (39.2%)	83 (34.2%)	<0.001	<0.001	<0.001
Jugular catheter present				<0.001	<0.001	0.263
No catheter	381 (57.5%)	301 (43.1%)	108 (44.4%)			
Ipsilateral catheter	100 (15.1%)	145 (20.7%)	50 (20.6%)			
Contralateral catheter	182 (27.5%)	253 (36.2%)	85 (35.0%)			
Pre-operative ultrasound						
Target vein diameter	2.9 ± 0.8 mm	3.9 ± 1.3 mm	3.9 ± 1.4 mm	<0.001	<0.001	<0.001
Artery diameter	2.6 ± 0.6 mm	4.3 ± 1.1 mm	4.5 ± 1.0 mm	<0.001	<0.001	<0.001

Cause of renal failure				0.163	0.092	0.112
Diabetes mellitus	132 (19.9%)	165 (23.6%)	72 (29.6%)			
Glomerulonephritis	72 (10.9%)	80 (11.4%)	22 (9.1%)			
Vascular disease	147 (22.2%)	140 (20.0%)	52 (21.4%)			
Interstitial nephropathy	43 (6.5%)	48 (6.9%)	14 (5.8%)			
Cystic kidney disease	50 (7.5%)	34 (4.9%)	14 (5.8%)			
Congenital/hereditary disease	17 (2.6%)	21 (3.0%)	7 (2.9%)			
Multisystem disease	29 (4.4%)	39 (5.6%)	5 (2.1%)			
Other	91 (13.7%)	109 (15.6%)	27 (11.1%)			
Unknown	82 (12.4%)	63 (9.0%)	30 (12.3%)			
Comorbid conditions						
Diabetes mellitus	242 (36.5%)	282 (40.3%)	128 (52.7%)	0.005	0.841	<0.001
Coronary artery disease	173 (26.1%)	182 (26.0%)	59 (24.3%)	0.818	0.845	0.558
Peripheral vascular disease	125 (18.9%)	127 (18.2%)	41 (16.9%)	0.603	0.937	0.545
Cerebrovascular disease	94 (14.2%)	97 (13.9%)	39 (16.0%)	0.844	0.649	0.406
Medication use						
Antiplatelet	227 (34.2%)	238 (34.0%)	77 (31.7%)	0.739	0.835	0.456
Anticoagulant	100 (15.1%)	139 (19.9%)	47 (19.3%)	0.016	0.057	0.501
ACE inhibitor	244 (36.8%)	240 (34.3%)	83 (34.2%)	0.300	0.465	0.679
Angiotensin receptor blocker	197 (29.7%)	188 (26.9%)	62 (25.5%)	0.162	0.453	0.378
Calcium channel blocker	292 (44.0%)	340 (48.6%)	113 (46.5%)	0.109	0.117	0.977
Aldosterone antagonist	15 (2.3%)	9 (1.3%)	4 (1.6%)	0.184	0.219	0.899
Phosphate binder	346 (52.2%)	400 (57.2%)	151 (62.1%)	0.012	0.343	0.033

non-calcium-based						
Phosphate binder calcium-based	282 (42.5%)	259 (37.1%)	105 (43.2%)	0.117	0.022	0.307
Vitamin D	519 (78.3%)	558 (79.8%)	187 (77.0%)	0.697	0.355	0.457
Corticosteroids	59 (8.9%)	97 (13.9%)	23 (9.5%)	0.016	0.002	0.364
Other immunosuppressant	19 (2.9%)	51 (7.3%)	9 (3.7%)	0.001	<0.001	0.341
Laboratory measurements						
Calcium	2.28 ± 0.18 mmol/l	2.27 ± 0.19 mmol/l	2.25 ± 0.20 mmol/l	0.191	0.670	0.234
Phosphate	1.67 ± 0.51 mmol/l	1.67 ± 0.54 mmol/l	1.65 ± 0.48 mmol/l	0.751	0.983	0.681
PTH	37.2 ± 46.6 pmol/l	35.7 ± 38.3 mmol/l	31.5 ± 25.3 mmol/l	0.273	0.999	0.138
HbA1c-IFCC	44.5 ± 13.5 mmol/mol	45.1 ± 13.2 mmol/mol	44.8 ± 16.3 mmol/mol	0.635	0.615	0.960

Table 1 Patient characteristics at vascular access creation.

Results

Patient characteristics and VA configurations

Data from 1656 VAs (1383 AVF and 273 AVG) in 1221 patients were obtained (table 1). The earliest VA available in the cohort was created in 1997 (Supplement, table 5). RCAVFs and upper arm AVFs and AVGs were the most common configurations. The 51 other configurations constituted 3.1% of the cohort and were excluded from the analysis (figure 1). Baseline measurements for arterial and venous diameters were missing in 43% and 25%, respectively, in cases where diameters were only described as 'suitable' in clinical practice. Additionally, the perioperative mean arterial pressure was unknown for 12.1% of cases and the BMI was missing for 7.5%.

VA configuration (n) n=1 605	On HD at time of VA creation			First access for patient
	Yes	No but started within 3 months	No started after 3 months or never	
RCAVF (663)	44.8 % (297)	16.6 % (110)	38.6% (256)	89.9 % (596)
BCAVF (547)	56.5 % (309)	17.4 % (95)	26.1% (143)	62.9 % (344)
BBAVF (152)	76.3 % (116)	8.6% (13)	15.1 % (23)	46.1 % (70)
AVG (243)	65.8 % (160)	18.1 % (44)	16.0 % (39)	46.5 % (113)

Table 2 Timing of VA surgery for VA configurations.

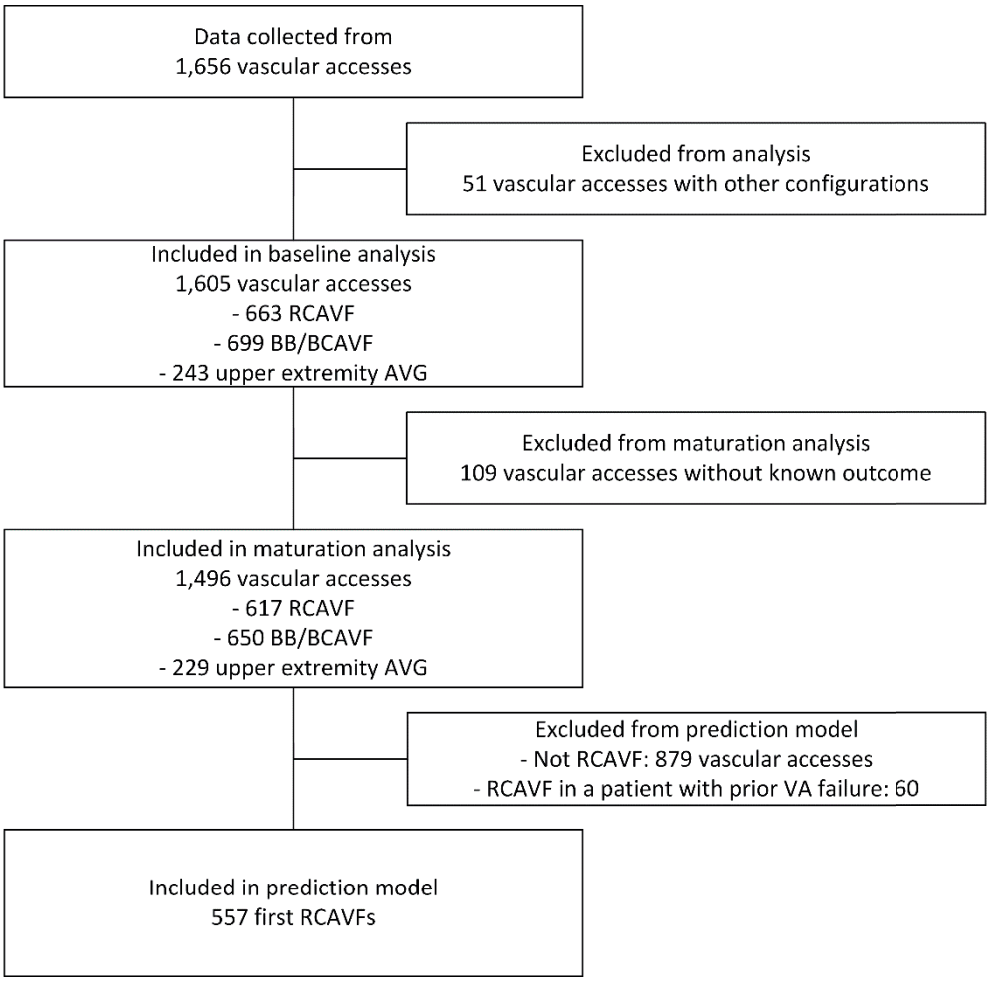


Figure 2 Flow chart demonstrating exclusion of VAs from analysis.

Females and patients with diabetes more frequently received an AVG and females more frequently received an upper arm AVF. Fifty-five percent of RCAVFs were pre-emptively created, compared to 39% and 34% for upper arm AVFs and AVGs, respectively. RCAVFs were most often the first VA, with 90% created in patients without a prior VA (table 2).

Post-operative ultrasound examinations were not routinely performed during the historical timeframe of the study and were available for 28% (448/1605) of VAs. For 1496 out of 1605 VAs (93.2%), the maturation outcome could be determined (figure 1 and Supplement, table 6).

Incidence of nonmaturation

The incidence of nonmaturation was 24% for RCAVFs. This was lower than the nonmaturation incidence of upper arm AVFs and functional failure of AVGs ($p<0.001$ for RCAVF versus upper arm AVF, table 3). The short-term follow-up of VAs, defined as achieving 3 months or 6 months of functional patency, was similar for upper arm AVFs (3 months: 77.8%, 6 months: 69.5%) and AVGs (3 months: 77.7%, 6 months: 68.6%) and worse for RCAVFs (3 months: 66.6%, 6 months: 59.5%) (Supplement, table 7).

Unassisted maturation was lowest for RCAVFs, at 60% (370/617), versus 79% for upper arm AVFs. Assisted maturation could be achieved even after multiple procedures (Supplement, table 8 and Supplement, figure 4). 80% of AVGs did not require procedures before first use.

	Patients on HD at time of VA creation			**Started HD within 3 months**	**All VAs with known outcome n=1 496**
	Use at 6 weeks	**Use at 3 months**	**Time until use (days ± SD)**	**Use at 3 months**	**AVF nonmaturation/ AVG functional failure**
RCAVF	17.4 % (50/287)	61.3 % (176/287)	68 ± 44	81.1 % (86/106)	24.1% (149/617)
Upper arm AVF	22.0 % (89/404)	72.5 % (293/404)	66 ± 43	93.5 % (100/107)	10.6% (69/650)
AVG	71.0 % (110/155)	91.6 % (142/155)	31 ± 19	97.6 % (41/42)	5.7% (13/229)

Table 3 6-week and 3-month cannulation rates and primary failure per VA configuration. Patients who did not initiate HD or did not use their VA for reasons unrelated to nonmaturation were excluded.

Of RCAVFs pre-emptively created in patients who initiated HD within 3 months, 81 % were cannulated within 3 months (table 3). In prevalent HD patients, 61% of RCAVFs were cannulated within 3 months. AVGs were cannulated earlier than RCAVFs and upper arm AVFs, which were rarely used within 6 weeks (table 3, figure 2). The 3-month cannulation rates in prevalent HD patients differed substantially between hospitals, ranging from 48-70% for RCAVFs and 33-80% for upper arm AVFs (Supplement, table 9).

Over the timeframe of the study, no significant change in maturation of AVFs or primary success of AVGs was observed (Supplement, table 10).

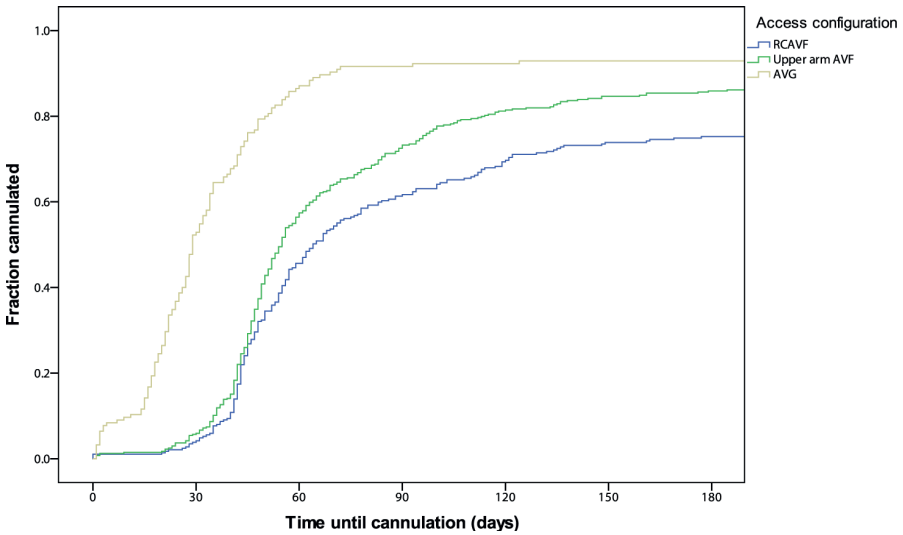


Figure 3 Time until first cannulation in patients prevalent on HD at the time of VA creation.

Fifty-nine patients received subsequent RCAVFs in both arms. Of the first RCAVFs, 34 (57%) did not mature, the remainder failed after initial successful use. 41 out of 59 (69%) subsequently created contralateral RCAVFs matured without procedures. As 5 RCAVFs reached maturation with procedures, the assisted maturation of these contralateral RCAVFs was 78%. 13 out of 59 (22%) RCAVFs failed due to nonmaturation. For 462 RCAVFs, the pre-operative venous diameter and the maturation outcome were recorded (table 1). Of RCAVFs with a recorded pre-operative venous diameter of 2.5mm or more, 225/295 (76%) were successful. From the group of AVFs with a pre-operative venous diameter below 2.5mm, 113/167 (68%) matured successfully (p=0.045).

Variable	Beta	Odds ratio (95% confidence interval)	p
Pre-operative cephalic vein diameter <2.5mm	0.426	1.53 (1.01 – 2.32)	0.044
Female gender	0.787	2.20 (1.47 – 3.29)	<0.001
Peripheral vascular disease	0.326	1.39 (0.84 – 2.28)	0.198
Cerebrovascular disease	-0.784	0.46 (0.23 – 0.89)	0.022

Table 4 Predictors based on multivariate logistic regression analysis. The intercept of the model was -1.452.

Prediction of nonmaturation

In the logistic regression analysis, 4 out of 13 predictor variables were significant at p<0.30 with backward selection in at least 7 of 10 imputed datasets (table 4). In the sensitivity analysis restriction of the removal criterion for backward selection to p<0.25 removed the predictor peripheral vascular disease, while p<0.40 added the predictor arterial diameter <2.5mm. These results were stable with forward selection. The risk equation of this model predicted RCAVF nonmaturation with a median area under the ROC-curve of 0.629 (interquartile range 0.626 – 0.633). Calibration of the model was assessed by comparing observed and predicted risk (figure 3).

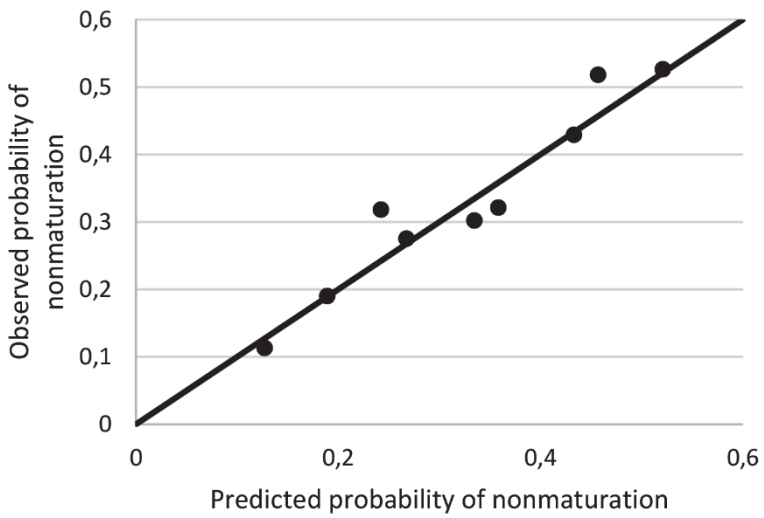


Figure 4 Calibration of the prediction model for nonmaturation of first RCAVFs.

Discussion

In the present study, we retrospectively evaluated primary outcomes of 1656 VAs in a multicentre cohort of 1221 HD patients in the Netherlands. Comorbidities are comparable to previous American cohorts, whereas the BMI of patients in our cohort (27 kg/m^2) is slightly lower, when compared to previous studies (28-30 kg/m^2) [7,12]. The proportion of pre-emptively created RCAVFs (55%) was higher than in Northern American studies ranging between 46% and 49% [7,9].

Incidence of nonmaturation

The 24% rate of primary failure of RCAVFs appears lower than the rates reported by Dember, et al. (65%), Huijbrechts, et al. (40%) and Schinstock, et al. (37%) [7,19,20]. In the study by Dember, et al., 14% of AVFs were considered nonmature as determined by ultrasound criteria, although they were being used for HD [7]. We found no improvement of AVF maturation over time.

It is important to notice that the definition of nonmaturation in our retrospective study differs from prospective studies. As follow-up ultrasound examinations were not routinely performed and a large proportion of AVFs was created pre-emptively, a composite measure of functional use and ultrasound criteria was created.

Although AVGs have a lower 5.7% incidence of functional failure than the nonmaturation incidence of upper arm AVFs (10.6%), this advantage is offset by the higher loss of AVG patency after cannulation, resulting in similar rates of 3- and 6-months functional patency.

RCAVF versus other configurations

Like previous studies, we demonstrate that RCAVFs have the highest rate of delayed cannulation and nonmaturation. Over the duration of the study since 1997, no improvement of maturation has been observed. Our findings confirm the findings by Masengu, et al. [21] that age, gender and vascular disease are associated with, but do not reliably predict nonmaturation. In contrast, Lok, et al. [9] were able to predict nonmaturation in their model. Possible explanations are the different population in the US and Canada and differences in patient selection and surgical practice, compared to Europe. Comparable to previous studies, we found a high rate of nonmaturation in females [22–24].

RCAVFs were commonly created in patients without a history of a failed VA. It is assumed that patients receiving an upper arm AVF as their first VA often had forearm vasculature not suitable for an RCAVF. It remains unclear whether this reflects local anatomical variations or a more generalized unsuitability of the patients' vasculature. Based on our results, we hypothesize RCAVF nonmaturation is not solely explained by demographics and comorbidities. The anatomy of the RCAVF itself appears prone to nonmaturation.

If nonmaturation were strongly associated with comorbidities and demographics, one would expect a high nonmaturation rate of contralateral AVFs in individual patients with prior VA failure. In this respect, an important observation was the not increased 22% primary failure rate

of RCAVFs in patients with a non-matured contralateral RCAVF, similar to the overall 24% risk of RCAVF nonmaturation in our cohort. This illustrates that comorbidities do not explain nonmaturation substantially. One possible explanation is preferential creation of the first VA in the non-dominant arm, even if the vasculature of the dominant arm is more suitable (i.e. larger vessels).

Interventions to promote maturation

Out of a total of 142 RCAVFs undergoing procedures to improve maturation, 98 (69%) matured. Although it cannot be ruled out that these also would have matured spontaneously, procedures to assist maturation appeared to be a worthwhile strategy to promote AVF usability. Similar results were observed by Shin, et al., achieving successful cannulation in 14 out of 19 cases (74%) of balloon angioplasty for AVF nonmaturation due to localized stenosis[25]. In a study by Miller et al., extensive balloon angioplasty and side branch interruption of 75 nonmature AVFs with a diameter of 2.0-5.0 mm resulted in successful cannulation of 71 AVFs after a median of 2.6 procedures [26].

Variability amongst hospitals

In our cohort, patients from both academic and referral hospitals were included. The variability in maturation rates of AVFs amongst centres was remarkable. Based on the current data, it cannot be determined whether these differences result from the process of care or demographic characteristics of the patients that we did not include in our analysis.

Limitations

Due to the retrospective design, the maturation outcome could not be determined for 10% of VAs. Another limitation of the current study is the unavailability of routine 6-week ultrasound examinations. Postoperative ultrasound examinations were often performed for symptoms or suspected nonmaturation. These therefore cannot be extrapolated to the entire cohort.

The time until first cannulation in prevalent hemodialysis patients should be interpreted with caution. As Robbin, et al. [27] demonstrated, most of the maturation occurs within two weeks after surgery. We cannot distinguish if the differences between the 6-week and 3-month cannulation rates of 17% and 61%, respectively, reflect actual delayed maturation or clinicians' reluctance to early cannulation. Only a prospective study in which serial ultrasound examinations or early cannulation attempts are performed can reliably assess the potential for early cannulation of AVFs.

As the weak prediction model did not result in a clinically applicable risk equation, we did not perform external validation. One limitation could be the lack of data on ethnicity, an important factor in the scoring system by Lok et al. [9].

Future directions

One approach to prevent nonmaturation is careful patient selection. New strategies are needed to identify patients at high risk of nonmaturation. A shift towards upper arm AVFs as the primary VA option seems attractive. However, losing distal VA options may not be acceptable for all patients and high-flow symptoms more often occur with upper arm AVFs. Therefore, such paradigm shift seems not to be the right solution.

Conclusion

While the AVF has the best long-term outcome, the choice of VA should be tailored for each individual patient. Clinicians should weigh the benefits of future options and a lower incidence of high-output symptoms in RCAVFs to the risk of nonmaturation. This study demonstrates that for patients clinically eligible to receive an RCAVF, demographic parameters and comorbid conditions explain only a small part of AVF nonmaturation. In case of a failed RCAVF, a new RCAVF at the contralateral arm should not be avoided if the vasculature is suitable.

Acknowledgments

We thank Paul Hamstra, Denise de Jong, Laurens Pierik and Desirée Vergroesen for their contributions to data entry in the study.

Dutch Vascular Access Study Group

Leiden University Medical Center: Bram M. Voorzaat, MD, Koen E.A. van der Bogt, MD, Cynthia J. Janmaat, MD, Jan van Schaik, MD, Friedo W. Dekker, PhD, Joris I. Rotmans, MD, PhD. Academic Medical Center: Liffert Vogt, MD, PhD, Laurens Huisman, MD. Alrijne Hospital: Bas A.Th.F. Gabreëls, MD, PhD. Dianet: Frans T.J. Boereboom, MD, PhD. Haga Hospital: Irene M. van der Meer, MD, PhD, Randolph G.S. van Eps, MD, PhD. Haaglanden Medical Center: Daniël Eefting, MD, PhD. OLVG: Marcel C. Weijmer, MD, PhD, Roos C. van Nieuwenhuizen, MD. UMC Utrecht: Alferso Abrahams, MD, Raechel J. Toorop, MD, PhD

References

1. Vascular Access 2006 Work Group. Clinical practice guidelines for vascular access. Am J Kidney Dis. 2006 Jul;48 Suppl 1:S176-247.
2. Tordoir J, Canaud B, Haage P, Konner K, Basci A, Fouque D, et al. EBPG on Vascular Access. Nephrol Dial Transplant. 2007 May 1;22 Suppl 2(suppl_2):ii88-117.
3. Scheltinga MR, van Hoek F, Bruijninckx CMA. Time of onset in haemodialysis access-induced distal ischaemia (HAIDI) is related to the access type. Nephrol Dial Transplant. 2009 Oct;24(10):3198–204.
4. Amerling R, Ronco C, Kuhlman M, Winchester JF. Arteriovenous fistula toxicity. Blood Purif. 2011 Jan;31(1–3):113–20.
5. Voorzaat BM, van Schaik J, Siebelink H-MJ, Tordoir JH, Rotmans JI. The pros and cons of preserving a functioning arteriovenous fistula after kidney transplantation. The Journal of Vascular Access 2016; 17 (Suppl 1): S16-S22.
6. Rothuizen TC, Wong C, Quax PHA, van Zonneveld AJ, Rabelink TJ, Rotmans JI. Arteriovenous access failure: more than just intimal hyperplasia? Nephrol Dial Transplant. 2013 May 1;28(5):1085–92.
7. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA. 2008 May 14;299(18):2164–71.
8. Miller PE, Tolwani A, Luscy CP, Deierhoi MH, Bailey R, Redden DT, et al. Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. Kidney Int. 1999 Jul;56(1):275–80.
9. Lok CE, Allon M, Moist L, Oliver MJ, Shah H, Zimmerman D. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). J Am Soc Nephrol. 2006 Nov;17(11):3204–12.
10. Fissell RB, Fuller DS, Morgenstern H, Gillespie BW, Mendelssohn DC, Rayner HC, et al. Hemodialysis patient preference for type of vascular access: variation and predictors across countries in the DOPPS. J Vasc Access. 14(3):264–72.
11. Saran R, Dykstra DM, Pisoni RL, Akiba T, Akizawa T, Canaud B, et al. Timing of first cannulation and vascular access failure in haemodialysis: an analysis of

practice patterns at dialysis facilities in the DOPPS. Nephrol Dial Transplant. 2004 Sep;19(9):2334–40.

12. Asano M, Thumma J, Oguchi K, Pisoni RL, Akizawa T, Akiba T, et al. Vascular Access Care and Treatment Practices Associated with Outcomes of Arteriovenous Fistula: International Comparisons from the Dialysis Outcomes and Practice Patterns Study. Nephron Clin Pract. 2013;124(1–2):23–30.
13. Robbin ML, Chamberlain NE, Lockhart ME, Gallichio MH, Young CJ, Deierhoi MH, et al. Hemodialysis arteriovenous fistula maturity: US evaluation. Radiology. 2002 Oct;225(1):59–64.
14. Schafer JL. Multiple imputation: a primer. Stat Methods Med Res. 1999 Mar;8(1):3–15.
15. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007 Jun;16(3):219–42.
16. Steyerberg E. Chapter 11 Selection of Main Effects. In: Clinical prediction models A practical approach to development, validation, and updating. New York: Springer Science; 2009. p. 195–6.
17. Vergouwe Y, Royston P, Moons KGM, Altman DG. Development and validation of a prediction model with missing predictor data: a practical approach. J Clin Epidemiol. 2010 Feb;63(2):205–14.
18. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol. 2009 Jul 28;9(1):57.
19. Huijbregts HJT, Bots ML, Wittens CHA, Schrama YC, Moll FL, Blankestijn PJ. Hemodialysis arteriovenous fistula patency revisited: results of a prospective, multicenter initiative. Clin J Am Soc Nephrol. 2008 May;3(3):714–9.
20. Schinstock CA, Albright RC, Williams AW, Dillon JJ, Bergstralh EJ, Jenson BM, et al. Outcomes of arteriovenous fistula creation after the Fistula First Initiative. Clin J Am Soc Nephrol. 2011 Aug;6(8):1996–2002.
21. Masengu A, Maxwell AP, Hanko JB. Investigating clinical predictors of arteriovenous fistula functional patency in a European cohort. Clin Kidney J. 2016 Feb;9(1):142–7.

22. Farber A, Imrey PB, Huber TS, Kaufman JM, Kraiss LW, Larive B, et al. Multiple preoperative and intraoperative factors predict early fistula thrombosis in the Hemodialysis Fistula Maturation Study. J Vasc Surg. 2016 Jan;63(1):163-170.e6.

23. Wilmink T, Hollingworth L, Powers S, Allen C, Dasgupta I. Natural History of Common Autologous Arteriovenous Fistulae: Consequences for Planning of Dialysis. Eur J Vasc Endovasc Surg. 2016 Jan;51(1):134–40.

24. Miller CD, Robbin ML, Allon M. Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients. Kidney Int. 2003 Jan;63(1):346–52.

25. Shin SW, Do YS, Choo SW, Lieu WC, Choo I-W. Salvage of Immature Arteriovenous Fistulas with Percutaneous Transluminal Angioplasty. Cardiovasc Intervent Radiol. 2005 May 30;28(4):434–8.

26. Miller GA, Goel N, Khariton A, Friedman A, Savransky Y, Trusov I, et al. Aggressive approach to salvage non-maturing arteriovenous fistulae: a retrospective study with follow-up. J Vasc Access. 2009 Jun 5;10(3):183–91.

27. Robbin ML, Greene T, Cheung AK, Allon M, Berceli SA, Kaufman JS, et al. Arteriovenous Fistula Development in the First 6 Weeks after Creation. Radiology. 2016 May;279(2):620–9.

Chapter 3

Patency outcomes of arteriovenous fistulas and grafts for hemodialysis access: a trade-off between nonmaturation and long-term complications

Bram M. Voorzaat, Cynthia J. Janmaat, Koen E.A. van der Bogt, Friedo W. Dekker and Joris I. Rotmans; on behalf of the Vascular Access Study Group

Kidney 360 2020; 1 (9) 916-924. DOI: 10.34067/KID.0000462020

Abstract

Background Arteriovenous fistulas (AVFs) for hemodialysis (HD) are often associated with better outcomes than arteriovenous grafts (AVGs). We aimed to investigate vascular access (VA) outcomes and assessed if AVF nonmaturation outweighs long-term complications of AVGs.

Methods In this multicenter, retrospective cohort study in The Netherlands, 1- and 3-year primary, primary assisted, secondary, and functional patency rates were calculated, and the incidence of adverse events and procedures was assessed. Functional patency of RCAVFs, upper arm AVFs, and AVGs was compared using Cox analyses.

Results In total, 1041 patients who received their first VA were included, of whom 863 had VAs that successfully matured. These patients were analyzed with a median follow-up of 25 months. The 1-year functional patency rates were 67%±2.0% for RCAVFs, 83%±2.0% for upper arm AVFs, and 85%±3.5% for AVGs. Three-year functional patency rates were 62%±2.0% for RCAVFs, 74%±2.0% for upper arm AVFs, and 69%±5% for AVGs. AVGs required more procedures per year (3.3 per year) of functional patency when compared with upper arm AVFs (1.8 per year).

Conclusions The functional patency of AVFs and AVGs is comparable, although AVGs required more interventions to maintain usability for HD. The choice of VA is a trade-off between short-term advantages, favoring AVGs, and long-term advantages, favoring AVFs. Which VA is most appropriate depends on the patient's prognosis and preferences.

Introduction

Patients on maintenance hemodialysis (HD) require a reliable vascular access (VA). The European Society for Vascular Surgery and the European Best Practice Guidelines recommend to use native arteriovenous fistulas (AVFs) as the primary VA option. Indeed, AVFs are typically associated with fewer complications and longer VA survival when compared with prosthetic arteriovenous grafts (AVGs) and central venous catheters (CVCs) [1,2]. However, a major disadvantage of AVFs is nonmaturation characterized by intimal hyperplasia and inadequate remodeling of the venous outflow tract, which precludes adequate use of the VA for HD. After initial successful use of an AVF, loss of patency may result from intimal hyperplasia, causing luminal narrowing and eventually resulting in thrombosis [3]. As a consequence, patients on HD require multiple surgical or endovascular procedures to maintain patency or to create a new VA conduit.

Compared with AVFs, AVGs tend to have a lower primary failure rate but a lower long-term patency, requiring more procedures to maintain patency [4]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) on VA published in 2002 revealed large differences between the United States and Europe with regard to VA access use and outcomes [5].

We have previously reported on the maturation outcomes in a multicenter cohort of patients on HD in The Netherlands [6]. The incidence of nonmaturation in our cohort was 24% for radiocephalic arteriovenous fistulas (RCAVFs) and 11% for upper arm AVFs. A primary failure rate of 6% for AVGs was observed. In this study, we report patency outcomes of arteriovenous HD access conduits in our cohort, as well as the incidence of VA-related adverse events and procedures.

Materials and Methods

Study design and patient selection

Approval for the data collection was obtained from the ethics committee of the Leiden University Medical Center. Analyses were limited to RCAVFs, upper arm AVFs, and AVGs in the upper extremity. VAs were only included if no previous permanent VA was created in these patients and the clinical outcome of the VA could be retrieved. Patients were excluded if they were lost to follow-up before HD initiation. On the basis of these criteria, this study presents an analysis of the VA patency outcomes of 1041 patients from eight hospitals in The Netherlands who received their first arteriovenous VA between 1997 and 2016.

Definitions of end points

A nonmatured VA was defined as a VA that could not be used successfully for HD or a VA that was abandoned in a patient not yet on HD [6]. To standardize patency outcomes, the patency definitions as described by Sidawy et al. [7] were used. Primary patency is the time from VA creation until the first procedure, occlusion, or VA abandonment, whichever occurs first. Primary assisted patency is the time from VA creation until the first procedure to re-establish patency of an occluded VA or VA abandonment. Secondary patency is the time from VA creation until VA abandonment. Functional patency is defined as the time between first use of the VA and the abandonment of the VA. A VA was deemed successfully used for dialysis if it could be used with two-needle cannulation for three consecutive HD sessions.

We additionally calculated the postcannulation primary patency defined as the time from first successful cannulation to the first subsequent procedure to maintain or re-establish patency. For procedures, the postintervention primary patency was calculated starting at the index procedure and ending at the next procedure, occlusion, or abandonment. Patients were censored if a functioning VA was abandoned due to death, transplantation, or end of follow-up. Figure 1 provides a graphical presentation of the patency measures for an example VA.

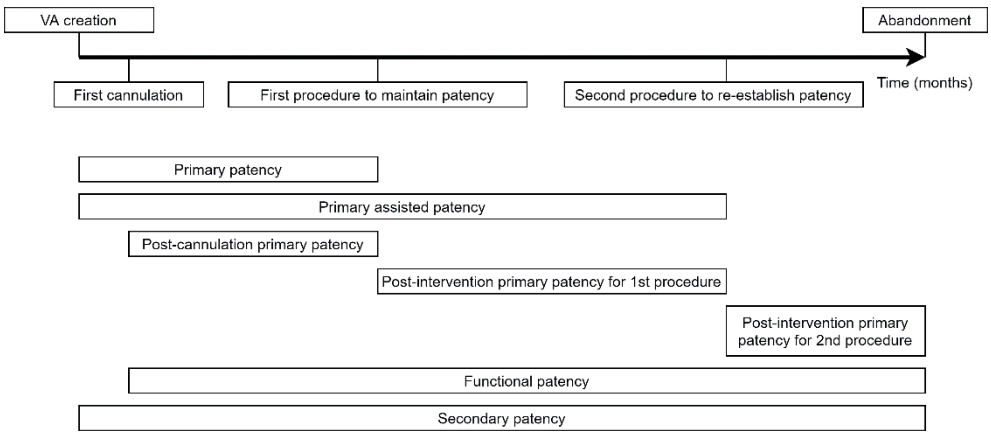


Figure 1 Visual example of patency measures. VA, vascular access.

If major revision surgery was performed and a new anastomosis was created between different vessels than the original VA, this was registered as abandonment of the old VA and creation of a new VA.

Statistical Analyses

Baseline characteristics are summarized as mean ± SD for continuous variables and frequency (percentage) for categorical variables. Baseline characteristics are reported only for patients receiving their first VA; those of the entire cohort were reported previously [6]. Primary, primary assisted, and functional patency rates are presented as survival analyses using Kaplan–Meier curves with 1- and 3-year patency, expressed as percentage patent ± SEM. Rates of procedures and adverse events are expressed as both the number of events per year of functional patency and the proportion of VAs experiencing at least one event per event type.

Functional patency rates of the RCAVF, upper arm AVF, and AVG arteriovenous access conduits were compared using Cox regression analysis without adjustment for confounders and with adjustment for patient age, sex, body mass index, diabetes mellitus, cerebrovascular disease, coronary artery disease, peripheral vascular disease, and access configuration as covariates. IBM SPSS Statistics version 25 was used for all analyses (IBM Corp., Armonk, NY).

Results

Of 1656 VAs in the original cohort, 1041 patients were included in the analysis as they received their first arteriovenous access during the study period while we could retrieve the clinical outcome parameters of their VA (Table 1). Of these 1041 VAs, 863 (83%) successfully matured (Figure 2). The median follow-up of VAs that were successfully used for HD was 25 months.

	RCAVF (557)	Upper arm AVF (378)	AVG (106)
Gender			
Male	392 (70.4%)	199 (52.6%)	44 (42.5%)
Female	165 (29.6%)	179 (47.4%)	62 (58.5%)
Follow-up duration	28.6 ± 30.1 months	24.2 ± 21.4 months	33.5 ± 28.7 months
Patient age	62.7 ± 15.0 years	63.4 ± 14.4 years	65.4 ± 14.0 years
BMI	27.0 ± 5.8 kg/m^2	26.3 ± 6.0 kg/m^2	27.7 ± 6.7 kg/m^2
Pre-emptive	318 (57.1%)	186 (49.2%)	61 (57.5%)
Pre-operative vein Diameter (lumen)	2.9 ± 0.8 mm	3.7 ± 1.3 mm	4.0 ± 1.5 mm
Pre-operative artery Diameter (lumen)	2.6 ± 0.5 mm	4.1 ± 0.8 mm	4.4 ± 0.9 mm
Ipsilateral CVC	72 (12.9%)	69 (18.3%)	8 (7.5%)

Cause of renal failure			
Diabetes mellitus	117 (21.0%)	93 (24.6%)	37 (34.9%)
Renal vascular disease	128 (23.0%)	76 (20.1%)	27 (25.5%)
Cystic kidney disease	44 (7.9%)	20 (5.3%)	4 (3.8%)
Glomerulonephritis	60 (10.8%)	34 (9.0%)	5 (4.7%)
Congenital/hereditary	16 (2.9%)	12 (3.2%)	2 (1.9%)
Interstitial nephropathy	35 (6.3%)	21 (5.6%)	5 (4.7%)
Multisystem disease	25 (4.5%)	20 (5.3%)	3 (2.8%)
Other	70 (12.6%)	59 (15.6%)	11 (10.4%)
Unknown	62 (11.1%)	43 (11.4%)	12 (11.3%)
Comorbidities			
Diabetes mellitus	205 (36.8%)	150 (39.7%)	66 (62.3%)
Coronary artery disease	153 (27.5%)	105 (27.8%)	32 (30.2%)
Peripheral vascular disease	105 (18.9%)	76 (20.1%)	21 (19.8%)
Cerebrovascular disease	83 (14.9%)	58 (15.3%)	15 (14.2%)

Table 1 Baseline characteristics of patients. RCAVF: radiocephalic arteriovenous fistula; AVG: arteriovenous graft; CVC, central venous catheter. Numbers denote mean ± standard deviation for continuous variables or count (percentage) for categorical variables.

Maturation and procedures to promote maturation

Fifty-nine percent of RCAVFs, 79% of upper arm AVFs, and 79% of AVGs did not require any intervention before these could be used for HD.

From the 230 RCAVFs that did not mature spontaneously, the RCAVF was abandoned in 98 patients. In the remaining 132 patients, one or multiple procedures were performed to promote maturation, resulting in successful use of the RCAVF for HD in 93 patients (70% of patients in whom procedures were performed to promote maturation). In 36% of patients, a surgical revision was performed, and the remaining patients underwent an endovascular procedure.

Functional patency of RCAVFs that required a procedure to assist maturation was comparable with patency of RCAVFs that matured spontaneously, with 1- and 3-year functional patency rates of 91% and 83%, respectively. The time until the first procedure after successful use of the AVF was also not different between RCAVFs that matured with or without additional procedures (Figure 3).

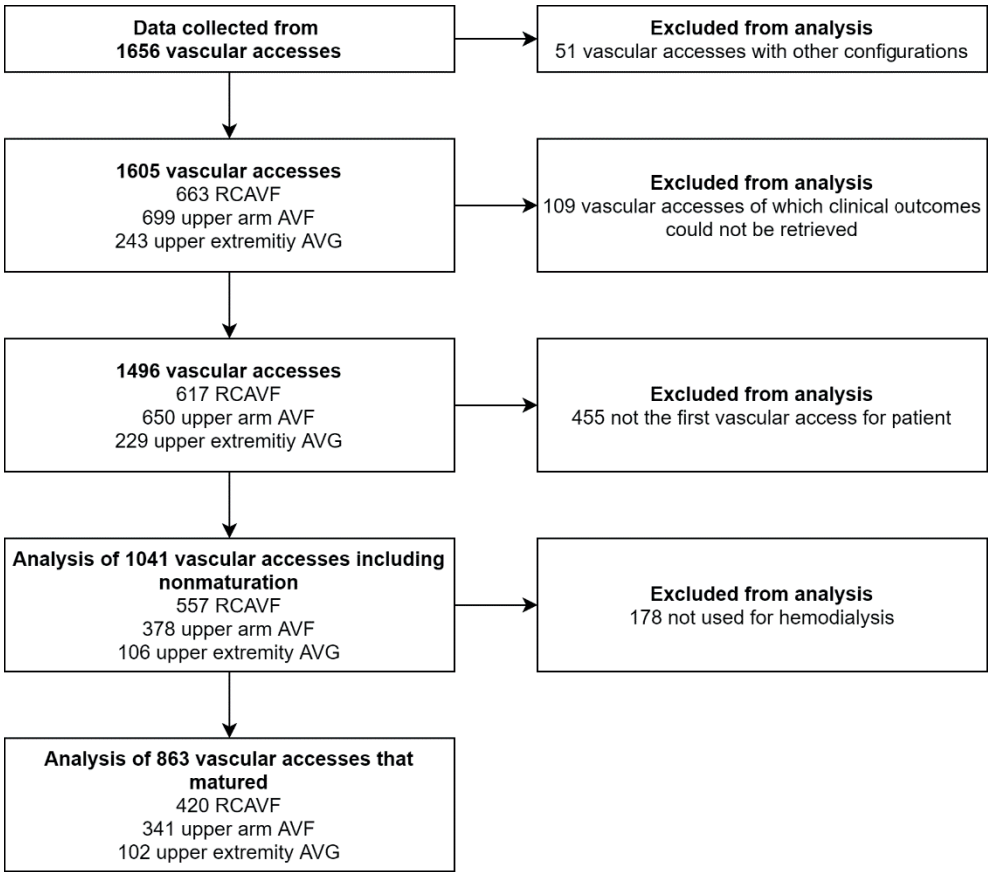
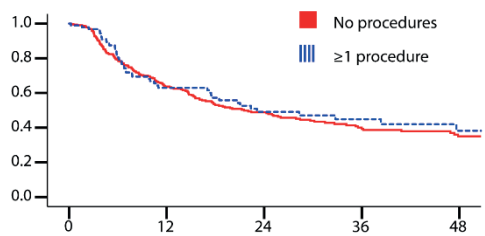


Figure 2 Flowchart of inclusion and exclusion from analysis. AVF, arteriovenous fistula; AVG, arteriovenous graft; RCAVF, radiocephalic arteriovenous fistula.



No at risk	0	12	24	36	48
No procedures	327	159	96	58	36
≥1 procedure	93	47	27	17	10

Figure 3 Postcannulation primary patency of RCAVF that matured with and without interventional procedures, excluding RCAVFs that never matured.

From the group of 22 AVGs that were not suitable for cannulation, three AVGs were abandoned without additional interventions. In the remaining 19 AVGs, one or more interventions were performed, which resulted in successful use for HD in 18 patients (95%).

Patency outcomes

The 1-year primary patency rates of VAs that matured were 51% for RCAVFs, 65% for upper arm AVFs, and 47% for AVGs (Figure 4, Table 2). Primary patency most often ended due to a procedure to maintain patency (RCAVF, 69%; upper arm AVF, 66%; and AVG, 54%) or a procedure to re-establish patency (RCAVF, 22%; upper arm AVF, 25%; and AVG, 43%). Rarely, primary patency ended with immediate VA abandonment (RCAVF, 8%; upper arm AVF, 6%; and AVG, 3%).

	1-year patency			3-year patency		
	RCAVF	**Upper arm AVF**	**AVG**	**RCAVF**	**Upper arm AVF**	**AVG**
Patency measures of VAs, excluding VAs that did not mature (n = 863)						
Primary	51 ± 3%	65 ± 3%	47 ± 5%	35 ± 3%	43 ± 3%	13 ± 4%
Primary assisted	78 ± 2%	81 ± 2%	67 ± 5%	53 ± 3%	52 ± 3%	32 ± 5%
Secondary	93 ± 1%	94 ± 1%	94 ± 3%	86 ± 2%	84 ± 3%	78 ± 5%
Functional	91 ± 1%	92 ± 2%	89 ± 3%	83 ± 2%	83 ± 3%	72 ± 6%
Patency measures of VAs, including VAs that did not mature (n = 1041)						
Primary	39 ± 2%	59 ± 3%	45 ± 5%	26 ± 2%	39 ± 3%	12 ± 4%
Primary assisted	59 ± 2%	73 ± 2%	65 ± 5%	40 ± 2%	47 ± 3%	31 ± 5%
Secondary	71 ± 2%	85 ± 2%	90 ± 3%	64 ± 2%	75 ± 3%	75 ± 5%
Functional	67 ± 2%	83 ± 2%	85 ± 4%	62 ± 2%	74 ± 3%	69 ± 5%

Table 2 One- and three-year primary, primary assisted, secondary and functional patency for RCAVFs, upper arm AVFs and AVGs. Patency rates are percentage of VAs still patent ± standard error. Patients are censored for death and transplantation.

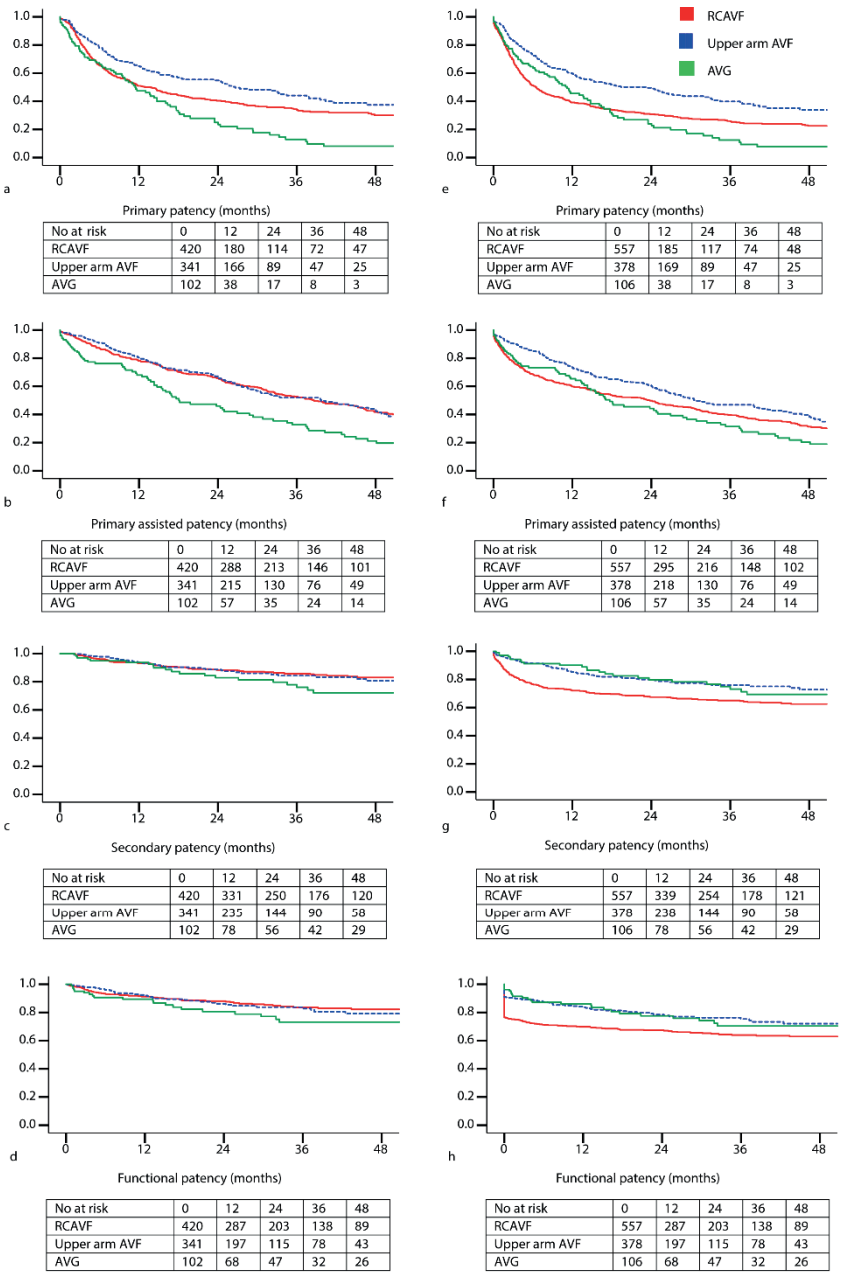


Figure 4 Primary, primary assisted, secondary, and functional patency for RCAVFs, upper arm AVFs, and AVGs. Patients are censored for death and transplantation. (A–D) Clinical outcomes of all VAs, excluding VAs that did not mature (n=863). (E–H) Clinical outcomes of all VAs, including nonmatured VAs (n=1041).

The 1-year functional patency rate of VAs that matured was 90% for all types of VAs (RCAVFs, upper arm AVFs, and AVGs). When nonmaturated VAs were included in the analysis as well, the 1-year functional patency was lower for RCAVFs at 67% compared with 83%±2% for upper arm AVFs and 85%±4% for AVGs. Functional patency rates at 3 years were 62% for RCAVFs, 74% for upper arm AVFs, and 69% for AVGs, with no statistically differences between groups (data not shown). In contrast, the functional patency of RCAVFs was significantly lower when compared with upper arm AVFs (unadjusted hazard ratio [HR], 1.6; 95% confidence interval [95% CI], 1.28 to 2.13; adjusted HR, 1.8; 95% CI, 1.4 to 2.4) or AVGs (unadjusted HR, 1.4; 95% CI, 1.0 to 2.1; adjusted HR, 1.6; 95% CI, 1.0 to 2.4).

Procedures and adverse events in matured vascular access conduits

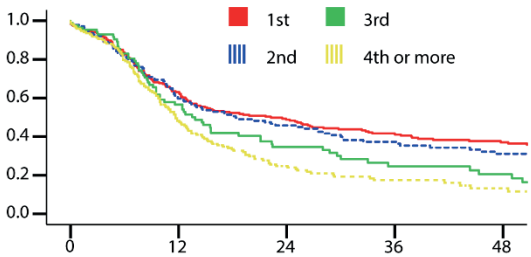
Of the VAs that maturated successfully, 49% of RCAVFs, 38% of upper arm AVFs, and 68% of AVGs required at least one balloon angioplasty procedure during their lifetimes (Table 3). The event rate, expressed as the number of procedures per year of functional patency, was also different at 1.0 balloon angioplasty procedure per year for RCAVFs, 1.6 balloon angioplasty procedures per year for upper arm AVFs, and 1.8 balloon angioplasty procedures per year for AVGs. For thrombectomy procedures, these differences were more pronounced, as only 5% of AVFs required a thrombectomy to restore patency compared with 34% for AVGs. The thrombectomy rate was highest for AVGs at 1.1 per year of patency compared with 0.03 per year for RCAVFs and 0.05 per year for upper arm AVFs.

	VA type			**Event rate**		
	RCAVF (420)	Upper arm AVF (341)	AVG (102)	RCAVF (420)	Upper arm AVF (341)	AVG (102)
Adverse events						
VA site infection	7 (1.7%)	15 (4.4%)	11 (10.8%)	0.0049 ± 0.040	0.07 ± 0.45	0.10 ± 0.40
Thrombosis	69 (16.4%)	37 (10.9%)	36 (35.3%)	0.46 ± 5.1	0.14 ± 0.61	1.83 ± 8.34
Procedures						
Percutaneous procedure – only balloon angioplasty – still functional VA	204 (48.6%)	129 (37.8%)	69 (67.6%)	1.01 ± 2.79	1.64 ± 8.96	1.84 ± 4.37
Percutaneous procedure including thrombectomy – occluded VA	21 (5.0%)	16 (4.7%)	35 (34.3%)	0.03 ± 0.24	0.05 ± 0.32	1.13 ± 4.04
Stenting	1 (0.2%)	16 (4.7%)	5 (4.9%)	0.001 ± 0.024	0.04 ± 0.33	0.02 ± 0.10

Surgical revision	80 (19.0%)	24 (7.0%)	21 (20.6%)	0.29 ± 2.62	0.05 ± 0.28	0.31 ± 1.55
Flow reduction	3 (0.7%)	32 (6.2%)	0 (0%)	0.0043 ± 0.060	0.05 ± 0.32	0.00 ± 0.00

Table 3 Cumulative incidence and event rates of adverse events and procedures. Event rates are expressed as number of events per year of functional patency ± standard deviation. VA, vascular access; RCAVF, radiocephalic arteriovenous fistula; AVG, arteriovenous graft.

After the first procedure to maintain or re-establish patency, the 1-year postintervention primary patency rates were 63% ± 3.2% for RCAVFs, 60% ± 4.2% for upper arm AVFs, and 57% ± 5.5% for AVGs. After each subsequent procedure aimed at improving patency, the time until the next procedure decreased (Figure 5).



No at risk	0	12	24	36	48
1st	238	135	98	75	60
2nd	141	80	56	40	28
3rd	86	44	24	12	10
4thor more	177	74	33	15	8

Figure 5 Postintervention primary patency of RCAVF after subsequent procedures. Postintervention patency starts at the index procedure and ends at the next procedure, occlusion, or abandonment of the VA, and patients are censored for death and transplantation.

The number of infections per year of functional patency was highest for AVGs at 0.10 per year and lowest for RCAVFs at 0.0049 per year (Table 3). Of upper arm AVFs, 6% required flow-reducing procedure compared with 0.7% for RCAVFs. The 1-year postintervention secondary patency after these procedures was 77% ± 9.2%.

Subgroup Analyses

Functional patency of upper arm AVFs was significantly better for men than for women (1-year functional patency, 87% ± 3.0% for men versus 74% ± 3% for women; adjusted HR, 0.49; 95% CI, 0.30 to 0.79). This difference was mainly due to nonmaturation occurring more frequently

in women. For AVGs, no differences were observed in patency between men and women (1-year functional patency, 84% ± 6% versus 82% ± 5%; adjusted HR, 0.77; 95% CI, 0.32 to 1.84). Age over 70 years was not significantly associated with functional patency of AVFs (1-year functional patency, 80% ± 3% in nonelderly patients and 82%±3% in elderly patients; adjusted HR, 1.57; 95% CI, 0.96 to 2.58) nor AVGs (1-year functional patency, 89% ± 4% in nonelderly patients and 77% ± 6% in elderly patients; adjusted HR, 0.32; 95% CI, 0.07 to 1.41).

Discussion

In this study, we examined patency outcomes for arteriovenous access conduits and observed that the functional patency of matured AVFs and AVGs is comparable, although AVGs required more interventions to maintain usability for HD.

Functional Patency and Nonmaturation

For VAs that maturated successfully, 1-year functional patency was approximately 90% for all types of access, whereas at 3 years, functional patency was still rather good (73% for AVGs and 83% for AVFs). This demonstrates that after an AVF has reached functional maturation, loss of functional patency is uncommon. Functional patency of RCAVFs may seem better than for AVGs, but this is only true if RCAVFs that failed to mature are not taken into account. When nonmaturated VAs are taken into account, functional patency of AVGs is superior to RCAVFs.

The results obtained in our study are in line with two large recent meta-analyses in which VA patency was investigated. Al-Jaishi et al. [8] included both upper arm and forearm AVFs. Like in our study, upper arm AVFs performed better than forearm AVFs. The incidence of primary failure was 28% for forearm AVFs and 20% for upper arm AVFs, similar to the 24% and 11%, respectively, in our cohort. The authors found a 1-year primary patency rate of 55% for forearm AVFs versus 65% for upper arm AVFs if nonmatured VAs were included. Most strikingly, forearm primary patency differed from our cohort, in which a 1-year primary patency of 39% was observed for RCAVFs and 59% was observed for upper arm AVFs. Because primary patency ends with any procedure to improve patency, this may for a significant part be the result of a "doctor's decision," and this outcome is sensitive to local surveillance practices and subsequent preemptive interventions. Conversely, the 1-year secondary patency was similar in the study by Al-Jaishi et al. [8] for forearm AVFs (68%) and upper arm AVFs (70%). In our cohort, 1-year secondary patency rates were slightly higher at 71% and 85%, respectively.

A more recent meta-analysis by Bylsma et al. [9] demonstrated a 1-year primary patency 64% of all AVFs, with upper arm AVFs at 69% performing better than forearm AVFs at 55%. Secondary patency rates of upper arm AVFs and forearm AVFs were similar at 67% and 71%, respectively.

Although the pooled patency rates of AVFs are relatively constant in the various large meta-analyses, there is a significant variability in patency outcomes in the included studies, which is most pronounced for primary patency. This suggests that the influence of local practices and experience in maintaining AVF patency may be significant on primary patency but less on the overall longevity of the VA.

The AVGs in our cohort had similar functional patency as autologous AVFs. This contrasts the findings from the DOPPS, where a shorter functional patency was observed for AVGs compared with AVFs, with a relative risk for AVF failure of 0.56 compared with AVGs (5). In the DOPPS, the 1-year functional patency of AVG was only 49%, which is substantially lower when compared with our study (85%). This difference might be explained by a higher proportion of AVGs created in patients predialysis in our study, as AVGs survive shorter if created in patients who initiated HD with a CVC [5]. The better functional patency of AVG in our cohort might also relate to a more "aggressive" surveillance strategy. In The Netherlands, surveillance by measurements of VA flow is currently advised on a monthly basis for AVGs and a 3-monthly basis for AVFs [10]. Of note, the usefulness of routine ultrasound surveillance for AVGs remains a topic of debate [11].

Elderly Patients

In concordance with previous studies [12], functional VA patency was not associated with age. This observation implies that one should not refrain from creating a permanent VA in elderly patients eligible for maintenance HD. However, the optimal VA strategy in frail elderly patients is a topic of debate as they have a higher chance of dying before reaching ESKD [13]. They may be saved from the burden of preemptively creating an AVF by opting for an "early stick" AVG or CVC only when HD initiation is imminent.

Procedures Related to Patency

The incidence of procedures differed between AVFs and AVGs. Most remarkably, the fraction of AVGs for which a thrombectomy was performed was sevenfold higher than of AVFs. This observation is in agreement with data from a meta-analysis in which procedure rates from nine different studies were reported [14]. All studies showed an at least twofold higher incidence of

procedures per access-year for AVGs compared with AVFs, with some studies reporting differences up to sevenfold. Malik et al. [11] reviewed five clinical trials on routine ultrasound surveillance of AVGs and found that the ultrasound criteria for a hemodynamically significant stenosis differed among these studies, possibly explaining the different incidences of subsequently performed procedures. In the Netherlands, VA surveillance using flow measurements is common practice and may influence the intervention policy, resulting in more balloon angioplasty procedures to maintain patency and possibly fewer procedures to re-establish patency because unexpected VA occlusion is less likely to occur. However, as early thrombus removal is more urgent in AVFs compared with AVGs [2], the adherence to surveillance guidelines might have been lower in AVGs, resulting in a relatively high rate of procedures to restore patency.

Study Limitations

Maturation and patency of different VA configurations should be compared with caution. The choice for a specific VA configuration is on the basis of the anatomy of the patient, prior history of VA failure, and patient preference. Because current guidelines advise to start VA creation as distal as possible, most patients who received an upper arm AVF or AVG were not eligible for an RCAVF: for instance, due to more advanced vascular abnormalities. This selection bias limits the validity of direct comparisons of VA outcomes, and residual confounding after correction for patient characteristics cannot be ruled out.

In addition, it is important to notice that the loss of functional patency of a VA results not solely from pathophysiologic processes to result in VA failure but also, from the clinical decision to stop investing in a problematic VA. It is likely that upper arm AVFs and AVGs are more often a "last resort" option rather than a first choice. We assume that an RCAVF will on average be abandoned earlier as these patients will often have options to "move on" to a more proximal VA and the need to repeatedly perform procedures to maintain functional patency is less urgent, whereas the need to maintain an upper arm AVF or AVG may be more pressing.

Further Directions

Although patency outcomes of different VA configurations that have reached maturation are comparable, nonmaturation remains the Achilles' heel of RCAVFs. Functional patency of RCAVFs in our study remained lower than of AVGs. The price to pay was a two- to threefold higher incidence of procedures required to maintain patency in patients with AVGs. In other

words, VA planning is a trade-off between short-term outcomes, including nonmaturation and the odds of creating an unnecessary VA, and long-term outcomes, including functional patency and the number of procedures involved. The decisions of which VA to create and when to create it should be individualized, taking the short- and long-term properties of each VA into account while considering the patient's prognosis and preferences. Performing a randomized controlled trial that randomizes patients to RCAVFs, upper arm AVFs, or AVGs as their first permanent VA may finally elucidate the performance of these configurations.

Disclosures

All authors have nothing to disclose.

Funding

This research received unrestricted funding from Proteon Therapeutics Inc.

Acknowledgments

Patency outcomes from this study were presented at the 11th Congress of the Vascular Access Society in Rotterdam, The Netherlands on April 11–13, 2019.

References

1. Tordoir J, Canaud B, Haage P, Konner K, Basci A, Fouque D, Kooman J, Martin-Malo A, Pedrini L, Pizzarelli F, Tattersall J, Vennegoor M, Wanner C, Wee Pt, et al.R: EBPG on vascular access. Nephrol Dial Transplant 22[Suppl 2]: ii88–ii117, 2007
2. Schmidli J, Widmer MK, Basile C, de Donato G, Gallieni M, Gibbons CP, Haage P, Hamilton G, Hedin U, Kamper L, Lazarides MK, Lindsey B, Mestres G, Pegoraro M, Roy J, Setacci C, Shemesh D, Tordoir JHM, van Loon M, Kolh P, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Lindholt J, Naylor R, Vega de Ceniga M, Vermassen F, Verzini F, Mohaupt M, Ricco JB, Roca-Tey R; ESVS Guidelines Committee; ESVS Guidelines Reviewers: Editor's choice—vascular access: 2018 Clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 55: 757–818, 2018
3. Rothuizen TC, Wong C, Quax PHA, van Zonneveld AJ, Rabelink TJ, Rotmans JI: Arteriovenous access failure: More than just intimal hyperplasia? Nephrol Dial Transplant 28: 1085–1092, 2013
4. Lok CE, Sontrop JM, Tomlinson G, Rajan D, Cattral M, Oreopoulos G, Harris J, Moist L: Cumulative patency of contemporary fistulas versus grafts (2000-2010). Clin J Am Soc Nephrol 8: 810–818, 2013
5. Pisoni RL, Young EW, Dykstra DM, Greenwood RN, Hecking E, Gillespie B, Wolfe RA, Goodkin DA, Held PJ: Vascular access use in Europe and the United States: Results from the DOPPS. Kidney Int 61: 305–316, 2002
6. Voorzaat BM, van der Bogt KEA, Janmaat CJ, van Schaik J, Dekker FW, Rotmans JI; Dutch Vascular Access Study Group: Arteriovenous fistula maturation failure in a large cohort of hemodialysis patients in The Netherlands. World J Surg 42: 1895–1903, 2018
7. Sidawy AN, Gray R, Besarab A, Henry M, Ascher E, Silva M Jr.., Miller A, Scher L, Trerotola S, Gregory RT, Rutherford RB, Kent KC: Recommended standards for reports dealing with arteriovenous hemodialysis accesses. J Vasc Surg 35: 603–610, 2002
8. Al-Jaishi AA, Oliver MJ, Thomas SM, Lok CE, Zhang JC, Garg AX, Kosa SD, Quinn RR, Moist LM: Patency rates of the arteriovenous fistula for hemodialysis: A systematic review and meta-analysis. Am J Kidney Dis 63: 464–478, 2014

9. Bylsma LC, Gage SM, Reichert H, Dahl SLM, Lawson JH: Arteriovenous fistulae for haemodialysis: A systematic review and meta-analysis of efficacy and safety outcomes. Eur J Vasc Endovasc Surg 54: 513–522, 2017
10. Betjes M, Hoogeveen E, Tordoir J: Dutch Federation for Nephrology—Guideline on Vascular Access 2009 [in Dutch], 2009. Available at: https://www.nefro.nl/sites/www.nefro.nl/files/richlijnen/Richtlijn-Vaattoegang-2009%5B1%5D.pdf. Accessed April 19, 2018
11. Malik J, Kudlicka J, Novakova L, Adamec J, Malikova H, Kavan J: Surveillance of arteriovenous accesses with the use of duplex Doppler ultrasonography. J Vasc Access 15[Suppl 7]: S28–S32, 2014
12. Jennings WC, Landis L, Taubman KE, Parker DE: Creating functional autogenous vascular access in older patients. J Vasc Surg 53: 713–719, 2011
13. Moist LM, Lok CE, Vachharajani TJ, Xi W, AlJaishi A, Polkinghorne KR, Vazquez M, Lee TC: Optimal hemodialysis vascular access in the elderly patient. Semin Dial 25: 640–648, 2012
14. Allon M: Current management of vascular access. Clin J Am Soc Nephrol 2: 786–800, 2007

Chapter 4

Improvement of radiocephalic fistula maturation: rationale and design of the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study - a randomized controlled trial

Bram M. Voorzaat, Jan van Schaik, Koen E.A. van der Bogt, Liffert Vogt, Laurens Huisman, Bas A. Th. F. Gabreëls, Irene M. van der Meer, Randolph G. Statius van Eps, Daniël Eefting, Marcel C. Weijmer, Han O. Groeneveld, Roos C. van Nieuwenhuizen, Henk Boom, Cornelis A. Verburgh, Karien van der Putten, Joris I. Rotmans

The Journal of Vascular Access 2017; 18 (Suppl 1): S114-S117. DOI: 10.5301/jva.5000673

Abstract

Background Non-maturation is a frequent complication of radiocephalic arteriovenous fistulas (RCAVF). In an animal model, liposomal prednisolone improved maturation of experimental fistulas. The Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study investigates if liposomal prednisolone improves RCAVF maturation.

Methods and results The LIPMAT study is an investigator-initiated, multicenter, double-blinded, placebo-controlled randomized controlled trial with 1:1 randomization to liposomal prednisolone or placebo. Eighty patients receiving an RCAVF will be included. The primary outcome is the cephalic vein diameter six weeks after surgery, measured by ultrasound. The LIPMAT study started in May 2016. Enrollment is expected to be completed by the end of 2017.

Conclusion The LIPMAT study is the first to evaluate the efficacy of liposomal prednisolone to enhance RCAVF maturation.

Introduction

AVF maturation

Maintenance hemodialysis patients require a reliable vascular access. The autologous arteriovenous fistula (AVF) is the preferred type of vascular access, with superior long-term patency rates and lower infection rates compared to arteriovenous grafts (AVGs) and central venous catheters (CVCs). The suitability of an AVF for hemodialysis depends on its diameter, blood flow, depth and usable length [1, 2]. Patients requiring hemodialysis while their AVF has not matured may be exposed to the risks and burden of CVC use, angioplasty procedures and surgical reconstructions.

Upon AVF creation, the vein is exposed to arterial blood pressure and a high blood flow, increasing wall shear stress and wall tension. The vein adapts favorably by outward remodeling, increasing luminal dimensions, and unfavorably by intimal hyperplasia, decreasing luminal dimensions [3].

Maturation of AVFs can be disrupted by arterial abnormalities, pre-existing venous damage, surgical failure or a mismatch between outward remodeling and intimal hyperplasia. Non-maturation of AVF occurs frequently, as illustrated by the results from a large clinical trial by Dember et al[4] in which 60% of AVFs did not meet suitability criteria. Non-maturation was higher (64%) for radiocephalic AVFs (RCAVF) when compared to upper-arm AVFs (53%).

Improvement of maturation by liposomal prednisolone

In preclinical studies in pigs [5] and mice [6], significant vascular inflammation was observed in the vein near the arteriovenous anastomosis early after AVF creation. This most likely relates to injury by surgical manipulation or blood flow and shear stress far beyond values normally found in veins. This transient inflammation was hypothesized to inhibit maturation by initiating migration of vascular smooth muscle cells and myofibroblasts and limiting outward remodeling, thereby promoting the formation of stenosis [5]. In an observational human study, elevated inflammatory markers were indeed associated with AVF non-maturation [7]. We hypothesized that inhibiting this inflammation may improve AVF maturation.

Glucocorticoids (GCs) are potent inhibitors of inflammation, although the therapeutic use of systemic GCs is hampered by various adverse side effects on non-target tissues [8]. Nanoparticle therapeutics such as liposomes have been shown to facilitate selective delivery of drugs to

inflamed tissues, thereby limiting systemic side effects [9]. PEG-liposomal prednisolone sodium phosphate (Nanocort®, Enceladus Pharmaceuticals B.V., Naarden, The Netherlands) consists of lipid vesicles encapsulating prednisolone, a potent glucocorticoid. The intact endothelial lining is poorly permeable to circulating liposomal prednisolone. Together with low degradation in the reticuloendothelial system, this results in a plasma half-life of around three days and therapeutic efficacy of two weeks after a single intravenous infusion. The leaky endothelium at sites of inflammation is permeable to liposomes, resulting in high concentrations of liposomal prednisolone in target tissues [10]. This results in a strong therapeutic effect with limited side effects. After successful pre-clinical proof of concept studies, the efficacy of liposomal prednisolone in active rheumatoid arthritis is under evaluation in a multicenter phase 3 study (EudraCT identifier: 2015-002924-17).

We selected liposomal prednisolone as the candidate drug to evaluate the hypothesis that inhibition of inflammation improves AVF maturation. In mice, two weeks after creation of a carotid-jugular AVF, liposomal prednisolone increased the juxta-anastomotic venous circumference by 27% ($p = 0.004$) and the luminal area by 47% ($p = 0.042$) when compared to saline [11]. In contrast, free prednisolone and empty liposomes did not improve circumference or luminal area. No significant differences in intimal area were observed, indicating that the differences in luminal area are the result of improved outward remodeling rather than inhibited intimal hyperplasia.

Study design and treatment

The Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study (ClinicalTrails.gov identifier: NCT02495662) is a phase 2, investigator-initiated, multicenter, double-blinded, placebo-controlled randomized controlled trial evaluating the effect of liposomal prednisolone on the maturation of RCAVFs. Patients will be asked for informed consent when referred for creation of an RCAVF, based on pre-operative vein mapping according to local care standards in each hospital. Exclusion criteria include an ipsilateral CVC, current malignancy, latent or active infections with tuberculosis or hepatitis B and C, uncontrolled diabetes mellitus and known contraindications to glucocorticoids. In addition, the use of systemic glucocorticoids, immunosuppressant medication or NSAIDs is not allowed.

The trial subjects will receive AVF surgery in their own hospitals, with surgical techniques and anesthesia according to local care standards. If an RCAVF has been successfully created, subjects

are randomized 1:1 to liposomal prednisolone or placebo (Fig. 1). Subjects are treated twice: one day after surgery and two weeks thereafter to achieve a treatment effect lasting four weeks following surgery. At each treatment visit, 150 mg liposomal prednisolone in 500 mL normal saline is administered in the arm contralateral to the AVF, or 500 mL normal saline as a sham infusion. The patients, investigator and the patients' physicians are blinded to the group allocation. Blinding is achieved through a fully opaque IV set equipped with an air filter permeable to the 110 nm liposomes (IVSTAR-F 4.3cm^2 1.2 μm pore size, CODAN GmbH, Lensahn, Germany) and an opaque cover around the infusion bag. Prior to each infusion, the AVF is evaluated for patency and wound complications by physical examination. If patency cannot be determined by palpation and auscultation, a duplex ultrasound is performed prior to treatment.

After AVF creation and study treatment, subjects receive follow-up in their own hospitals. Surgical, endovascular or drug treatments aimed to improve the AVF outcome are allowed and at the discretion of the patient's treating physician. Maturation of these AVFs is considered assisted.

Endpoints

The main study endpoint is the diameter of the cephalic vein at 1 cm downstream from the anastomosis, measured by duplex ultrasound 6 weeks after AVF creation. Secondary endpoints are the cephalic vein diameter at the elbow and mid upper arm and the blood flow in the cephalic vein, radial artery and brachial artery. As secondary endpoints, these measurements are repeated at 3 months after AVF creation. Ultrasound technicians in all participating hospitals perform these follow-up ultrasound measurements, according to the study protocol, in addition to any measurements normally performed in routine care. Occlusions of the AVF and procedures performed to improve AVF maturation are recorded as secondary endpoints.

Statistics

Sample size calculation

In a pilot analysis in our center, the mean distal cephalic vein diameter at six weeks after AVF creation was 5.4 mm with a standard deviation of 1.5 mm. A 20% improvement of the distal cephalic vein diameter was chosen as a clinically relevant treatment effect, corresponding with a

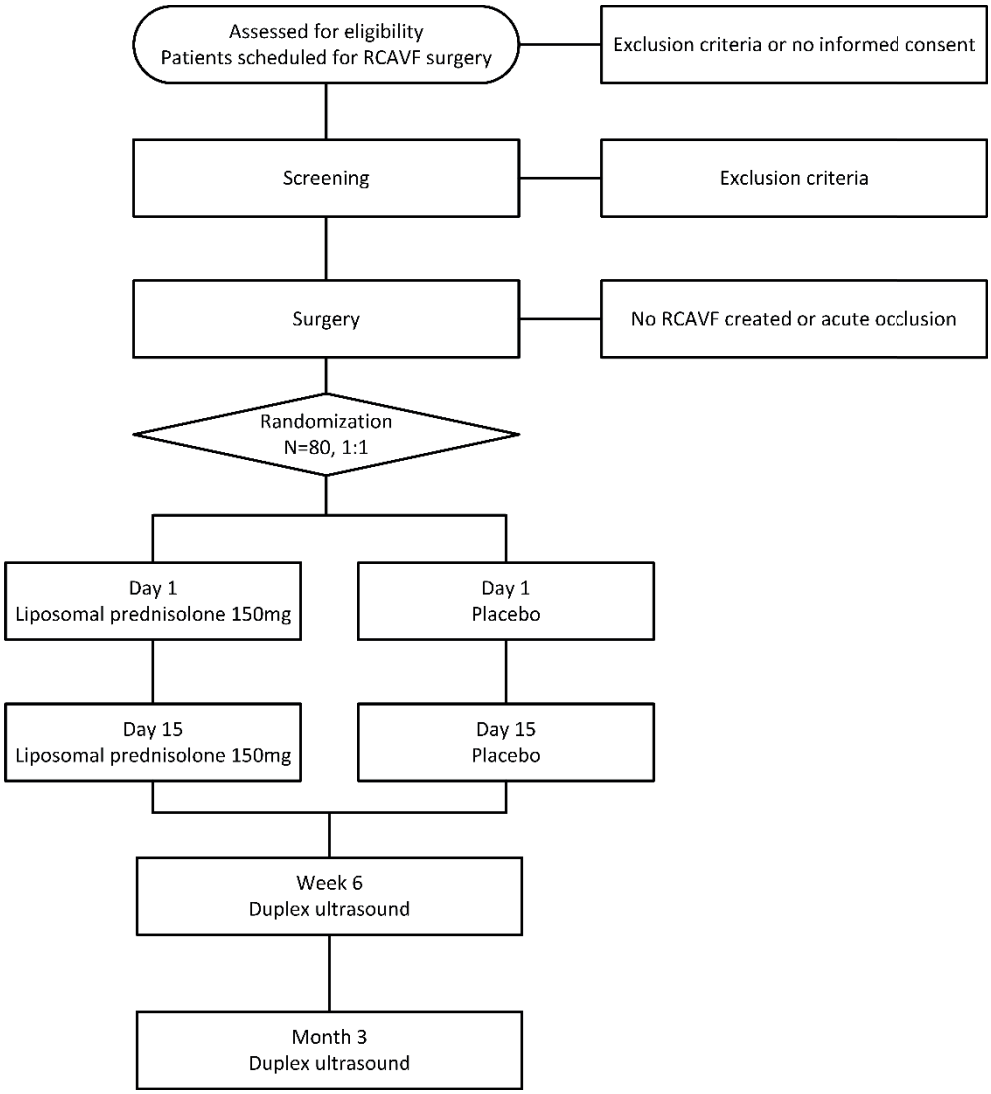


Figure 1 Flow chart of the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study.

1.0 mm increase. The sample size of the LIPMAT study was chosen to detect this 1.0 mm difference between the study groups with a power of 80% at an alpha level of 5%. Based on these assumptions, 36 subjects per group are required. Allowing for a 10% drop-out, 40 subjects per group will be included, for a total of 80 subjects.

Efficacy analysis

The primary and secondary endpoints will be reported descriptively as mean ± standard deviation. The means of the continuous variables in the primary endpoint will be compared between groups for statistically significant difference using the two independent sample t-tests. In case of non-normality, a non-parametric test will be used. The proportions of AVF occlusion and assisted maturation will be reported as percentages per treatment group.

Time line

The protocol was approved by the ethics committee in November 2015. The first patient was treated in the trial in May 2016. Currently, nine centers have agreed to participate in the LIPMAT study. As of November 2016, 15 subjects have provided informed consent for the study, of which 11 have received the study treatment. Two subjects were not randomized because no RCAVF was created, one withdrew consent before AVF surgery and one was excluded for latent tuberculosis. Thirty-five more patients provided consent for screening, but were excluded for comorbidities or prohibited concomitant medication.

Discussion

Non-maturation of RCAVFs is the most important limitation of this type of vascular access. The LIPMAT study is one of the few current randomized controlled trials aimed at improving AVF maturation with a novel pharmacological intervention.

Choice of endpoints

In this phase 2 study, our goal is to evaluate whether medical treatment improves maturation of RCAVFs. As a continuous endpoint provides greater power with a feasible sample size, the cephalic vein diameter at a standardized location was chosen, rather than criteria for maturation by The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) [1] or Robbin et al [2]. Since the majority of patients who receive an RCAVF in our region have not yet initiated hemodialysis, successful cannulation is not a feasible endpoint in the current study as this would significantly prolong follow-up. We aim to evaluate long-term functional outcomes in a follow-up study.

Timing of study procedures

In practice, surgeons may decide to create another type of vascular access if vessels are smaller than expected. As no measurement of endpoint is possible in these subjects, they are not

included in the study. Although subjects are screened before the planned RCAVF surgery, actual inclusion and randomization is performed only if an RCAVF was successfully created.

The timing of the first treatment one day after surgery was chosen to prevent treatment of subjects who cannot benefit from treatment and cannot provide endpoint measurements. By not treating preoperatively, subjects who unexpectedly receive another AVF configuration are not treated unnecessarily. In cases of early postoperative RCAVF thrombosis and no successful AVF salvage-interventions, subjects are not treated. Finally, as glucocorticoids are known to impair wound healing, the treatment at one day after surgery allows for inspection of the wound to exclude subjects with early wound complications and prevent treatment harm. Subjects are treated twice with a two-week interval to achieve four weeks of drug activity. As shown by Robbin et al [12], most of the diameter and flow increase during maturation occurs within this time frame.

Improvement of inclusion

The current rate of inclusion reflects the start-up phase of the study, with several centers starting inclusion recently. An additional factor could be the relatively high frequency of upper-arm AVFs in our region. Several patients have also been excluded for concomitant use of immunosuppressant medication. We aim to increase the rate of inclusion by further expanding the study to other hospitals within the Netherlands.

Conclusions

AVF non-maturation remains a challenge for nephrologists, vascular surgeons and dialysis patients. With promising results from preclinical experiments in AVF maturation and growing human experience with liposomal prednisolone, the LIPMAT study is the first to investigate this novel drug for AVF maturation. The LIPMAT study started in May 2016 and the expected inclusion of the 80th subject will be late 2017.

References

1. NKF KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations [Internet]. 2006 [cited 2016 Dec 5]. Available from: http://www2.kidney.org/professionals/KDOQI/guideline_upHD_PD_VA/. Accessed Jan 4, 2017.
2. Robbin, ML Chamberlain, NE Lockhart, ME et al. Hemodialysis arteriovenous fistula maturity: US evaluation. Radiology 2002;225 (1):59-64
3. Rothuizen, TC Wong, C Quax, PHA van Zonneveld, AJ Rabelink, TJ Rotmans, JI Arteriovenous access failure: more than just intimal hyperplasia? Nephrol Dial Transplant 2013;28 (5):1085-1092
4. Dember, LM Beck, GJ Allon, M et al; Dialysis Access Consortium Study Group. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA 2008;299 (18):2164-2171
5. Roy-Chaudhury, P Khan, R Campos, B et al. Pathogenetic role for early focal macrophage infiltration in a pig model of arteriovenous fistula (AVF) stenosis. J Vasc Access 2014;15 (1):25-28
6. Wong, C-Y de Vries, MR Wang, Y et al. Vascular remodeling and intimal hyperplasia in a novel murine model of arteriovenous fistula failure. J Vasc Surg 2014;59 (1):192-201.e1
7. Kaygin, MA Halici, U Aydin, A et al. The relationship between arteriovenous fistula success and inflammation. Ren Fail 2013;35 (8):1085-1088
8. Poetker, DM Reh, DD A comprehensive review of the adverse effects of systemic corticosteroids. Otolaryngol Clin North Am 2010;43 (4):753-768
9. Dams, ET Oyen, WJ Boerman, OC et al. 99mTc-PEG liposomes for the scintigraphic detection of infection and inflammation: clinical evaluation. J Nucl Med 2000;41 (4):622-630
10. Lobatto, ME Calcagno, C Otten, MJ et al. Pharmaceutical development and preclinical evaluation of a GMP-grade anti-inflammatory nanotherapy. Nanomedicine 2015;11 (5):1133-1140
11. Wong, C Bezhaeva, T Rothuizen, TC et al. Liposomal prednisolone inhibits vascular inflammation and enhances venous outward remodeling in a murine arteriovenous fistula model. Sci Rep 2016;630439

12. Robbin, ML Greene, T Cheung, AK et al; Hemodialysis Fistula Maturation Study Group. Arteriovenous fistula development in the first 6 weeks after creation. Radiology 2016;279 (2):620-629

Chapter 5

A Randomized Trial of Liposomal Prednisolone (LIPMAT) to Enhance Radiocephalic Fistula Maturation: A Pilot Study

Bram M. Voorzaat, K.E.A. van der Bogt, Taisiya Bezhaeva, Jan van Schaik, Daniel Eefting, Karien van der Putten, Roos C. van Nieuwenhuizen, Johannes O. Groeneveld, Ellen K. Hoogeveen, Irene M. van der Meer, Randolph G. Statius van Eps, Liffert Vogt, Laurens Huisman, Bas A.Th.F. Gabreëls, Henk Boom, Cornelis A. Verburgh, Diederik Boon, Josbert M. Metselaar, Marcel C. Weijmer and Joris I. Rotmans

Kidney International Reports (2020) 5, 1327–1332. DOI: 10.1016/j.ekir.2020.05.030

Abstract

Introduction Maturation failure of radiocephalic arteriovenous fistulas (RCAVF) is a significant clinical issue. Vascular inflammation after AVF surgery is associated with non-maturation.

Objective To evaluate whether liposomal prednisolone improves RCAVF maturation in end-stage renal disease (ESRD) patients.

Methods The LIPMAT-study was a multi-center, double-blind, 1:1 randomized, placebo-controlled trial. Subjects were enrolled after RCAVF creation and treated with placebo or 150 mg of liposomal prednisolone at days 1 and 15 after AVF surgery. The primary end point was the juxta-anastomotic diameter of the cephalic vein at 6 weeks after surgery. Secondary end points were the diameter of the cephalic vein, brachial and radial artery at 6 weeks and 3 months after surgery as well as AVF flow and functional use for hemodialysis. Adverse events were compared to assess safety.

Results 29 subjects were included of which 13 received placebo and 16 received liposomal prednisolone. The juxta-anastomitic cephalic vein diameter at 6 weeks was 3.9 mm (95% confidence interval 2.7 – 5.8 mm) in the placebo group and 3.7 mm (95% confidence interval 3.0 – 5.3 mm) in the liposomal prednisolone group (p=0.88). No significant differences in secondary end point parameters were observed. Treatment of end-stage renal disease patients with liposomal prednisolone was not associated with significant side effects.

Conclusion Liposomal prednisolone treatment of ESRD patients was safe, but did not result in enhanced RCAVF maturation.

Introduction

Patients on maintenance hemodialysis (HD) require a reliable vascular access; however, only half of newly created radiocephalic arteriovenous fistulas (RCAVF) can be used for HD without additional procedures to promote maturation and up 25% fail to provide adequate vascular access for HD [1]. The need for subsequent creation of upper arm arteriovenous fistulas (AVFs) and arteriovenous grafts may decrease if maturation can be improved. Currently, no pharmacological treatments have been proven to improve clinical maturation of AVFs.

Although the underlying pathophysiology of nonmaturation is incompletely understood, impaired outward remodeling and neointimal hyperplasia in the venous outflow tract seem to contribute [2]. Studies in murine and porcine models of AVF failure revealed a pronounced inflammatory response in the venous outflow tract in the early phase after AVF surgery [3]. Recent studies suggest that this inflammatory response impairs AVF maturation [4].

Pegylated liposomes have emerged as an attractive tool to facilitate selective delivery of drugs to inflamed tissues with a highly permeable microvasculature, where liposomes are being phagocytized by macrophages. It has a potent and long-lasting anti-inflammatory effect at sites of inflammation, while minimizing exposure of noninflamed tissues. In a murine model of AVF failure, we have demonstrated that liposomal prednisolone inhibits inflammation of the juxta-anastomotic vein and improves outward remodeling of the venous outflow tract [5].

We hypothesized that maturation of RCAVFs in humans can be improved by inhibition of juxta-anastomotic inflammation using liposomal prednisolone. In the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study, we aimed to assess if liposomal prednisolone improves maturation of RCAVFs and if it can be safely administered to patients with end-stage renal disease. The design of this multicenter randomized placebo-controlled trial has been reported earlier in detail [6].

Methods

Study design

The Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) was a phase 2, investigator-initiated, multi-center, double-blinded, randomized, placebo-controlled trial. Subjects were recruited in 11 participating hospitals in the Netherlands. Patients were

eligible for enrolment if RCAVF creation was planned based on local hospital protocols, including a baseline ultrasound examination, as recommended by the Dutch Vascular Access Guidelines [7]. Treating physicians identified eligible patients based on the in- and exclusion criteria (Supplementary Materials). Patients who provided written informed consent were then assessed for eligibility at a screening visit by the investigators, using medical history, physical examination and laboratory investigations. If an RCAVF could be successfully created, patients were enrolled and randomized stratified per hospital 1:1 to two infusions of each 150mg liposomal prednisolone or matching placebo in 500ml normal saline. Treatments were administered at 1 (± 1) day and 15 (± 2) days after surgery. Although the plasma half-life of liposomal prednisolone is 3 days, previous studies in humans revealed a therapeutic effect of 2 weeks after a single dose of 150 mg liposomal prednisolone [8]. Therefore, we anticipated that the treatment regime in our study would results in an anti-anti-inflammatory effect that would last 4 weeks. All patients were pre-treated with paracetamol and clemastine before each infusion to mitigate any allergic responses. Blinding methods have been described previously in detail, the investigators and patients were blinded to treatment allocation [6]. The protocol was approved by the ethics committee of the Leiden University Medical Center and the Institutional Review Boards of all participating hospitals and the study was performed in accordance with the principles of the Declaration of Helsinki.

End points

The primary end point was the juxta-anastomotic diameter of the cephalic vein, measured by ultrasonography at 1cm downstream from the arteriovenous anastomosis at 6 weeks (± 5 days) after surgery. Secondary end points were the diameter of the cephalic vein at the elbow and mid upper arm and blood flow in the upstream radial and brachial arteries at 6 weeks and 3 months (± 14 days). The 6-week and 3-month time points chosen for AVF evaluation are similar to other studies evaluating the effect of pharmaceutical interventions on AVF maturation [9, 10]. Ultrasound examinations were performed by qualified personnel in the participating hospitals. In case of AVF occlusion, diameters and flow were analysed as 0 mm and 0 ml/min respectively. Adverse events were recorded up to 3 months after surgery. Adverse events were classified as 'severe' if these met the criteria for Serious Adverse Events according to Good Clinical Practice guidelines, stating that an adverse event is serious if it is fatal, and/or is life-threatening for the subject, and/or makes hospital admission or an extension of the admission necessary, and/or causes persistent or significant invalidity or work disability, and/or manifests itself in a congenital

abnormality or malformation, and/or could, according to the person that carries out the research, have developed to a serious undesired medical event, but was however prevented due to premature interference. Functional outcomes were assessed in December 2018 for all subjects.

Statistical analysis

In a pilot cohort, a 1.5 mm standard deviation of the 6-week distal cephalic vein diameter was observed. A difference of 1.0 mm between the treatment and control group was considered clinically relevant. The sample size was calculated at 40 patients per group, allowing for a drop-out of 10%. The non-normally distributed end points were described as median and interquartile range (IQR) and were tested for significance using the Mann-Whitney U-test. The proportions of AVF occlusions were reported as percentages per treatment group. The study was not powered to demonstrate differences in AVF occlusions, side effects and functional outcomes and no statistical analysis was performed for these parameters.

Results

Study Population

From April 2016 through May 2018, 109 patients were planned for RCAVF creation and assessed for study eligibility. A total of 64 patients were excluded for known exclusion criteria from their medical history (n = 24), not consenting to study participation (n = 34), or late referral (n = 6, Figure 1). Of the remaining 45 patients who provided informed consent, 32 were randomized (Table 1). Reasons for dropout are shown in Figure 1. After randomization, but before treatment, 2 patients experienced clinical events constituting exclusion criteria. The remaining 30 patients received the study treatment. The trial was stopped prematurely in May 2018 because of slow enrollment.

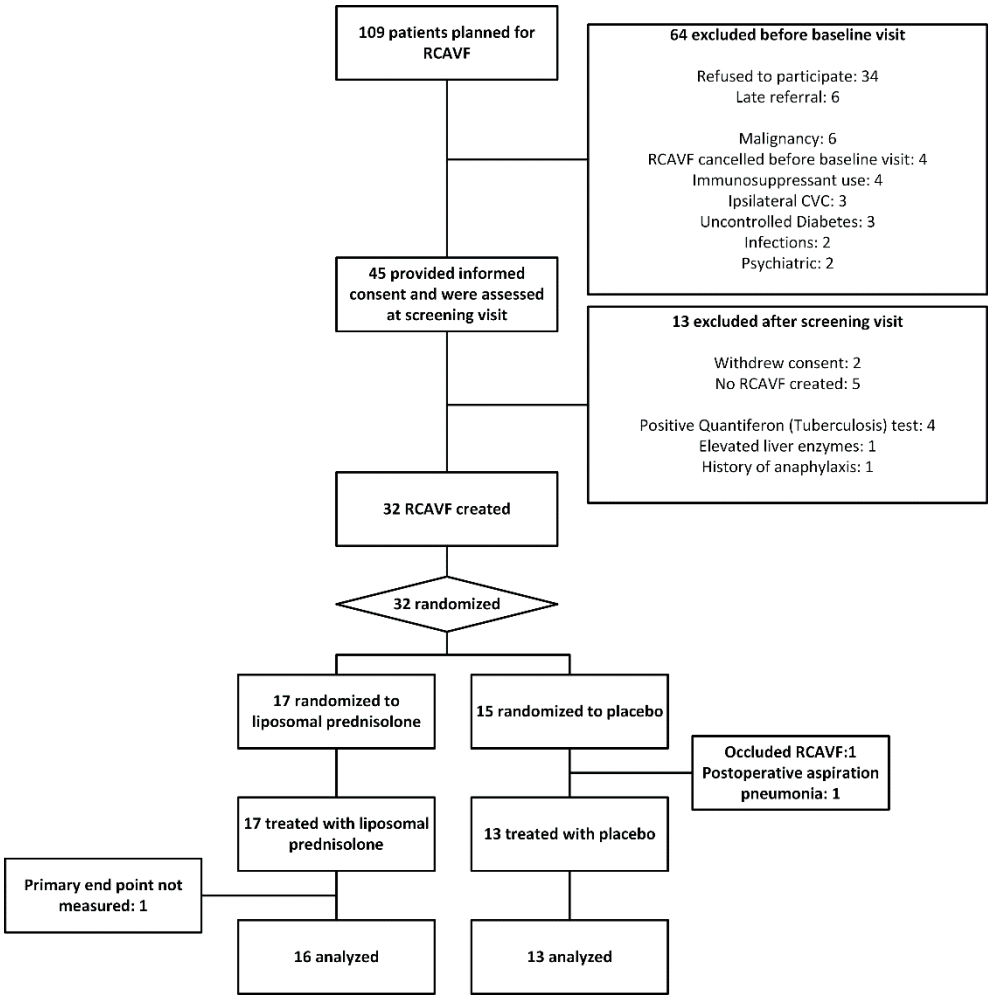


Figure 1 Study flowchart. CVC, central venous catheterization; RCAVF, radiocephalic arteriovenous fistula.

	Placebo (n=13)	Liposomal prednisolone (n=16)	Total (n=29)
Age, yrs	70 ± 8.5	65 ± 12	67 ± 11
Gender			
Female	5 (38%)	1 (6%)	6 (21%)
Male, no (%)	8 (62%)	15 (94%)	23 (79%)
Race			
Caucasian	11 (85%)	13 (81%)	24 (83%)
Hindustani Surinamese	1 (8%)	2 (13%)	3 (10%)
Moroccan	0 (0%)	1 (6%)	1 (3%)
Asian	1 (8%)	0 (0%)	1 (3%)
Cause of renal failure			
Diabetes mellitus	4 (31%)	6 (38%)	10 (35%)
Renal vascular disease	5 (39%)	4 (25%)	9 (31%)
Glomerulonephritis	3 (23%)	2 (13%)	5 (17%)
Interstitial nephropathy	1 (8%)	2 (13%)	3 (10%)
Cystic kidney disease	0 (0%)	2 (13%)	2 (7%)
Comorbidities			
Diabetes mellitus	7 (54%)	7 (44%)	14 (48%)
Coronary artery disease	6 (46%)	4 (25%)	10 (35%)
Peripheral artery disease	4 (31%)	3 (19%)	7 (24%)
Cerebrovascular disease	5 (39%)	4 (25%)	9 (31%)
Medication			
ACE inhibitor	1 (8%)	6 (38%)	7 (24%)
Angiotensin 2 receptor blocker	8 (62%)	5 (31%)	13 (45%)
Loop diuretic	8 (62%)	9 (56%)	17 (59%)
Aldosterone receptor antagonist	0 (0%)	1 (6%)	1 (3%)
Beta blocker	10 (77%)	8 (50%)	18 (62%)
Calcium channel blocker	8 (62%)	11 (69%)	19 (66%)
Platelet inhibitor	4 (31%)	10 (63%)	14 (48%)
Anticoagulant	2 (15%)	3 (19%)	5 (17%)
Vitamin D	12 (92%)	13 (81%)	25 (86%)

Table 1 Baseline characteristics of 29 patients in the LIPMAT study by treatment group. ACE, angiotensin-converting enzyme; LIPMAT, Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation. Data are reported as mean ± SD or n (%).

End Points

The primary end point was assessed in 29 patients. The distal cephalic diameter was 3.9 mm (95% confidence interval, 2.7–5.8 mm) in the placebo group and 3.7 mm (95% confidence interval, 3.0–5.3 mm) in the treatment group ($p = 0.88$). No significant results were observed for secondary end points (Table 2).

6 weeks	Placebo median (IQR)	Liposomal prednisolone median (IQR)	p (Mann Whitney U)
Cephalic vein			
Juxta-anastomotic diameter	3.9 (2.7 – 5.8) mm	3.7 (3.0 – 5.3) mm	0.88
Elbow diameter	5.5 (4.7 – 6.7) mm	5.0 (4.0 – 6.1) mm	0.47
Mid upper arm diameter	4.0 (2.3 – 5.3) mm	4.8 (4.1 – 5.4) mm	0.22
Radial artery			
Juxta-anastomotic diameter	3.6 (2.9 – 4.2) mm	3.6 (3.0 – 4.0) mm	0.83
Flow	456 (277 – 688) ml/min	406 (300 – 772) ml/min	0.81
Brachial artery			
Flow	523 (342 – 985) ml/min	550 (417 – 1201) ml/min	0.79
3 months			
Cephalic vein			
Juxta-anastomotic diameter	4.2 (2.3 – 6.1) mm	4.9 (3.9 – 5.8) mm	0.43
Elbow diameter	6.2 (4.7 – 6.9) mm	5.7 (4.4 – 6.3) mm	0.35
Mid upper arm diameter	5.8 (2.8 – 4.5) mm	5.7 (3.6 – 6.2) mm	0.83
Radial artery			
Juxta-anastomotic diameter	4.0 (2.1 – 5.0) mm	3.6 (3.0 – 4.6) mm	1.00
Flow	546 (110 – 1037) ml/min	560 (334 – 970) ml/min	0.65
Brachial artery			
Flow	800 (434 – 1485) ml/min	798 (479 – 1019) ml/min	0.60

Table 2 Effect of liposomal prednisolone on primary and secondary end points in 29 patients in the LIPMAT study. IQR, interquartile range; LIPMAT, Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation.

Functional Outcomes

At the time of assessment of the functional outcomes, 54% of AVFs in the placebo arm and 69% in the liposomal prednisolone arm were successfully used for HD (p = 0.41). Seven patients (44%) in the liposomal prednisolone arm and 4 patients (31%) in the placebo group underwent an endovascular or surgical procedure to achieve RCAVF maturation. During follow-up, in the placebo and liposomal prednisolone groups, respectively 23% and 13% of RCAVFs had failed (p = 0.45). The functional outcome could not be determined for 6 patients, because of loss to follow-up (2 patients who moved abroad) or not initiating HD (Table 3).

	Placebo (n=13)	Liposomal prednisolone (n=16)
AVF used		
Without procedures to improve maturation	3 (23%)	4 (25%)
With procedures to improve maturation	4 (31%)	7 (44%)
AVF not used		
Failed due to nonmaturation	3 (23%)	2 (13%)
Kidney transplantation	0 (0%)	1 (6%)
Did not reach ESRD	1 (8%)	1 (6%)
Deceased before ESRD	0 (0%)	1 (6%)
Loss to follow up	2 (16%)	0 (0%)

Table 3 Effect of liposomal prednisolone on functional outcomes of RCAVF in 29 patients in the LIPMAT study. Values are n (%). AVF, arteriovenous fistula; ESRD, end-stage renal disease; LIPMAT, Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation.

Safety

No infusion reactions were observed except for 1 subject in the liposomal prednisolone arm who was known to have symptoms of orthostatic hypotension, and experienced mild dizziness without hypotension on postural change during the infusion. The incidence of symptoms related to progressive renal failure and cardiovascular events was similar in both treatment arms (Table 4).

	Placebo (n=13)	Liposomal prednisolone (n=16)
AVF related events		
Angiography/angioplasty	3	6
Revision surgery	1	0
Coiling or ligation of collateral veins	1	2
Hematoma or bleeding	2	1
New AVF within 3 months	1	1
Nerve damage	1	0
Edema	1	0
Infusion related events		
Orthostatic symptoms (no hypotension)	0	1
Renal and metabolic		
Fluid overload	3	2
Gout	1	0
Uremia (worsening)	1	0
Anemia (worsening)	1	1
Cardiovascular		
Atrial fibrillation/flutter	2	4
Myocardial infarction	1	2
Angina pectoris (worsening)	0	1
Intermittent claudication (worsening)	1	0
Infectious		
AVF site infection	0	1
Cellulitis (non-AVF site)	0	1

Upper airway infection including rhinosinusitis	0	2
Septicemia	0	1
Dental	1	0
Other		
Accidental injury	3	2
Fatigue and sleep disorders	4	4
Liver enzyme abnormalities	2	2
Hyperthyroidism	0	1
Hair loss	1	0
Intoxication	0	1
Aspecific thoracic pain	0	1
Constipation	0	1
Sunburn	0	1
Melanoma	1	0
Gastric pain	0	1
Hematoma non-AVF site	0	1
Urinary catheter placement	0	1

Table 4 Adverse events reported in the LIPMAT study. Myocardial infarction includes non-ST-elevation myocardial infarction. AVF, arteriovenous fistula; LIPMAT, Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation.

Infections

In the liposomal prednisolone arm, 5 infections were observed in the 3 months of follow-up. One subject was treated with antibiotics due to erythema in the AVF arm, without fever or systemic symptoms. One subject experienced 2 episodes of mild rhinosinusitis that resolved without specific treatment. One subject died 72 days after AVF surgery, because of progressive fluid overload, complicated by septicemia from a possible catheter-related infection or pneumonia. In the placebo group, 1 subject experienced a dental abscess 3 months after AVF surgery.

Discussion

In the LIPMAT study, we evaluated if liposomal prednisolone improves maturation of RCAVFs. The trial was terminated because of slow enrollment after inclusion of 30 of the 80 subjects initially aimed for. We present the study to investigate feasibility and to report preliminary outcomes. Liposomal prednisolone was safe and well-tolerated by patients with end-stage renal disease. No severe infusion reactions were observed and no severe infections were observed within the expected duration of effect of liposomal prednisolone. Liposomal prednisolone did not result in improved RCAVF maturation as measured by ultrasound at 6 weeks and 3 months after surgery. The 62% successful cannulation rate observed in the LIPMAT study was

comparable to previous studies on functional AVF maturation [1,8]. Although the nonsignificant result may be a mere result of a lack of power due to the small sample size, also no trend toward any difference between the treatment and control group was observed. Apart from a lack of statistical power, several factors might explain the lack of therapeutic efficacy of liposomal prednisolone to improve AVF maturation. First, the local concentration of liposomal prednisolone in the vessel wall of the AVF might not have been sufficient to exert a strong anti-inflammatory effect. The local accumulation of liposomal prednisolone could not be examined, as the AVFs could not be sacrificed for examination. In addition, no approved formulation of the compound was available to trace the liposomes in vivo in humans. Second, the inflammatory response in the RCAVF might have been too limited to induce significant local vascular accumulation of the liposomes. Previous clinical studies revealed substantial localization of liposomal prednisolone in the atherosclerotic arterial wall [12]. As the prevalence of atherosclerosis was high in the LIPMAT subjects (Table 1), a significant proportion of liposomal prednisolone may therefore have accumulated in nontarget vessel walls instead of the AVF vein. In future studies, tissue samples of AVFs that failed early may be acquired during surgical revisions and analyzed for liposomal prednisolone content.

The extent and timing of venous inflammation after AVF surgery in humans is not fully known. To avoid potential detrimental effects on wound healing, liposomal prednisolone was not administered before surgery. As most of outward remodeling of AVFs has been shown to occur within the first 4 weeks after surgery [13], we aimed to cover this interval by administering the drug at day 1 and 15 after surgery. This might have been too short, with significant inflammation persisting at 4 weeks after surgery.

Conclusion and Further Directions

The LIPMAT study was the first to study an anti-inflammatory strategy to improve AVF maturation in humans. We could not demonstrate a clinically significant impact on RCAVF maturation. Future studies are needed to elucidate the role of inflammation in AVF maturation and the clinical promise of liposomal formulations of anti-inflammatory drugs to promote AVF maturation.

Acknowledgments

LIPMAT Study Group

Leiden University Medical Center: Bram M. Voorzaat, MD, Jan van Schaik, MD, Koen E.A. van der Bogt, MD, PhD, Joris I. Rotmans, MD, PhD. Academic University: Liffert Vogt, MD, PhD, Laurens Huisman, MD. Alrijne Hospital: Bas A.Th.F. Gabreëls, MD, PhD. Jeroen Bosch Hospital: Ellen K. Hoogeveen, MD, PhD. Haaglanden Medical Center: Daniël Eefting, MD, PhD. Haga Hospital: Irene M. van der Meer, MD, PhD, Randolph G. Statius van Eps, MD, PhD. OLVG: Marcel C. Weijmer, MD, PhD, Johannes O. Groeneveld, MD, Roos C. van Nieuwenhuizen, MD. Reinier de Graaf Hospital: Henk Boom, MD, PhD. Spaarne Hospital: Cornelis A. Verburgh, MD, PhD. Tergooi Hospital: Karien van der Putten, MD, PhD, Niek A. Koedam, MD, PhD. Dijklander Hospital: D. Boon, MD, PhD.

Data Safety Monitoring Board

Erasmus Medical Center: H.J.M. Verhagen, MD, PhD (Chair). University Medical Center Groningen: M.H. de Borst, MD, PhD. Leiden University Medical Center: S. le Cessie, PhD (statistician).

Registration

The study was registered at ClinicalTrials.gov, identifier NCT02495662.

This study has received financial support from an unrestricted grant from Enceladus Pharmaceuticals B.V.

Disclosure

EKH is a member of the Guideline Committee of the Dutch Federation of Nephrology. All the other authors declared no competing interests.

JMM is affiliated with Enceladus Pharmaceuticals which contributed financially to the work reported in this publication.

Supplementary materials

Supplementary materials are available at the *Kidney International Reports* website via https://doi.org/10.1016/j.ekir.2020.05.030

References

1. Voorzaat BM, van der Bogt KEAA, Janmaat CJ, van Schaik J, Dekker FW, Rotmans JI, et al. Arteriovenous Fistula Maturation Failure in a Large Cohort of Hemodialysis Patients in the Netherlands. World J Surg. 2018; 42(6): 1895–903.
2. Rothuizen TC, Wong C, Quax PHA, van Zonneveld AJ, Rabelink TJ, Rotmans JI. Arteriovenous access failure: more than just intimal hyperplasia? Nephrol Dial Transplant. 2013 May 1; 28(5): 1085–92.
3. Dundon BK, Torpey K, Nelson AJ, Wong DT, Duncan RF, Meredith IT, et al. The deleterious effects of arteriovenous fistula-creation on the cardiovascular system: a longitudinal magnetic resonance imaging study. Int J Nephrol Renovasc Dis. 2014 Jan; 7: 337–45.
4. Bezhaeva T, de Vries MR, Geelhoed WJ, van der Veer EP, Versteeg S, van Alem CMA, et al. Relaxin receptor deficiency promotes vascular inflammation and impairs outward remodeling in arteriovenous fistulas. FASEB J. 2018 Nov 8; 32(11): 6293–304.
5. Wong C, Bezhaeva T, Rothuizen TC, Metselaar JM, de Vries MR, Verbeek FPR, et al. Liposomal prednisolone inhibits vascular inflammation and enhances venous outward remodeling in a murine arteriovenous fistula model. Sci Rep. 2016; 6: 30439.
6. Voorzaat BM, van Schaik J, van der Bogt KEA, Vogt L, Huisman L, Gabreëls BATF, et al. Improvement of radiocephalic fistula maturation: rationale and design of the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study – a randomized controlled trial. J Vasc Access. 2017 Mar 3;18(1_suppl): S114–7.
7. Guideline vascular access ("Richtlijn vaattoegang") - Dutch Federation of Nephrology ("Nederlandse Federatie voor Neffrologie"). 2009.
8. van Assche G, Rutgeerts P, Ferrante M, Noman M, Fidder H, Oldenburg B, et al. Safety and efficacy of a novel IV targeted pegylated liposomal prednisolone product (Nanocort): results from a phase 2a study in patients with active ulcerative colitis. In: European Crohn's and Colitis Organisation. 2016.
9. Peden EK, Leeser DB, Dixon BS, El-Khatib MT, Roy-Chaudhury P, Lawson JH, et al. A Multi-center, Dose-escalation Study of Human type I Pancreatic Elastase (PRT-201) Administered after Arteriovenous Fistula Creation. J Vasc Access. 2013 Apr 20; 14(2): 143–51.

10. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA. 2008 May 14; 299(18): 2164–71.
11. Bleyer AJ, Scavo VA, Wilson SE, Browne BJ, Ferris BL, Ozaki CK, et al. A randomized trial of vonapanitase (PATENCY-1) to promote radiocephalic fistula patency and use for hemodialysis. J Vasc Surg. 2019 Feb; 69(2): 507–15.
12. der Valk FM van, van Wijk DF, Lobatto ME, Verberne HJ, Storm G, Willems MCM, et al. Prednisolone-containing liposomes accumulate in human atherosclerotic macrophages upon intravenous administration. Nanomedicine. 2015 Mar 17;
13. Robbin ML, Greene T, Cheung AK, Allon M, Berceli SA, Kaufman JS, et al. Arteriovenous Fistula Development in the First 6 Weeks after Creation. Radiology. 2016 May; 279(2): 620–9.

Chapter 6

The pros and cons of preserving a functioning arteriovenous fistula after kidney transplantation

Bram M. Voorzaat, Jan van Schaik, Hans-Marc J. Siebelink, Jan H. Tordoir, Joris I. Rotmans

The Journal of Vascular Access 2016; 17 (Suppl 1): S16-S22. DOI: 10.5301/jva.5000525

Abstract

The autologous arteriovenous fistula (AVF) for hemodialysis burdens the cardiovascular system with increased cardiac output and pulmonary artery pressure, increasing cardiovascular risk. This article reviews literature on the benefits and drawbacks of a functioning AVF after kidney transplantation and discusses the cardiovascular effects of AVF closure. Several cohort studies demonstrate a significant cardiac burden of an AVF and improvement of cardiac dimensions after AVF ligation. However, no randomized trials have been conducted on routine AVF closure after successful kidney transplantation. Therefore, clinical trials are warranted to evaluate whether the cardiovascular benefits of routine AVF closure outweigh the potential harm for patients after successful kidney transplantation.

Introduction

In maintenance hemodialysis patients, the autologous arteriovenous fistula (AVF) is the preferred type of vascular access. Benefits of the AVF are superior long-term patency and low risk of infections, compared to central venous catheters and prosthetic arteriovenous grafts [1, 2]. However, important drawbacks of AVFs are the occurrence of hand ischemia and high-output heart failure by volume overload [3-6]. The presence of a functioning AVF is associated with a higher left ventricular mass and pulmonary hypertension. The true incidence of high-output heart failure is probably underestimated, as fluid retention can be managed by adapted ultrafiltration in hemodialysis patients.

Enormous efforts are made to create and maintain an adequately functioning vascular access when patients are on hemodialysis. With the increasing kidney allograft survival, we face the dilemma of deciding what to do with a functioning AVF after successful kidney transplantation.

The optimal approach towards asymptomatic patients after kidney transplantation is a topic of debate. In current clinical practice, the AVF is often neglected if the patient with a functional kidney allograft is not reporting any symptoms related to their AVF. However, in some clinics, routine closure is performed [7]. Routine surgical closure of the AVF might be beneficial for these patients in reverting left ventricular dysfunction, or preventing its progression. It is striking to notice that despite the sheer magnitude of care for vascular access related complications for patients on hemodialysis, not a single remark is made about vascular access care after transplantation in any of the current vascular access guidelines from EBPG and NKF KDOQI nor the KDIGO guideline on post-transplantation care [1,8,9]. In the present review, we discuss the benefits and drawbacks of a functioning AVF after kidney transplantation, as well as the previous literature on the cardiac effects of AVF closure.

Why should we aim to maintain a functional vascular access after kidney transplantation?

The advantage of maintaining the AVF after kidney transplantation is to have a functional vascular access if the allograft fails and hemodialysis is again required. Whether or not this strategy of vascular access preservation is defensible, depends on the chance that a specific patient will lose allograft function in the near future. The report from the US Renal Data System from 2014 revealed that the 10-year probability of allograft failure after transplantation in 2002, is 35.5% for recipients of a deceased donor transplant and 25.8% for living donor transplants [10].

The percentage of patients with a failed allograft declined in subsequent years, illustrating an ongoing improvement in long-term kidney allograft survival. In the Netherlands, the current 5-year survival with a functioning allograft is 84% for living donor transplants and 70% for deceased donor transplants [11].

Another issue that should be taken into account is the chance of spontaneous occlusion of the AVF after transplantation. In a retrospective study of 542 kidney transplantation recipients in 2005, long-term AVF patency was evaluated with an up to 10 year follow-up [12]. Spontaneously occluded AVFs were observed in 45% of patients, both in patients with a functioning transplant as well as in cases of transplant failure. In 55% of patients requiring hemodialysis, their previous AVF was used. Another European study found similar results in a cohort of 160 patients [13].

These studies suggest that long-term AVF patency after kidney transplantation is approximately 50%. Approximately 30% of all kidney transplantation recipients return to hemodialysis within 10 years. With routine closure in all kidney transplantation recipients, 15% would have the disadvantage of needing a new vascular access, when the previous AVF could have been used otherwise.

The question rises if patients at high risk of kidney allograft failure can be identified to allow an individualized decision regarding vascular access management after transplantation, excluding them from routine AVF closure. In this respect, it is important to notice that the incidence of kidney allograft loss is highest in the first year after transplantation [14]. Therefore, the estimated glomerular filtration rate (eGFR) at one year after transplantation could be used to predict long-term allograft survival, especially when combined with the slope of eGFR in the first year [15].

Another reason to maintain the arteriovenous access is the use of this conduit for venipunctures and intravenous administration of medication in patients with severely damaged superficial veins. Routine closure should therefore only be considered in patients whose venous anatomy is suitable for venipunctures and future vascular access creation. Obviously, also for patients with a functional kidney allograft, vein preservation is of vital importance.

Potential harm of a functional vascular access after kidney transplantation

Local symptoms like aneurysm formation, steal, cosmetic objections, infection or functional limitations of the extremity are common reasons for surgical AVF closure. While these local

complications are very obvious, the hemodynamic and cardiac effects of the AVF are often much more insidious in nature [6].

To appraise this so-called arteriovenous cardiotoxicity, one needs to know how the cardiovascular system responds to AVF surgery. As already described by Guyton in 1961, an immediate increase in cardiac output occurs upon creation of an AVF [16]. This increase is required to compensate for the drop in vascular resistance and the additional blood flow through the AVF, whilst maintaining organ perfusion.

As vascular resistance decreases after AVF surgery, blood pressure lowers and venous return increases [16,17]. As a result of the increased venous return, more blood is available for diastolic filling of both the left and right ventricle [18]. This increased diastolic filling causes an immediate increase in left ventricular diastolic diameter and volume. In accordance with the Frank-Starling mechanism, stroke volume and thus cardiac output increase [18]. Serum concentrations of atrial and brain natriuretic peptide rise, reflecting the immediate hemodynamic burden of the AVF [17].

Figure 1 provides a schematic representation of the effect of AVF creation on cardiac output in an otherwise healthy cardiovascular system. As demonstrated by Basile, a near linear correlation exists between vascular access flow and cardiac output (Figure 2) [19]. In this study, the mean cardiac output was 5.6 L/min in patients with a forearm AVF and 6.9 L/min with an upper arm AVF.

Even more important than the acute functional adaptation, persisting structural cardiac remodeling also occurs. A 13% increase in left ventricular mass at 6 months after AVF surgery has been observed [18]. As the resulting cardiomyopathy progresses and the heart begins to fail, the initially high cardiac output may decrease to within the normal range. The effective cardiac output, defined as the cardiac output minus the AVF flow, steadily decreases, resulting in systemic hypoperfusion. This state of pseudonormalization is often overlooked, as the cardiac output appears normal if the AVF flow is not subtracted from it. Therefore, it is of vital importance to take the AVF flow into account when assessing cardiac output and to recognize pseudonormalization as a sign of severe cardiac impairment.

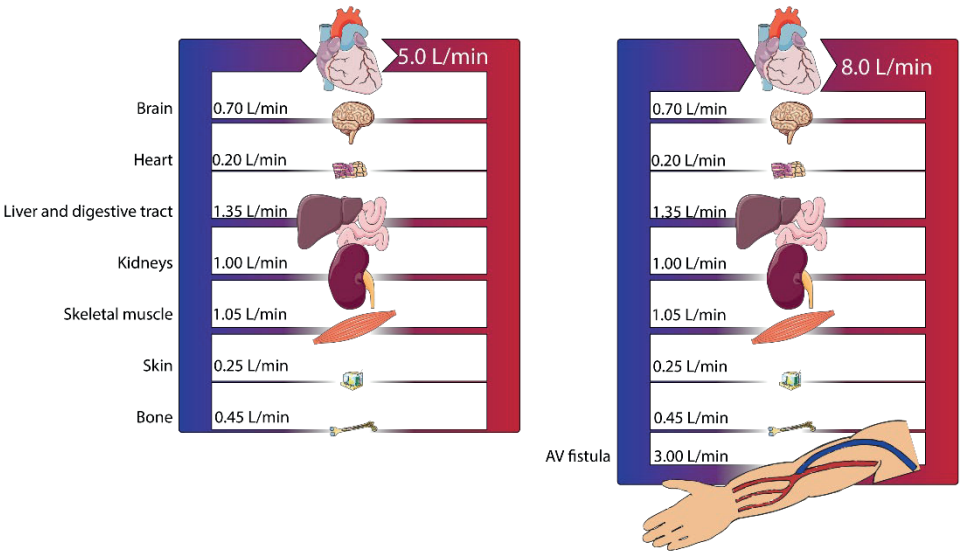


Figure 1 Systemic circulation with organ sizes reflecting relative perfusion, without AVF, with an AVF, resulting in increased cardiac output. AVF; arteriovenous fistula.

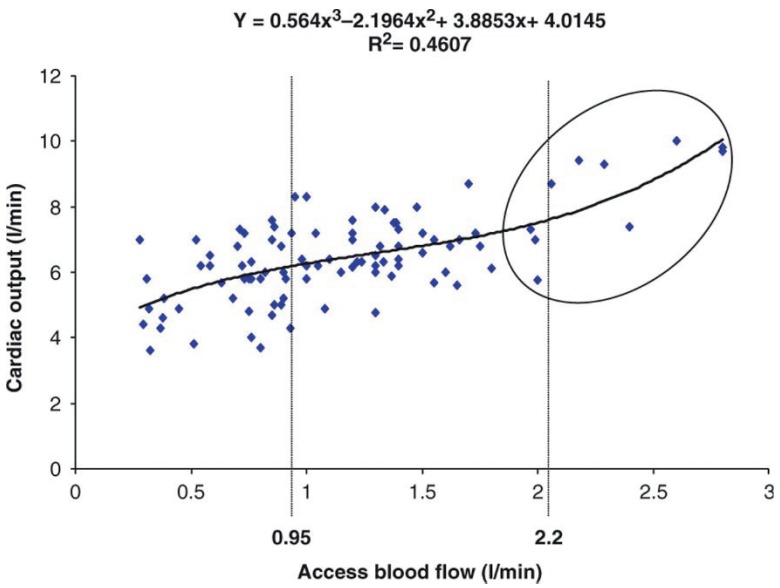


Figure 2 Correlation between vascular access blood flow and cardiac output. Reproduced from Basile et al [19], with permission from European Renal Association-European Dialysis and Transplant Association.

Inevitably, AVF surgery also affects the pulmonary circulation, with increased pulmonary artery pressure (PAP) [20,21]. This increase, along with the increase in left ventricular mass might have serious consequences for the prognosis of patients since both are independent predictors for mortality in hemodialysis patients [22,23] as well as in renal allograft recipients [24–27]. After initiating hemodialysis, the left ventricular mass increases significantly [28]. LVH is common in hemodialysis patients, with a recent study demonstrating a 71% prevalence [26]. Although these observations may also be in part caused by altered hemodynamics and fluid overload due to progressive chronic kidney disease itself, volume overload due to the AVF is an important contributor to left ventricular hypertrophy and pulmonary hypertension.

Since the fluid status of hemodialysis patients is in part regulated by the nephrologist by modifying ultrafiltration rate, the diagnosis of high-output heart failure is easily overlooked. Dyspnea and weight gain are often attributed to non-compliance with the prescribed fluid restriction for hemodialysis patients.

Several observational studies on cardiac changes after kidney transplantation have shown a substantial decline in left ventricular mass, (LVM) although complete normalization of the LVM rarely occurs [29–31]. The cardiac burden of persistent hypertension and the AVF might play a role in this incomplete normalization of LVM.

Improvement of left ventricular dimensions and function after AVF closure

Two different cohort studies of kidney transplant recipients revealed that the mean LVM was significantly higher in patients with a functioning AVF, when compared to patients without a patent AVF [32,33]. These observations suggest that the unfavorable effect of the AVF remains relevant after kidney transplantation [33]. The question arises whether AVF ligation could indeed result in further normalization of LVM after kidney transplantation.

Through Pubmed, Embase and the Cochrane Collaboration, we identified 8 cohort studies that report on the cardiac effects of AVF closure (table 1). Two studies have shown that temporary occlusion of an AVF instantly improves hemodynamics, reducing both heart rate and cardiac output [34,35]. A couple of cases of AVF closure in patients with high-output heart failure have been described [36–39]. Both cardiac output and PAP decrease after surgical closure of the AVF while the functional performance of patients improves. Timely AVF closure could be very important, since irreversible cardiac changes and possibly fixed pulmonary hypertension can

Study and design	Patient characteristics	Indication for closure	Number of patients	Follow-up (months)	LVMI at baseline (g/m²) ± SD	LVMI at follow-up (g/m²) ± SD	LVMI change (%) ± SD	Difference between groups (g/m²)
Duijnhoven 2001 Prospective observational, single-arm	Renal transplant patients No heart failure or NYHA ≤ II	Routine	20 AVF closed	5	135.0 ± 34.1	119.8 ± 23.2	-11.3% p<0.01	-15.2 ± 9.2
Unger 2004 Prospective observational, case-control	Renal transplant patients 10 (40%) heart failure patients	Cardiac symptoms, venous hypertension, cosmetic	17 AVF closed	21 ± 10	139 ± 44	117 ± 40	-15.8% p=0.0167	-22 ± 14.4
			8 controls	24 ± 14	114 ± 19	115 ± 18	+1% p=0.85	+1 ± 9.3
Movilli 2010 Prospective cohort	Hemodialysis patients No heart failure	Malfunctioning AVF	25 AVF closed	6	135 ± 40	123 ± 35	-8.2% ± 5.6 p < 0.001	-12 ± 8.1 *
			36 controls		138 ± 35	138 ± 33	-1% ± 8.8 p=NS	0 ± 11.3 *
Kurita 2011 Retrospective cohort	Hemodialysis patients All patients refractory heart	Refractory heart failure	33 AVF closed	1	160 ± 79	162 ± 81	+1% p=NS	+2 ± 19.7

	failure NYHA ≥ II							
Glowinski 2012 Retrospective cohort	Renal transplant patients No heart failure	Cosmetic (56%), spontaneous thrombosis (44%)	9 AVF closure	3	118.5 ± 26.3	113.1 ± 21.6	-4% p=0.09	-5.4 ± 11.3
			9 controls		116.0 ± 22.5	115.6 ± 18.5	0% p=0.16	-0.4 ± 9.7
Dundon 2014 Prospective cohort	Renal transplant patients No heart failure	Cosmetic	18 AVF closed	6	166 ± 56	149 ± 51	-10% p=0.0001	-17 ± 17.9
Sheashaa 2004 Prospective cohort	Renal transplant patients	Spontaneous occlusion	17 AVF closed	12	210 ± 80 (Am Soc echocardiogr formula)	169.5 ± 61.3	-19%	-4.5 ± 24.4
			34 controls		248 ± 83.5	176.3 ± 41.4	-29%	-71.7 ± 16.0
Gorgulu 2011 Cross-sectional	Renal transplant patients	Spontaneous occlusion (67%), ligation for: aneurysm (18%), cardiac symptoms (6%), cosmetic (6%), thrombus (2%)	49 AVF closed	Unknown	n/a	125 ± 42	n/a	+4 ± 7.7
			60 AVF patent			129 ± 37		

Table 1 Studies that evaluated change in left ventricular mass index after AVF closure. Data from Movilli, 2010 have been calculated from raw data supplied by the author.

eventually occur [7]. Pulmonary hypertension can be fully reversible if AVF closure is performed timely [39].

A prospective study was performed by Van Duijnhoven, et al. in which the effect of routine closure of vascular accesses was assessed [40]. Nineteen patients with native AVFs and 1 patient with a PTFE-graft were included, with a mean flow of 1790 ml/min, without heart failure higher than NYHA class 2. Cardiac ultrasound examinations were performed 2 and 4-5 months after AVF closure. The mean LVMI decreased from 135 g/m^2 to 120 g/m^2 at 4-5 months after closure. The prevalence of LVH decreased from 60 to 33%. In a subgroup analysis in patients more than 18 months after kidney transplantation, the reduction of LVMI was also significant (136 to 123 g/m^2). The authors assumed LVMI was expected to remain stable in these patients if the AVF would not have been closed, and concluded that the improvement in this subgroup was likely due to the AVF closure.

Smaller studies by Unger and Dundon also demonstrated a significant improvement in LVMI after AVF closure in patients with and without heart failure [41,42].

Movilli, et al. performed a study in which cardiac ultrasound examinations were prospectively performed in 25 hemodialysis patients who underwent AVF closure and conversion to a tunneled central venous catheter (CVC) and 36 controls who continued hemodialysis through an AVF [43]. Cardiac ultrasound examinations were performed at baseline and 6 months after AVF closure. While baseline measurements were not significantly different between groups, LVMI regressed from 135 g/m^2 at baseline to 123 g/m^2 at 6 months after AVF closure, whereas the LVMI in the control group did not change.

In a retrospective study by Sheashaa in 17 patients with a spontaneously occluded AVF after kidney transplantation and 34 controls [44]. The LVM at 1 year was improved in both groups. However, no significant difference was observed between groups. Cardiac output was significantly lower in the group with a closed AVF compared to the group with a patent AVF (4.3 L/min vs 5.8 L/min, p=0.010). This study concludes that even though cardiac output is significantly higher with a patent AVF, this did not result in detectable structural cardiac changes in a 1-year follow-up.

In contrast, the studies by Gorgulu, Glowinski and Kurita did not show a significant improvement of LVM, although it's important to notice that their follow up was limited to 3

months. This limited follow up precludes firm conclusions regarding the effects of AVF closure on cardiac dimensions [45–47]. In addition, a large proportion of patients with spontaneously rather than surgically occluded AVF were included in the studies by Gorgulu, Glowinski. Indeed, spontaneous occlusion of AVFs may be an indication of impaired cardiac function at baseline, resulting in a substantial confounding. In general, one should be cautious with interpreting the results of the above-mentioned studies as none of them had a prospective and randomized trial design.

Another possible source of error is the use of the left ventricular mass index, which corrects for weight or body surface area. In most transplantation patients, body weight changes when fluid retention is resolved, lowering body mass, and when fat mass increases after starting steroids, increasing body mass. Since the body surface area is derived from weight, this parameter also changes. These changes may influence the LVMI even if the actual LVM does not change.

Conclusions and future directions

Although several studies indicate a benefit of AVF closure, the current evidence is not conclusive. The remarkable differences in how AVFs are treated in kidney transplantation recipients in different hospitals, regions and countries, clearly demonstrate the lack of consensus amongst clinicians on this topic. No recommendations for routine AVF closure have yet found their way into vascular access or transplant guidelines. Based on the current literature, it is still unclear how to weigh the pros and cons of AVF ligation in these patients. With the continuously improving outcomes of kidney transplantation, the question arises whether this balance will shift further towards benefit of routine closure.

In order to increase the scientific foundation for recommendations regarding vascular access management after transplantation, we intend to initiate a randomized, controlled trial evaluating the effect of closure of asymptomatic high-output AVFs in post-kidney transplantation patients. Patients will only be included if the renal function is adequate and stable. We believe this strategy will result in a low incidence of patients who need to re-initiate hemodialysis after surgical AVF closure. In addition, patients without other reasonable options to create a new AVF will be excluded. Cardiac MRI will be used at baseline and at two years after AVF closure to evaluate cardiac structure and function.

In conclusion, a patent AVF contributes to the persisting LVH after transplantation and could therefore contribute to the observed high risk of cardiovascular disease in kidney transplant

patients. However, more research is needed to determine whether closure of AVFs in asymptomatic patients is indeed beneficial for their cardiovascular health. Such benefit should then be weighed against the increased risk of future vascular access complications in case of a repeated need for hemodialysis.

Disclosures

Financial support: JR has received research grants from Enceladus Pharmaceuticals B.V. and Proteon Therapeutics, Inc.

References

1. NKF KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations [Internet]. 2006 [cited 2015 Jan 21]. Available from: http://www2.kidney.org/professionals/KDOQI/guideline_upHD_PD_VA/
2. Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. J Am Soc Nephrol. 2013 Feb;24(3):465–73.
3. Ahearn DJ, Maher JF. Heart failure as a complication of hemodialysis arteriovenous fistula. Ann Intern Med. 1972 Aug;77(2):201–4.
4. Anderson CB, Codd JR, Graff RA, Groce MA, Harter HR, Newton WT. Cardiac failure and upper extremity arteriovenous dialysis fistulas. Case reports and a review of the literature. Arch Intern Med. 1976 Mar;136(3):292–7.
5. Amerling R, Ronco C, Kuhlman M, Winchester JF. Arteriovenous fistula toxicity. Blood Purif. 2011 Jan;31(1-3):113–20.
6. MacRae JM, Levin A, Belenkie I. The cardiovascular effects of arteriovenous fistulas in chronic kidney disease: a cause for concern? Semin Dial. 2006 Jan;19(5):349–52.
7. Pascual J, Martins J, Bouarich H, Galeano C, Barrios V, Marcén R, et al. Sudden death after arteriovenous fistula ligation in a renal transplant patient. Ann Vasc Surg. 2008 Jan;22(1):134–5.
8. Tordoir J, Canaud B, Haage P, Konner K, Basci A, Fouque D, et al. EBPG on Vascular Access. Nephrol Dial Transplant. 2007 May 1;22 Suppl 2(suppl_2):ii88–117.
9. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009 Nov;9 Suppl 3:S1–155.
10. United States Renal Data System, 2014 USRDS annual data report: An overview of the epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.
11. Survival statistics - Dutch Transplantation Foundation [in Dutch] [Internet]. Available from: http://www.transplantatiestichting.nl/cijfers/overlevingscurves
12. Manca O, Pisano GL, Carta P, Manca EM, Piredda GB, Pili G, et al. The management of hemodialysis arteriovenous fistulas in well functioning renal transplanted patients: many doubts, few certainties. J Vasc Access. 2005 Jan;6(4):182–6.

13. Patard J-J, Bensalah K, Lucas A, Rodriguez A, Manunta A, Rivalan J, et al. Management of vascular access for hemodialysis after successful kidney transplantation. Scand J Urol Nephrol. 2002 Jan;36(5):373–6.
14. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000 Mar 2;342(9):605–12.
15. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int. 2002 Jul;62(1):311–8.
16. Guyton A, Sagawa K. Compensations of cardiac output and other circulatory functions in areflex dogs with large A-V fistulas. Am J Physiol. 1961 Jun;200:1157–63.
17. Iwashima Y, Horio T, Takami Y, Inenaga T, Nishikimi T, Takishita S, et al. Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. Am J Kidney Dis. 2002 Nov;40(5):974–82.
18. Dundon BK, Torpey K, Nelson AJ, Wong DT, Duncan RF, Meredith IT, et al. The deleterious effects of arteriovenous fistula-creation on the cardiovascular system: a longitudinal magnetic resonance imaging study. Int J Nephrol Renovasc Dis. 2014 Jan;7:337–45.
19. Basile C, Lomonte C, Vernaglione L, Casucci F, Antonelli M, Losurdo N. The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. Nephrol Dial Transplant. 2008 Jan 1;23(1):282–7.
20. Abassi Z, Nakhoul F, Khankin E, Reisner SA, Yigla M. Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. Curr Opin Nephrol Hypertens. 2006 Jul;15(4):353–60.
21. Yigla M, Banderski R, Azzam ZS, Reisner SA, Nakhoul F. Arterio-venous access in end-stage renal disease patients and pulmonary hypertension. Ther Adv Respir Dis. 2008 Apr;2(2):49–53.
22. Yigla M, Fruchter O, Aharonson D, Yanay N, Reisner SA, Lewin M, et al. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. Kidney Int. 2009 May;75(9):969–75.
23. Malik J, Kudlicka J, Tesar V, Linhart A. Cardiac safety in vascular access surgery and maintenance. Contrib Nephrol. 2015 Jan;184:75–86.

24. Kim SJ, Oh HJ, Yoo DE, Shin DH, Lee MJ, Kim HR, et al. Electrocardiographic left ventricular hypertrophy and outcome in hemodialysis patients. PLoS One. 2012 Jan;7(4):e35534.
25. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. J Am Soc Nephrol. 2003 Feb;14(2):462–8.
26. Mostovaya IM, Bots ML, van den Dorpel MA, Goldschmeding R, den Hoedt CH, Kamp O, et al. Left ventricular mass in dialysis patients, determinants and relation with outcome. Results from the COnvective TRansport STudy (CONTRAST). PLoS One. 2014 Jan;9(2):e84587.
27. Sheashaa HA, Abbas TM, Hassan NA, Mahmoud KM, El-Agroudy AE, Sobh MA, et al. Association and prognostic impact of persistent left ventricular hypertrophy after live-donor kidney transplantation: a prospective study. Clin Exp Nephrol. 2010 Mar;14(1):68–74.
28. Foley RN, Curtis BM, Randell EW, Parfrey PS. Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. Clin J Am Soc Nephrol. 2010 May;5(5):805–13.
29. Peteiro J, Alvarez N, Calviño R, Penas M, Ribera F, Castro Beiras A. Changes in left ventricular mass and filling after renal transplantation are related to changes in blood pressure: an echocardiographic and pulsed Doppler study. Cardiology. 1994 Jan;85(5):273–83.
30. Ferreira SRC, Moisés VA, Tavares A, Pacheco-Silva A. Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. Transplantation. 2002 Dec 15;74(11):1580–7.
31. Paoletti E, Cannella G. Reducing the risk of left ventricular hypertrophy in kidney transplant recipients: the potential role of mammalian target of rapamycin. Transplant Proc. 2009 Jan;41(6 Suppl):S3–5.
32. Kolonko A, Kujawa-Szewieczek A, Szotowska M, Kuczera P, Chudek J, Więcek A. The association of long-functioning hemodialysis vascular access with prevalence of left ventricular hypertrophy in kidney transplant recipients. Biomed Res Int. 2014 Jan;2014:603459.
33. Cridlig J, Selton-Suty C, Alla F, Chodek A, Pruna A, Kessler M, et al. Cardiac impact of the arteriovenous fistula after kidney transplantation: a case-controlled, match-paired study. Transpl Int. 2008 Oct;21(10):948–54.

34. Cooper MW, Stanbaugh GH, Walling SB, Myers WD, Calvert JE. Effects of occlusion of fistulae on left ventricular dimensions in hemodialysis patients. Trans Am Soc Artif Intern Organs. 1981 Jan;27:625–8.
35. Aitken E, Kerr D, Geddes C, Berry C, Kingsmore D. Cardiovascular changes occurring with occlusion of a mature arteriovenous fistula. J Vasc Access. 2015 Jan 29;January([Epub ahead of print]).
36. Stern AB, Klemmer PJ. High-output heart failure secondary to arteriovenous fistula. Hemodial Int. 2011 Jan 12;15:104–7.
37. Rao N, Worthley M, Disney P, Faull R. Dramatic improvement in decompensated right heart failure due to severe tricuspid regurgitation following ligation of arteriovenous fistula in a renal transplant recipient. Semin Dial. 2014 Mar;27(2):E24–6.
38. Young PR, Rohr MS, Marterre WF. High-output cardiac failure secondary to a brachiocephalic arteriovenous hemodialysis fistula: two cases. Am Surg. 1998 Mar;64(3):239–41.
39. Clarkson MR, Giblin L, Brown A, Little D, Donohoe J. Reversal of pulmonary hypertension after ligation of a brachiocephalic arteriovenous fistula. Am J Kidney Dis. 2002 Sep;40(3):E8.
40. van Duijnhoven EC, Cheriex EC, Tordoir JH, Kooman JP, van Hooff JP. Effect of closure of the arteriovenous fistula on left ventricular dimensions in renal transplant patients. Nephrol Dial Transplant. 2001 Feb;16(2):368–72.
41. Unger P, Velez-Roa S, Wissing KM, Hoang AD, van de Borne P. Regression of left ventricular hypertrophy after arteriovenous fistula closure in renal transplant recipients: a long-term follow-up. Am J Transplant. 2004 Dec;4(12):2038–44.
42. Dundon BK, Torpey DK, Nelson AJ, Wong DTL, Duncan RF, Meredith IT, et al. Beneficial cardiovascular remodeling following arterio-venous fistula ligation post-renal transplantation: a longitudinal magnetic resonance imaging study. Clin Transplant. 2014 Aug;28(8):916–25.
43. Movilli E, Viola BF, Brunori G, Gaggia P, Camerini C, Zubani R, et al. Long-term effects of arteriovenous fistula closure on echocardiographic functional and structural findings in hemodialysis patients: a prospective study. Am J Kidney Dis. 2010 Apr;55(4):682–9.
44. Sheashaa H, Hassan N, Osman Y, Sabry A, Sobh M. Effect of spontaneous closure of arteriovenous fistula access on cardiac structure and function in renal transplant patients. Am J Nephrol. 2004 Jan;24(4):432–7.

45. Gorgulu N, Caliskan Y, Yelken B, Akturk F, Turkmen A. Effects of arteriovenous fistula on clinical, laboratory and echocardiographic findings in renal allograft recipients. Int J Artif Organs. 2011 Dec 12;34(10):1024–30.
46. Głowiński J, Małyszko J, Głowińska I, Myśliwiec M. To close or not to close: fistula ligation and cardiac function in kidney allograft recipients. Pol Arch Med Wewnętrznej. 2012 Jan;122(7-8):348–52.
47. Kurita N, Mise N, Tanaka S, Tanaka M, Sai K, Nishi T, et al. Arteriovenous access closure in hemodialysis patients with refractory heart failure: a single center experience. Ther Apher Dial. 2011 Apr;15(2):195–202.

Chapter 7

No consensus on physicians' preferences on vascular access management after kidney transplantation: Results of a multi-national survey

Bram M Voorzaat, Cynthia J Janmaat, Esther D Wilschut, Koen EA van der Bogt, Friedo W Dekker, Joris I Rotmans

The Journal of Vascular Access 2019, Vol. 20(1) 52–59. DOI: 10.1177/1129729818776905

Abstract

Objective Arteriovenous fistulas for hemodialysis vascular access are a burden for the cardiovascular system. After successful kidney transplantation, prophylactic arteriovenous fistula ligation may improve cardiac outcomes; however, evidence is scarce. This survey investigates physicians' preference for management of arteriovenous fistulas and identifies the factors associated with preference for either arteriovenous fistula ligation or maintenance.

Materials and methods A survey was sent to members of eight national and international Nephrology and Vascular Surgery societies. The survey comprised eight case vignettes of asymptomatic patients with a functioning arteriovenous fistula after kidney transplantation. Characteristics possibly associated with treatment preferences were arteriovenous fistula flow, left ventricular ejection fraction, and patient age. Respondents were asked to state preference to maintain or ligate the arteriovenous fistula. Linear mixed-effects models were used to investigate the association of treatment preference with case characteristics.

Results A total of 585 surveys were returned. A reduced left ventricular ejection fraction of 30% (beta 0.60, 95% confidence interval 0.55; 0.65) and a high flow of 2500mL/min (beta 0.46, 95% confidence interval 0.41; 0.51) were associated with a higher preference for arteriovenous fistula ligation. Disagreement among respondents was considerable, as in four out of eight cases less than 70% of respondents agreed on the arteriovenous fistula management strategy.

Conclusion Although respondents recognize a reduced left ventricular ejection fraction and a high flow as the risk factors, the high disagreement on management preferences suggests that evidence is inconclusive to recommend arteriovenous fistula ligation or maintenance after kidney transplantation. More research is needed to determine optimal arteriovenous fistula management after successful kidney transplantation.

Introduction

Nephrologists and surgeons often face patients with a functioning arteriovenous fistula (AVF) after kidney transplantation. Although the AVF is the preferred vascular access (VA) for patients on maintenance hemodialysis (HD), it burdens the cardiovascular system by increasing cardiac output, left ventricular mass, and pulmonary arterial pressure [1,2]. This process of "AVF cardiotoxicity" may result in symptoms of heart failure or may remain asymptomatic [3]. A higher left ventricular mass is associated with cardiovascular events and death in asymptomatic HD patients [4]. While on HD, the benefits of an adequately functioning AVF usually outweigh these detrimental cardiac effects of AVFs. This balance of pros and cons of AVFs might change for individual patients after successful kidney transplantation, as the cardiovascular burden persists while patients no longer benefit from the advantages of AVFs. The main disadvantages of routine ligation are the need for the construction of a new AVF in case HD needs to be reinitiated, the burden of the ligation surgery, and the loss of a VA site for blood sample collections, as some AVFs are used for this purpose in case no suitable veins are accessible for conventional venepuncture.

Small observational studies suggest that left ventricular mass could improve after AVF ligation in kidney transplantation recipients [5,6]. However, neither large observational studies, nor intervention trials have been performed to evaluate whether preservation or ligation of AVFs should be recommended in kidney transplantation recipients. Although AVF ligation may improve cardiac function, studies on the effect of a functional AVF on kidney function revealed conflicting results, suggesting that kidney allograft function may deteriorate after ligation [7,8].

Data on the current practice of VA management after kidney transplantation and recommendations in guidelines on this topic are scarce. The United Kingdom Renal Association and United States National Kidney Foundation guidelines on VA do not include any advice on VA management after kidney transplantation [9,10]. The European Best Practice Guideline on Vascular Access mentions possible improvement of cardiac function after AVF ligation, but does not recommend routine ligation after kidney transplantation [11]. Thus far, no studies on physicians' attitudes toward VA management after kidney transplantation have been published. Therefore, the aim of this study was to investigate physicians' preferences for AVF preservation or ligation in asymptomatic patients after successful kidney transplantation. We also aimed to identify the factors influencing these preferences and to assess differences in treatment preferences across specialties and other physician subgroups.

Methods

Participants

Eligible participants were physicians associated with the Journal of Vascular Access of the Vascular Access Society, the American Society of Diagnostic and Interventional Nephrology, the Vascular Access Society of Britain and Ireland, the Italian Society of Nephrology, the Australian and New Zealand Society of Nephrology, the European Society for Vascular Surgery, the Dutch Federation of Nephrology, and the Dutch Society for Vascular Surgery. An online survey was sent out in the societies' newsletters or as a separate e-mail.

Questionnaire

Interviews were performed with a focus group of vascular surgeons and nephrologists in one academic and one affiliated hospital. Factors influencing physicians' decisions to maintain or ligate a VA after kidney transplantation were identified. From these, a questionnaire was compiled. The complete questionnaire is available in the Supplementary materials. Respondents were asked to state their characteristics, including specialty, seniority, number of VA-related decisions per year, affiliation, and country. They were then asked if routine VA surveillance was performed in kidney transplantation patients in their hospital. Eight case vignettes were presented of patients with a good kidney transplantation prognosis, a functioning brachiocephalic AVF without local symptoms and with options for future AVF creation (Table 1). Case vignettes were presented with all possible combinations of age, AVF flow, and left ventricular ejection fraction (LVEF). Respondents were asked to state their preference for maintaining or ligating the AVF on a four-point Likert scale. We decided against a neutral midpoint option, as no clear preference to ligate the AVF in practice means that the AVF is maintained. By presenting a four-point Likert scale, we forced the respondents to decide on either maintenance or ligation [12].

We crafted the case vignettes in a way that decisions would focus on long-term outcomes, rather than being forced toward either ligating or maintaining the AVF. We assumed a poor transplant prognosis or no contralateral AVF options to result in a "maintain AVF" response by nearly all respondents, and symptoms of cardiac failure or complaints about the AVF itself to result in AVF ligation by nearly all respondents. Based on these assumptions, we did not vary these variables in the clinical cases.

40-year old male Good kidney transplant prognosis: 2 years after living donor kidney transplantation, no rejection, eGFR: 50 ml/min/1.73m^2 Cardiac status: **Preserved left ventricular ejection fraction (50%)** Current brachiocephalic AVF, left-sided, flow: **1000 ml/min** Asymptomatic with regard to the AVF Vein mapping right arm: Suitable for both radiocephalic and brachiocephalic AVF creation			
How do you approach the AVF?			
□ Strong preference to maintain the AVF	□ Tendency to maintain the AVF	□ Tendency to ligate the AVF	□ Strong preference for AVF ligation

Table 1 Example case vignette. Age, cardiac status, and AVF flow were varied for the eight clinical case vignettes. AVF: arteriovenous fistula; eGFR: estimated glomerular filtration rate.

The case vignettes were presented in a random order. A response to each Likert scale was required to continue to the next case. Partially filled-in questionnaires were included in the analysis. After the randomized case vignettes, respondents were presented with one case vignette of a patient with the characteristics shown in Table 1, but without a given AVF flow. Respondents were asked if they would never ligate the AVF, always ligate the AVF, or base their decision on the AVF flow. In the latter case, they were asked to specify at which minimum flow they would ligate the AVF. Finally, respondents could freely comment on which criteria are important to them in deciding on AVF management after kidney transplantation.

Statistical analysis

Descriptive statistics were used to describe respondents' characteristics. Preferences were coded on a four-point scale, with 1 representing a strong preference to maintain the AVF and 4 representing a strong preference to ligate the AVF. Analyses were performed for all respondents and separately for surgeons and nephrologists, academic and affiliated hospital physicians, and those who make less or more than the median number of 80 VA-related decisions per year. Mean scores for maintenance or ligation of AVFs were calculated per case vignette. If for a case vignette less than 70% of respondents prefer to ligate an AVF while more than 30% of respondents prefer to maintain the AVF, or vice versa, we considered disagreement to be considerable.

The factors influencing clinicians' preferences were assessed using linear mixed-effects models. Linear mixed-effects models can be used to estimate the preference of ligation across respondents, while accounting for the dependency of observations within respondents. The

patients' age (40 or 65 years), AVF flow (1000 or 2500 mL/min), and cardiac status (LVEF 30% or 50%) were entered as separate independent variables in the fixed-effects model and the individual respondents as the random effect. The case vignettes were entered as repeated measurements. In the model building phase, the model with the best fitting covariance matrix was selected based on the Akaike's information criterion (AIC; whereby a lower AIC indicated a better model fit). The AIC is based on the value of the maximum likelihood and on the number of parameters in the model and can be used to compare the fit between models [13]. The final model with unstructured covariance fit best (lowest AIC) and was then fit by restricted maximum likelihood to estimate the preference for ligation. The model outcomes were beta values, indicating by how many points the 1–4 Likert scale is affected in the presence of each independent variable. The values each beta could theoretically take range from −3 to +3. Lower beta scores systematically indicated stronger preference to maintain the AVF. Reference categories were defined as an age of 40 years, a flow of 1000 mL/min, and an LVEF of 50%. Analyses were performed in SPSS version 22 (SPSS, IBM Corporation).

Results

Participants

A total of 585 responses were received. Most respondents were surgeons (54.5%) or nephrologists (37.6%) with a median of 13 years of clinical experience and 80 VA-related treatment decisions in the past year. The characteristics of respondents are shown in Table 2. Nine (1.5%) respondents stated that they had not made any VA-related decisions in the past year. Routine VA surveillance after kidney transplantation was performed by 29% of respondents.

Specialty	Surgery	319 (54.5 %)
	Nephrology	220 (37.6 %)
	General Nephrology	163 (27.9%)
	Interventional Nephrology	57 (9.7%)
	Radiology	28 (4.8 %)
	Other	18 (3.1 %)
Affiliation	Academic hospital	326 (55.7 %)
	Affiliated hospital	169 (28.9 %)
	Other	90 (15.4 %)
Years of experience		13 (7 ; 20)
VA treatment decisions past year		80 (27 ; 265)
Routine VA surveillance after kidney transplantation	Yes	169 (28.9 %)
	No	384 (65.6 %)
	Unknown	32 (5.5 %)

Continent	Africa	7 (1.2 %)
	Asia	49 (8.4 %)
	Australia	28 (4.8 %)
	Europe	372 (63.6 %)
	North America	109 (18.6 %)
	South America	20 (3.4 %)

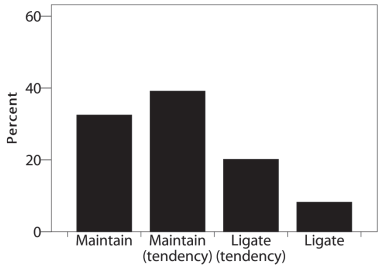
Table 2 Characteristics of respondents (n=585). Experience years and number of treatment decisions are median and interquartile ranges. VA: vascular access.

Treatment preferences

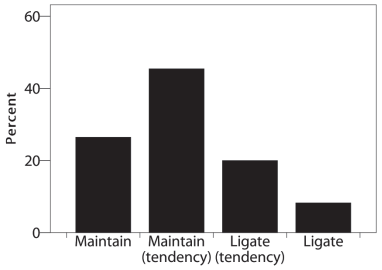
For four out of eight cases, disagreement was considerable with less than 70% of respondents preferring either AVF maintenance or ligation (Figure 1). The tendency to ligate the AVF was the highest in clinical cases with a high AVF flow of 2500 mL/min and a reduced LVEF of 30%, in which 55.3% (patient age 40 years) and 59.6% (patient age 65 years) of the respondents strongly preferred AVF ligation. On the other hand, 20.0% and 19.2% of respondents preferred to maintain the AVF in these cases, respectively. Only eight respondents (1.4%) strongly preferred maintenance of the AVF in all clinical cases, whereas 28 respondents (4.8%) always strongly preferred AVF ligation.

Impact of patient characteristics on VA treatment preference

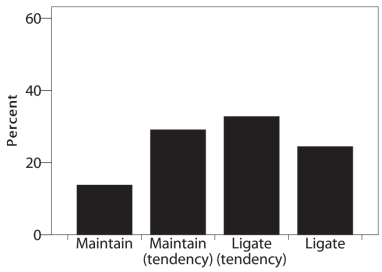
A high AVF flow of 2500 mL/min (beta 0.46, 95% confidence interval 0.41; 0.51) and a reduced LVEF of 30% (beta 0.60, 95% confidence interval 0.55; 0.65) were independently associated with an increased preference to ligate the AVF (Figure 2) and cases with these combinations scored highest on the mean tendency to ligate (Table 3). Age was not significantly associated with treatment preferences. In the subgroup analyses, the same pattern was observed for surgeons and nephrologists, physicians in academic and affiliated hospitals, physicians who made less than the median number of 80 versus 80 or more VA treatment decisions in the past year, and physicians who do versus do not perform routine AVF surveillance (Supplementary, Table 1). No clinically relevant interactions were observed between patient age, AVF flow, and LVEF (Supplementary, Table 2).



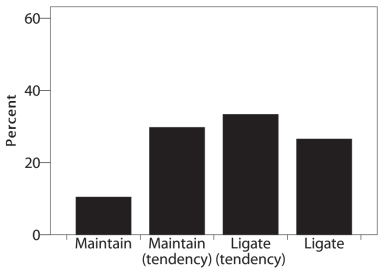
40 years, flow 1000 ml/min, LVEF 50%



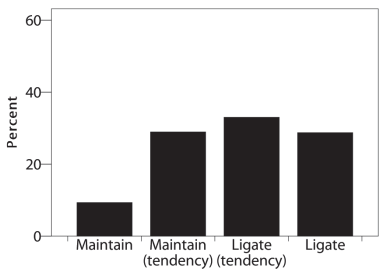
65 years, flow 1000 ml/min, LVEF 50%



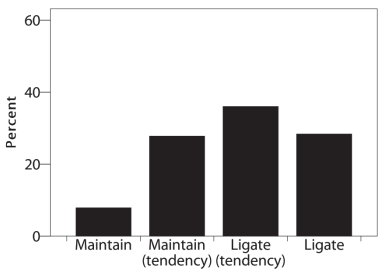
40 years, flow 2500 ml/min, LVEF 50%



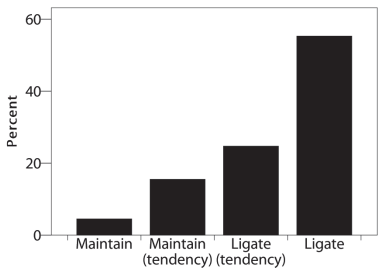
65 years, flow 2500 ml/min, LVEF 50%



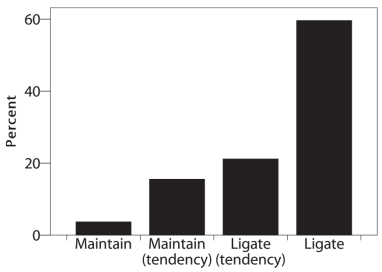
40 years, flow 1000 ml/min, LVEF 30%



65 years, flow 1000 ml/min, LVEF 30%



40 years, flow 2500 ml/min, LVEF 30%



65 years, flow 2500 ml/min, LVEF 30%

Figure 1 Distribution of preferences per case vignette. LVEF; left ventricular ejection fraction.

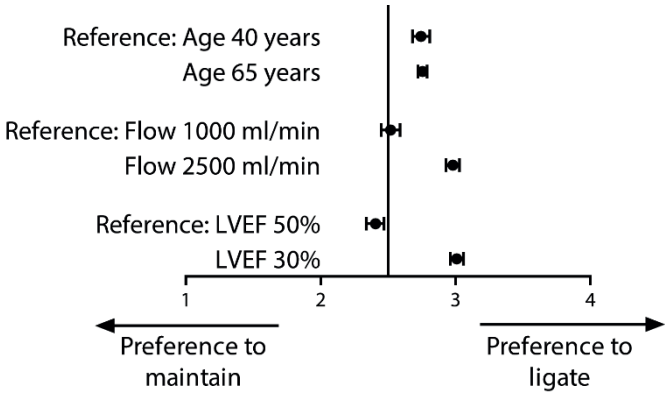


Figure 2 Associations of patient factors on the tendency to maintain or ligate AVFs. Age of 40 years, a flow of 1000mL/min, and a preserved LVEF of 50% were set as reference categories. AVF; arteriovenous fistula. LVEF; left ventricular ejection fraction.

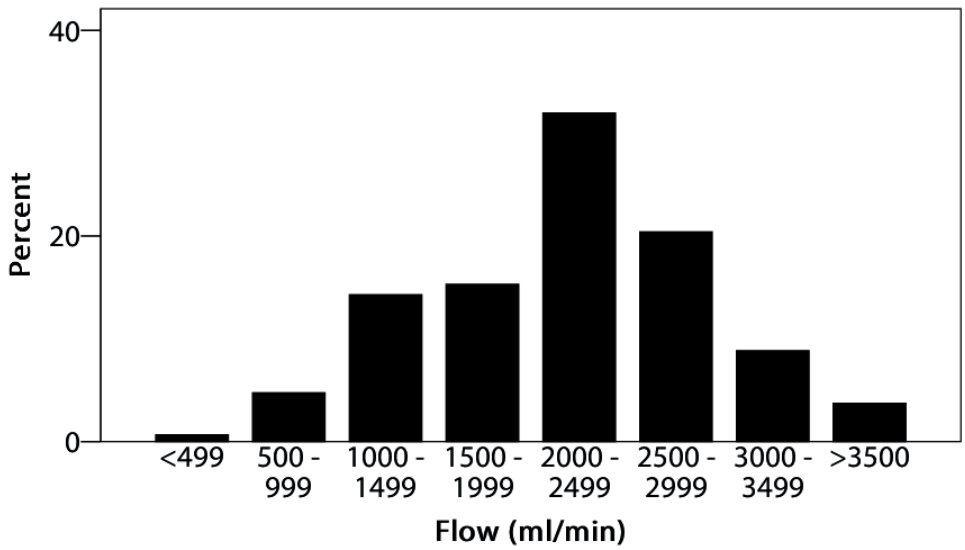


Figure 3 Cut-off value of flow (mL/min) above which AVF ligation is preferred by respondents who base their decision on AVF flow. AVF; arteriovenous fistula.

Influence of VA flow on the tendency to ligate

In the case of a 40-year-old patient with a preserved LVEF, 120 (24.9%) respondents would never ligate the AVF, 63 (13.1%) would always ligate the AVF, and 299 (62.0%) base their

decision on the AVF flow. For both nephrologists and surgeons, the mean cut-off value above which AVF ligation was preferred was at 2038 mL/min (Table 3 and Figure 3).

	Specialty		
	Surgery	Nephrology	All respondents
40 years, flow 1000 ml/min, LVEF 50%	2.05 ± 0.93	2.04 ± 0.92	2.04 ± 0.92
65 years, flow 1000 ml/min, LVEF 50%	2.17 ± 0.90	2.03 ± 0.87	2.10 ± 0.89
40 years, flow 2500 ml/min, LVEF 50%	2.65 ± 0.98	2.73 ± 0.98	2.68 ± 0.99
65 years, flow 2500 ml/min, LVEF 50%	2.77 ± 0.95	2.79 ± 0.96	2.76 ± 0.96
40 years, flow 1000 ml/min, LVEF 30%	2.83 ± 0.96	2.79 ± 0.94	2.81 ± 0.96
65 years, flow 1000 ml/min, LVEF 30%	2.90 ± 0.94	2.76 ± 0.91	2.85 ± 0.92
40 years, flow 2500 ml/min, LVEF 30%	3.25 ± 0.92	3.36 ± 0.83	3.31 ± 0.89
65 years, flow 2500 ml/min, LVEF 30%	3.39 ± 0.89	3.33 ± 0.86	3.37 ± 0.88
Flow (ml/min) above which AVF would be ligated	2034 ± 754	2049 ± 694	2038 ± 721

Table 3 Mean scores (± standard deviation) for case vignettes, nephrologists, and surgeons. Values range from 1 (strong preference to maintain AVF) to 4 (strong preference to ligate AVF). AVF: arteriovenous fistula; LVEF: left ventricular ejection fraction.

Other factors relevant for decision making

The respondents could comment optionally on which factors are important in their decision-making process. The most frequently encountered answers were on cardiac comorbidity and symptoms (n = 87), AVF flow (n = 61), expected kidney allograft survival (n = 52), local symptoms (n = 28), prospect to create another AVF (n = 27), and patient preference (n = 15). Flow reduction strategies including a Miller banding procedure or a revision using distal inflow were suggested by 43 respondents.

Discussion

No consensus exists on whether routine ligation should be performed in kidney transplantation recipients who are asymptomatic with regard to their VA, even though small studies suggest a beneficial effect of VA ligation on cardiac parameters including left ventricular mass. With this survey, we aimed to investigate physicians' attitudes toward treatment of VAs after kidney transplantation and to measure the influence of patient characteristics on this preference.

As the mean preference score was higher than 2.5 in six out of eight cases, we observed a preference for AVF ligation in the presented asymptomatic cases with a good renal allograft function. The management preferences did not differ between nephrologists and surgeons or other subgroups. A reduced LVEF and a high AVF flow were associated with a higher preference for AVF ligation.

Disagreement among respondents

In general, there was considerable disagreement among respondents with regard to the preferred treatment strategy for the case vignettes. While the majority of respondents prefer to ligate a VA in the patients with a high AVF flow and reduced LVEF, 20% of respondents prefer to maintain the VA in these patients. In patients with less pronounced risk factors, the variability in preferences was even greater. This demonstrates that the best treatment for these patients is unknown and there is no consensus among physicians on AVF management. Several factors should be taken into account when considering the optimal VA management after kidney transplantation.

Return to HD and resumed use of the AVF

Routine AVF ligation may harm patients who return to HD and might otherwise have resumed the use of their AVF. Whether this should be taken into account in patients with a stable kidney function depends on two aspects: (1) the likelihood that patients outlive their renal allograft and return to HD and (2) the chance that the AVF could still be used at that time.

Local differences of the prognosis of renal allografts may be an important explanation of the observed disagreement in physicians' preference. In a recent publication from the European ERA-EDTA registry, the 5-year death-censored allograft survival in recipients of a living donor kidney transplant approaches 90% and an increasing proportion of patients will die with a functioning kidney graft and never return to HD [14]. For deceased donors, the 5-year graft survival was 77% for all patients, while it was worse for elderly patients at 62%. In the United States, the 5-year graft survival of patients transplanted in 2010 was similar at 73% for deceased donors and 85% for living donors [15]. Other factors such as expanded donor criteria and choice of immunosuppressive regimens may contribute to regional differences in transplantation outcomes [16]. Of note, kidney allograft failure is not the same as return to HD, as patients may also be retransplanted preemptively or opt for peritoneal dialysis or conservative treatment.

The question arises what percentage of patients could use their VA for HD at time of renal allograft failure if the VA is not routinely ligated. In a retrospective study by Manca and coworkers [17] in which 542 transplanted patients with a functional AVF were included, 207 AVFs closed either spontaneously (156 patients) or surgically because of local symptoms (49 patients). During follow-up, 89 patients returned to HD, while only 49 of them reused the AVF they had

at the time of transplantation. Immediate routine ligation would therefore only harm 49/542 (9%) of patients and expose 156 of them (29%) to an unnecessary procedure.

Aitken and Kingsmore [18] observed similar outcomes in a cohort of 398 patients with a patent AVF at the time of kidney transplantation. In this cohort, 78 AVFs (19.6%) failed within 1 year or were ligated for symptoms or cosmetic reasons. In 98 patients, graft loss occurred and in 69 cases of graft loss (70%) the AVF was still patent or could be used after minor procedures. Routine ligation of all AVFs in this cohort would have harmed these 69 (17.3%) patients.

Why age does not seem to matter in physician's preferences?

In elderly patients, the major cause for kidney allograft loss is death with a functioning allograft [19]. This would favor AVF ligation in elderly patients. Inversely, if AVF ligation improves long-term cardiovascular outcomes, young patients could benefit more from timely ligation. On the contrary, younger patients are also more likely to return to HD in their lifetime. Based on our results, we could not determine how age was being weighted as a contributing factor to the preference of the physicians in the presented cases.

Banding as an intermediate option in VA management after kidney transplantation

Several respondents suggested a banding procedure rather than ligation for high-flow AVFs. Obviously, banding could be a sensible option, although it remains challenging to permanently reduce AVF flow, as recurrent high flow has been reported in up to 50% of patients [20]. A banding procedure may therefore not be the optimal strategy to improve long-term cardiovascular outcomes for all patients, but may be considered in patients who will likely return to HD.

Patients' preferences

Whether or not to ligate an AVF after kidney transplantation should be a process of shared decision making by the patient and the physician. To properly counsel patients on this topic, physicians should have an understanding of the pathophysiology of AVF cardiotoxicity and the risks and benefits of ligation. Patients may prefer to maintain their AVF if the cosmetic consequences of future contralateral AVF creation are not acceptable or if the AVF remains in use for blood collection.

Study limitations

We did not vary the transplant prognosis and did not include cardiac or local AVF symptoms in the case vignettes. Therefore, the survey only provides information on preferences for

prophylactic AVF ligation to improve long-term cardiovascular outcomes and does not reflect physicians' preferences for AVF management to treat current heart failure or local symptoms. In addition, it is important to emphasize that the survey responses solely reflect physicians' preferences, which may not match with clinical practice. As the majority of respondents do not perform routine VA surveillance after kidney transplantation, it is likely that AVF ligation is not as frequently performed in asymptomatic patients as suggested by the reported preferences of the physicians who participated in the survey.

Conclusion and future directions

The significant variability in preferences demonstrates that the current evidence is not convincing to recommend routine preservation or ligation of AVFs in kidney transplantation recipients. We hope that this research stimulates the discussion about optimal care for VAs after kidney transplantation and results in future studies on this underexposed part of VA management. It could be of great value to gain more insight into the protocols for surveillance that are currently being used all over the world and to propose a consensus-based guideline.

We aim to explore patients' attitudes toward their AVF in an upcoming survey, as the feasibility of an intervention trial on AVF ligation after kidney transplantation strongly depends on patients' attitude regarding AVF ligation and preservation. Ultimately, we aim to perform a randomized clinical trial investigating the effect of prophylactic AVF ligation on renal allograft function, cardiac parameters, cardiac and all-cause mortality as well as VA complications in patients who restart HD.

Supplementary materials

Supplementary materials are available at the *Journal of Vascular Access* website via https://doi.org/10.1177/1129729818776905

References

1. Basile C, Lomonte C, Vernaglione L, et al. The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. Nephrol Dial Transplant 2008; 23(1): 282–287.
2. Abassi Z, Nakhoul F, Khankin E, et al. Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. Curr Opin Nephrol Hypertens 2006; 15(4): 353–360.
3. Amerling R, Ronco C, Kuhlman M, et al. Arteriovenous fistula toxicity. Blood Purif 2011; 31(1–3): 113–120.
4. Foley RN, Curtis BM, Randell EW, et al. Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. Clin J Am Soc Nephrol 2010; 5(5): 805–813. [PMC free article]
5. Van Duijnhoven EC, Cheriex EC, Tordoir JH, et al. Effect of closure of the arteriovenous fistula on left ventricular dimensions in renal transplant patients. Nephrol Dial Transplant 2001; 16(2): 368–372.
6. Movilli E, Viola BF, Brunori G, et al. Long-term effects of arteriovenous fistula closure on echocardiographic functional and structural findings in hemodialysis patients: a prospective study. Am J Kidney Dis 2010; 55(4): 682–689.
7. Vajdič B, Arnol M, Ponikvar R, et al. Functional status of hemodialysis arteriovenous fistula in kidney transplant recipients as a predictor of allograft function and survival. Transplant Proc 2010; 42(10): 4006–4009.
8. Weekers L, Vanderweckene P, Pottel H, et al. The closure of arteriovenous fistula in kidney transplant recipients is associated with an acceleration of kidney function decline. Nephrol Dial Transplant 2016; 32(1): 196–200.
9. UK Renal Association. Clinical practice guideline: vascular access for haemodialysis, 2015, https://renal.org/wp-content/uploads/2017/06/vascular-access.pdf
10. NKF KDOQI. Clinical practice guidelines clinical practice recommendations, 2006, http://kidneyfoundation.cachefly.net/professionals/KDOQI/guideline_upHD_PD_VA/index.html (accessed 5 December 2016).
11. Tordoir J, Canaud B, Haage P, et al. EBPG on vascular access. Nephrol Dial Transplant 2007; 22(Suppl 2): ii88-ii117.

12. Nadler JT, Weston R, Voyles EC. Stuck in the middle: the use and interpretation of mid-points in items on questionnaires. J Gen Psychol 2015; 142(2): 71–89.
13. Littell RC, Pendergast J, Natarajan R. Modelling covariance structure in the analysis of repeated measures data. Stat Med 2000; 19(13): 1793–1819.
14. Pippias M, Jager KJ, Kramer A, et al. The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA registry. Nephrol Dial Transplant 2016; 31(5): 831–841.
15. United States Renal Data System. 2017 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2017, https://www.usrds.org/2017/view/Default.aspx (accessed 29 January 2018). [Google Scholar]
16. Legendre C, Canaud G, Martinez F. Factors influencing long-term outcome after kidney transplantation. Transpl Int 2014; 27(1): 19–27.
17. Manca O, Pisano GL, Carta P, et al. The management of hemodialysis arteriovenous fistulas in well functioning renal transplanted patients: many doubts, few certainties. J Vasc Access 2005; 6(4): 182–186.
18. Aitken E, Kingsmore D. The fate of the fistula following renal transplantation. Transpl Int 2014; 27(9): e90–e91.
19. Boesmueller C, Biebl M, Scheidl S, et al. Long-term outcome in kidney transplant recipients over 70 years in the Eurotransplant Senior Kidney Transplant Program: a single center experience. Transplantation 2011; 92(2): 210–216.
20. Vaes RHD, Wouda R, Van Loon M, et al. Effectiveness of surgical banding for high flow in brachial artery-based hemodialysis vascular access. J Vasc Surg 2015; 61(3): 762–766.

Chapter 8

Summary and discussion

Summary

A vascular access (VA) is required to accommodate chronic hemodialysis (HD) treatment. This thesis focused on the current outcomes of VAs, an attempt to improve arteriovenous fistula (AVF) maturation and the hemodynamic and cardiovascular downsides of AVFs.

Chapter 2 describes a retrospective cohort study in which we evaluated the maturation of radiocephalic AVFs (RCAVF) and upper arm AVFs, and compared it to the primary failure rate of arteriovenous grafts (AVG). We found that RCAVFs were most often the first access for an individual patient whereas upper arm AVFs were more commonly created in patients with a history of a failed VA. Even though, maturation failure was most common for RCAVFs at 24%, compared to 11% for upper arm AVFs. A significantly smaller proportion of AVGs was primarily not usable for HD, at less than 6%. We then attempted to create a model to predict nonmaturation of RCAVFs, which included a small vein diameter, female gender, peripheral vascular disease and cerebrovascular disease. With an area under the receiver-operator characteristic curve (ROC) of 0.6, this model lacked specificity to predict RCAVF maturation failure and thus was not clinically applicable to guide treatment decisions regarding the selection of AVF location for individual patients.

We then evaluated the patency outcomes of this cohort in **chapter 3**. We found that once a vascular access has successfully matured, the functional patency is very good, with a 3-year functional patency (censored for death and abandonment not related to the VA itself) of 83% for both RCAVFs and upper arm AVFs and 72% for AVGs. However, if all VAs are taken into account, and not only the matured VAs, the 3-year functional patency is worse for RCAVFs at 62% and better for upper arm AVFs at 74% and AVGs at 69%. Infections were more common in AVGs and AVGs required more maintenance procedures per year of patency, compared to AVFs.

It was previously shown that AVF maturation involves inflammation. In an animal model, prednisolone encapsuled in liposomes successfully inhibited this inflammatory response and resulted in an increased AVF lumen. **Chapter 4** presents the design of the LIPMAT study. In this double-blinded randomized controlled trial, we evaluated if liposomal prednisolone improves the maturation of RCAVFs in humans. Patients were treated twice with 150mg of liposomal prednisolone or placebo, at one day after surgery and two weeks thereafter. The study was powered to detect a 1.0 mm improvement of the juxta-anastomotic diameter at six weeks

after surgery. Secondary end-points of the LIPMAT study were cephalic vein downstream diameters and blood flow in the cephalic vein, radial artery and brachial artery. Adverse events and interventions were evaluated as safety end-points.

As described in **chapter 5**, 29 patients were treated in the LIPMAT study. The LIPMAT-study was the first to evaluate liposomal prednisolone for AVF maturation and was also the first study in which ESKD patients were treated with liposomal prednisolone. The juxta-anastomotic diameter at 6 weeks, the primary end point of the study, was 3.9 mm in the placebo group and 3.7 mm in the liposomal prednisolone group, a difference which was not statistically significant. At six weeks after surgery, the median AVF flow was 456 ml/min in the placebo group and 406 ml/min in the treatment group. The functional outcomes of RCAVFs in the LIPMAT study were comparable to those in literature, with 23% of RCAVFs in the placebo group failing due to nonmaturation, versus 13% in the treatment group.

Overall, liposomal prednisolone was tolerated well by this population. Although some infections were observed in the study, these were either minor, or well after the treatment effect of liposomal prednisolone had worn off. We therefore conclude that the LIPMAT study did not raise any safety concerns for liposomal prednisolone in ESKD patients and that these patients should not be excluded in any future studies evaluating the drug for other indications.

Until **chapter 6**, we focused on making and maintaining a VA suitable for hemodialysis. Chapter 6 introduces a drawback of AVFs and AVGs, which increase cardiac output by their nature of a low-resistance circuit. In patients with a reduced diastolic or systolic left ventricular function, the heart may not be able to provide adequate cardiac output to accommodate both the AVF flow and organ perfusion. The resulting condition is known as high output heart failure, which may be underestimated since volume overload in HD patients is often attributed to other factors. High output heart failure may cause clinical symptoms, but also increases the left ventricular mass and pulmonary artery pressure, measures commonly recognized as risk factors for mortality. This chapter reviews observational studies on this topic, which demonstrate an improvement of left ventricular mass and pulmonary artery pressure after AVF closure.

At the time this research was performed, no randomized controlled trials were available which investigated the potentially beneficial effect of AVF closure on cardiovascular risk factors. We clinically experience that important differences exist among attitudes of healthcare providers towards keeping or abandoning an AVF after kidney transplantation. In **chapter 7**, we measured

physicians' attitudes towards this topic. A survey was sent out to members of eight societies, consisting of clinical case vignettes presenting patients with a functioning AVF after kidney transplantation. Age, AVF flow and left ventricular function were varied and respondents were asked if they would maintain or ligate the AVF. Five-hundred and eighty-five surveys were returned. A reduced left ventricular function and a higher AVF flow were recognized as factors which increased the tendency to ligate. Disagreement was however considerable, with over 20% of respondents electing to maintain an AVF even in a patient with a high AVF flow and a poor cardiac function.

Discussion and future perspectives

With the increasingly aging population and the rising rates of risk factors for end-stage kidney disease (ESKD) such as diabetes mellitus, the number of patients requiring renal replacement therapy is expected to keep rising and many of them will require HD. The VA remains the Achilles' heel of chronic HD treatment. As more patients will require HD, patients and the healthcare system will be increasingly burdened with the cost of VAs and their complications. Research aimed at improving VA success rates whilst limiting side effects is therefore important both to improve patients' quality of life and limit healthcare expenses.

Can we improve maturation?

In chapter 3 of the thesis, we demonstrated that the native AVF requires less maintenance procedures than the AVG, albeit at the cost of a high initial failure rate. This nonmaturation rate seems to be a multifactorial process involving pre-existing vascular pathology, a pro-inflammatory milieu and postoperative changes favoring the formation of neointimal hyperplasia [1]. Interventions to improve maturation have been disappointing so far. Several pharmacological strategies to improve maturation have been evaluated in human trials over the past years, yet none have demonstrated to improve maturation in a clinically relevant amount.

Targeting inflammation

The LIPMAT study failed to demonstrate a significant improvement of AVF maturation by liposomal prednisolone. Does this mean that inflammation is not an important target in AVF maturation? Preclinical studies may provide some insight into that. First, transgenic animal studies show that inflammatory molecules, such as MCP-1, CD44 and the TLR4 regulatory molecule RP105 were linked to AVF failure, whereas anti-inflammatory HO-1 and HO-2 were

described to be protective [2–6]. Also in humans, Stirbu and colleagues showed in a cohort of 258 patients that higher serum CRP levels at the time of AVF placement are independently associated with an increased risk of AVF patency loss [7]. Martinez et al quantified RNA transcription in human vein specimens obtained at AVF surgery and found that an inflammatory fingerprint was associated with nonmaturation [8]. Based on these studies, we conclude that inhibiting inflammation should not be abandoned as a therapeutic target.

So, how can we improve the efficacy of anti-inflammatory therapy? First, we need to make sure that the active drug actually reaches the vein in a sufficiently high concentration whilst limiting systemic exposure and side effects. In AVFs, typically three delivery vehicles are feasible for targeted drug delivery. As tested in the LIPMAT-study, liposomes may reach high local concentrations at sites of inflammation, but this has not been proven for AVFs in uremic patients, who may lose a significant portion of the drug to other tissues, including atherosclerotic arteries. Before using liposomes for future AVF research, local tissue delivery should be proven using, for example, imaging with a radioactive tracer. Another method of drug delivery in AVFs is using drug-coated balloons or stents. These are currently used for the treatment of stenoses that occur after the AVF has been created [9]. Finally, the surgery in which the AVF is created provides an ideal opportunity to apply a drug directly to the anastomosis. This method has been used for several drugs in the field of AVF research. Secondly, we need to select a drug with an effect which is likely to improve the physiology of maturation. Compelling drugs to attempt in this configuration are the mammalian target of rapamycin (mTOR) inhibitors, which inhibit T-cells but also directly inhibit vascular smooth muscle cell proliferation, limiting neointimal formation.

Targeting the extracellular matrix

Another target for AVF maturation may be the extracellular matrix, by wither inhibiting its formation or by promoting its degradation. Martinez et al investigated the relationship between pre- and post-operative venous fibrosis and maturation in vein samples obtained from 161 human two-stage AVFs [10]. It was hypothesized that fibrosis is associated with vascular stiffness and therefore adversely impacts maturation. In the pre-operative samples. extensive medial fibrosis was observed, however neither pre-operative fibrosis nor the intima/media ratio was associated with nonmaturation. The post-operative samples revealed that both medial fibrosis and the intima/media ratio significantly increase after AVF creation. Nonmaturation, defined in this study as a luminal diameter of less than 6 mm, was significantly associated with high medial

fibrosis and a high intima/media ratio. Next, the characteristics of fibrosis were investigated, revealing that alignment of collagen fibers circumferentially around the lumen was associated with less maturation. This study shows that the postoperative increase in fibrosis was indeed associated with nonmaturation. Can we then attempt to inhibit this fibrosis from forming? This was investigated by Hernandez et al who applied the collagen-crosslinking inhibiting substance β-aminopropionitrile locally around the venous segment in a rat AVF model [11]. Treated AVFs achieved a significantly larger lumen than controls. To our knowledge, no human trial with a drug derived from this research is yet in preparation.

Degradation of elastin fibers is another therapeutic target. This was evaluated by the investigators of the PATENCY-1 and PATENCY-2 trials [12]. In these studies, the drug vonapanitase, a recombinant elastase, was applied to the AVF anastomosis at the time of surgery. By disrupting elastin fibers, vonapanitase facilitates outward remodeling of the venous segment of the AVF. In the PATENCY-1 study, the drug did not improve primary patency but was associated with associated with better unassisted (39 versus 25%, p=0.035) and assisted (64 versus 44%) use for HD compared to placebo. The PATENCY-2 study failed to demonstrate superiority over placebo at the end points of AVF use for HD and secondary patency. The drug is no longer under active development for AVF maturation. Other unsuccessful interventions include antiplatelets, cholecalciferol, fish oil and nitrates [13–16].

Non-pharmacological means to improve maturation

Maybe, rather than attempting to improve maturation by pharmacological means, other approaches may be more successful. A randomized controlled trial in 2015 by Fontseré et al investigated the effect of postoperative muscle exercises and found a significant improvement of AVF use for HD [17]. A similar approach is currently under investigation in the PINCH trial, which investigates if pre-operative forearm exercise increases the pre-operative cephalic vein diameter, making creation of a more distally placed AVF possible [18]. An automatic pneumatic device which intermittently occludes the AVF vein during the maturation phase was also shown to improve the AVF diameters at one month after surgery [19]. A device which irradiates the AVF with far-infrared radiation improved maturation from 76% to 90% in a randomized controlled trial [20]. An implanted device which optimizes the arteriovenous anastomosis geometry was associated with an 88% maturation rate of RCAVFs in a retrospective study [21]. A randomized controlled trial is currently ongoing, with safety as its primary outcome and maturation, blood flow and patency as secondary outcomes [22].

Can we improve AVF maturation by selecting the right patients?

Another approach to improve maturation is to identify those patients in whom an AVF is likely to fail and to elect for a VA which is more likely to succeed in those patients. A scoring system was developed by Lok et al in 2006, in which demographic characteristics and comorbidities predicted nonmaturation and classified the risk of nonmaturation into four groups, ranging from low (24% risk) to high (69% risk) [23]. Farrington et al retrospectively studied 300 patients who received a new AVF whilst on HD with a central venous catheter [24]. Significant predictors for maturation were the preoperative arterial diameter, blood pressure and cardiac function. A prediction model based on these variables could predict maturation with fair accuracy, with an area under the ROC of 0.69.

The ARCH project developed a more patient-specific prediction of AVF flow based on pre-operative ultrasound measurements, which predicted postoperative flow accurately [25]. In a randomized controlled trial, this model was tested as a tool to aid the surgeon in choosing the most appropriate AVF configuration [26]. This did not result in an improved rate of maturation failure, which was 29% in the control group and 32% in the intervention group [27].

No single 'golden bullet' treatment for AVF maturation exists yet and that the future likely lies in combinations of novel pharmacologic interventions and surgical and supportive therapies. Even though computational models may stratify patients in low-to-high risk of nonmaturation groups, the clinical applicability of such models is limited. None of these models are able to identify those patients in whom an AVF will fail with near certainty. Only in those patients, not attempting to create an AVF may be a sensible approach, as such a strategy limits the options available for future AVF creation.

Can we select the right vascular access?

As we have shown, a well-functioning AVF is associated with a relatively low incidence of maintenance procedures, compared to AVGs. Does this mean that every HD patient should receive an AVF? Not necessarily.

A major disadvantage of the AVF is the time required for maturation. To allow for maturation and any procedures which may be required to assist maturation, an AVF is typically created pre-emptively: well before a patient needs to initiate HD. This introduces a problem: can we predict when a patient will actually need HD, and do we know if a patient will live long enough to reach ESKD? We cannot. Lee et al found in a large cohort of patients aged over 70 years, that two

years after VA creation, 67% had initiated HD, whilst 15% had died before starting HD and another 18% survived dialysis free [28]. In the subgroup of patients over 85 years of age, only 60% had initiated HD two years after VA creation. Catheter dependence at the start of HD was higher in the group receiving an AVF at 46%, compared to 29% in the group receiving an AVG. These results demonstrate that a significant proportion of elderly patients who receive a permanent VA pre-emptively will be exposed to the burden and complications of surgery and maintenance procedures, but will not benefit from the VA. For these patients, waiting until HD initiation is imminent and starting with a central venous catheter or an 'early stick' AVG may limit unnecessary procedures. Indeed, the last decade there has been a paradigm shift towards an individualized approach rather than a 'fistula first' strategy [29,30].

A final thought is that we are not fully aware which disadvantages commonly attributed to AVFs and AVGs are the result of confounding by indication due to different patient populations, rather than actual side effects of the VA itself. The Optimizing Access Surgery In Senior hemodialysis patients (OASIS) study which is currently ongoing may shed some light upon this. This randomized controlled trial will randomize elderly patients between a central venous catheter, AVF, or AVG and investigate interventions and complications, functional outcomes, quality of life and healthcare expenses.

Is closing AVFs after kidney transplantation a sensible strategy?

As described in chapter 6, observational studies suggest that cardiac parameters may improve after closure of an AVF. Obvious disadvantages of elective AVF ligation are the cost and burden of the procedure and the loss of a future VA option if the patient needs to resume HD. Elective ligation of AVFs is not common practice, with a recent study finding that in a cohort of 16.845 patients who received a kidney transplant with a functioning AVF or AVG, in only 779 cases (4.6%) that VA was ligated [31]. Most of these ligations were performed because of symptoms, most commonly steal syndrome (adjusted HR 41.0; 95% confidence interval 34.6-48.6).

Our survey in chapter 7 also demonstrated considerable disagreement amongst physicians on how to approach these VAs. Patients also seem to have different opinions. A recent survey in 301 kidney transplantation recipients by Bardowska et al showed that 23% of respondents considered AVF ligation, while 39% do not want to have their AVFs ligated [32]. These findings demonstrate that the evidence available is at best not considered convincing, or conflicting at worst.

Recently, results from the first randomized controlled trial on this topic were published. Rao et al randomized 54 kidney transplantation recipients to AVF ligation or no ligation and performed cardiac magnetic resonance imaging at baseline and 6 months [33]. A significant improvement of -22 grams of left ventricular mass was observed in the treatment group, with no significant change in the control group. Improvements in other cardiac parameters were also observed.

These studies demonstrate that the AVF indeed has a detrimental effect on cardiac parameters and that ligation may reverse these changes, although evidence with benefit on hard clinical end points is not yet available.

Future perspectives

In recent years, VA research has seen several innovations and some have found their way into the clinic already. One novelty is the endovascular AVF (endoAVF), which is performed by placing catheters into the ulnar artery and vein, which attract each other using magnets and then create the anastomosis using a radiofrequency electrode. This method induces less surgical trauma to the vessels and may limit the formation of intimal hyperplasia. Its use is limited to a selected group of patients with anatomy suitable to create an endoAVF and the anastomosis is created at the proximal forearm, reducing length available for cannulation compared to RCAVFs. In patients enrolled in the NEAT study, 87% of endoAVFs were physiologically suitable for HD within 3 months [34]. Compared to matched patients who received a surgical AVF, the 70% of endoAVF patients did not need additional interventions in the first year, compared to 18% for surgical AVFs [35].

Another way to prevent catheter- or AVG-related complications is tissue engineering: to create a new blood vessel which is constructed of the patients' own tissue, but does not suffer from nonmaturation like AVFs do.

Human acellular vessels are created in the laboratory using patient- or donor-derived fibroblasts and smooth muscle cells which are placed on a biodegradable scaffold [36]. These cells then produce an extracellular matrix resembling an arterial wall. After decellularization, these grafts can be implanted as a VA, which over time gets populated with the recipients' own cells. Two single-arm studies with these grafts demonstrated a primary patency of 28% but a good 89% secondary patency at one year after surgery. The incidence of infections was very low, with one event per 89 patient-years [37].

Another approach is in-vivo tissue engineering, in which the patient grows his or her own blood vessel. A rod-shaped implant is placed into the subcutaneous tissue, which elicits a foreign-body response which starts off as an inflammatory process and results in the attraction of myofibroblasts which produce a collagen capsule around the implant. After the implant is removed, the capsule remains as a hollow tube. This tube can then be connected to an artery and vein, forming a VA [38]. This method has been tested in a preclinical model, in which endothelialization of the tissue capsule was observed, showing that these capsules indeed form true blood vessels. A safe margin of bursting pressure was demonstrated [39]. In a highly thrombogenic animal model, the patency of these tissue-engineered grafts was comparable to AVGs. A human trial which investigates the performance of these tissue-engineered blood vessels will commence soon.

Conclusion

For long, the AVF was considered the best VA and a 'fistula first' strategy was advocated. This belief also found its way into legislation, with the fraction of patients starting HD with an AVF currently used as a quality indicator in the Netherlands. The choice of VA remains however a trade-off between advantages and disadvantages, weighing the risks of not reaching ESKD, nonmaturation, starting HD with a catheter, cardiovascular complications and long-term VA related complications. No 'one size fits all' treatment exists and every decision should be individualized, weighing these advantages and disadvantages and taking the patients' preferences into account. This was recognized in the most recent update of the KDOQI guidelines, published in 2020 [40]. Rather than focusing on a 'fistula first' target, an individualized Life-Plan should be made, of which the choice of VA is an important part.

It is clear that the perfect VA does not exist, but that the demands placed on them will only increase in the future with advances such as the wearable kidney and the shift towards home hemodialysis, making this field of research of vital importance for the future success of treatment of patients.

References

1. Rothuizen TC, Wong C, Quax PHA, van Zonneveld AJ, Rabelink TJ, Rotmans JI. Arteriovenous access failure: more than just intimal hyperplasia? Nephrol Dial Transplant. 2013 May 1;28(5):1085–92.
2. Juncos JP, Grande JP, Kang L, Ackerman AW, Croatt AJ, Katusic ZS, et al. MCP-1 Contributes to Arteriovenous Fistula Failure. J Am Soc Nephrol. 2011 Jan;22(1):43–8.
3. Bezhaeva T, Wong C, de Vries MR, van der Veer EP, van Alem CMA, Que I, et al. Deficiency of TLR4 homologue RP105 aggravates outward remodeling in a murine model of arteriovenous fistula failure. Sci Rep. 2017 Dec 31;7(1):10269.
4. Kuwahara G, Hashimoto T, Tsuneki M, Yamamoto K, Assi R, Foster TR, et al. CD44 Promotes Inflammation and Extracellular Matrix Production During Arteriovenous Fistula Maturation. Arterioscler Thromb Vasc Biol. 2017 Jun;37(6):1147–56.
5. Juncos JP, Tracz MJ, Croatt AJ, Grande JP, Ackerman AW, Katusic ZS, et al. Genetic deficiency of heme oxygenase-1 impairs functionality and form of an arteriovenous fistula in the mouse. Kidney Int. 2008 Jul;74(1):47–51.
6. Shiu YT, Rotmans JI, Geelhoed WJ, Pike DB, Lee T. Arteriovenous conduits for hemodialysis: How to better modulate the pathophysiological vascular response to optimize vascular access durability. Am J Physiol - Ren Physiol. 2019 Feb 20;316(5):F794–806.
7. Stirbu O, Gadalean F, Pitea IV, Ciobanu G, Schiller A, Grosu I, et al. C-reactive protein as a prognostic risk factor for loss of arteriovenous fistula patency in hemodialyzed patients. J Vasc Surg. 2019 Feb 18;70(1):208–15.
8. Martinez L, Tabbara M, Duque JC, Selman G, Falcon NS, Paez A, et al. Transcriptomics of Human Arteriovenous Fistula Failure: Genes Associated With Nonmaturation. Am J Kidney Dis. 2019 Feb 27;74(1):73–81.
9. Lookstein RA, Haruguchi H, Ouriel K, Weinberg I, Lei L, Cihlar S, et al. Drug-Coated Balloons for Dysfunctional Dialysis Arteriovenous Fistulas. N Engl J Med. 2020 Aug 20;383(8):733–42.
10. Martinez L, Duque JC, Tabbara M, Paez A, Selman G, Hernandez DR, et al. Fibrotic venous remodeling and nonmaturation of arteriovenous fistulas. J Am Soc Nephrol. 2018 Mar 1;29(3):1030–40.

11. Hernandez DR, Wei Y, Andreopoulos F, Vazquez-Padron RI. Local Delivery of beta-aminopropionitrile improves arteriovenous fistula maturation and remodeling. FASEB J. 2017;31(1 Supplement 1):1078.2-1078.2.
12. Bleyer AJ, Scavo VA, Wilson SE, Browne BJ, Ferris BL, Ozaki CK, et al. A randomized trial of vonapanitase (PATENCY-1) to promote radiocephalic fistula patency and use for hemodialysis. J Vasc Surg. 2019 Feb;69(2):507–15.
13. Wasse H, Huang R, Long Q, Zhao Y, Singapuri S, McKinnon W, et al. Very high-dose cholecalciferol and arteriovenous fistula maturation in ESRD: A randomized, double-blind, placebo-controlled pilot study. J Vasc Access. 2014;15(2):88–94.
14. Irish AB, Viecelli AK, Hawley CM, Hooi L-S, Pascoe EM, Paul-Brent P-A, et al. Effect of Fish Oil Supplementation and Aspirin Use on Arteriovenous Fistula Failure in Patients Requiring Hemodialysis: A Randomized Clinical Trial. JAMA Intern Med. 2017 Feb 1;177(2):184–93.
15. Field M, McGrogan D, Marie Y, Joinson M, Andujar C, Dutton M, et al. Randomized clinical trial of the use of glyceryl trinitrate patches to aid arteriovenous fistula maturation. Br J Surg. 2016 Sep 1;103(10):1269–75.
16. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA. 2008 May 14;299(18):2164–71.
17. Fontseré N, Mestres G, Yugueros X, López T, Yuguero A, Bermudez P, et al. Effect of a postoperative exercise program on arteriovenous fistula maturation: A randomized controlled trial. Hemodial Int. 2016 Apr 1;20(2):306–14.
18. Wilschut ED, Rotmans JI, Bos EJ, van Zoest D, Eefting D, Hamming JF, et al. Supervised preoperative forearm exercise to increase blood vessel diameter in patients requiring an arteriovenous access for hemodialysis: Rationale and design of the PINCH trial. J Vasc Access. 2018;19(1):84–8.
19. Sullivan B, Desai S, Singh TM, Mitra A. Early application of an intermittent pneumatic compression device assists dilation of radiocephalic fistulas. J Vasc Access. 2019 Mar 1;20(2):146–52.
20. Lin CC, Yang WC, Chen MC, Liu WS, Yang CY, Lee PC. Effect of far infrared therapy on arteriovenous fistula maturation: An open-label randomized controlled trial. Am J Kidney Dis. 2013 Aug;62(2):304–11.

21. Shahverdyan R, Meyer T, Matoussevitch V. Patency and functionality of radiocephalic arteriovenous fistulas with an external support device (VasQ™): Real-world single-center experience. J Vasc Access. 2020 Feb 6;112972982090459.
22. Karydis N, Bevis P, Beckitt T, Silverberg D, Halak M, Calder F. An Implanted Blood Vessel Support Device for Arteriovenous Fistulas: A Randomized Controlled Trial. Am J Kidney Dis. 2020 Jan 1;75(1):45–53.
23. Lok CE, Allon M, Moist L, Oliver MJ, Shah H, Zimmerman D. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). J Am Soc Nephrol. 2006 Nov;17(11):3204–12.
24. Farrington CA, Robbin ML, Lee T, Barker-Finkel J, Allon M. Early predictors of arteriovenous fistula maturation: A novel perspective on an enduring problem. J Am Soc Nephrol. 2020 Jul 1;31(7):1617–27.
25. Caroli A, Manini S, Antiga L, Passera K, Ene-Iordache B, Rota S, et al. Validation of a patient-specific hemodynamic computational model for surgical planning of vascular access in hemodialysis patients. Kidney Int. 2013 Dec;84(6):1237–45.
26. Zonnebeld N, Huberts W, van Loon MM, Delhaas T, Tordoir JHM. Preoperative computer simulation for planning of vascular access surgery in hemodialysis patients. J Vasc Access. 2017 Mar 6;18(Suppl. 1):118–24.
27. Zonnebeld N, Tordoir JHM, van Loon MM, de Smet AAEA, Huisman LC, Cuypers PWM, et al. Pre-operative Patient Specific Flow Predictions to Improve Haemodialysis Arteriovenous Fistula Maturation (Shunt Simulation Study): A Randomised Controlled Trial. Eur J Vasc Endovasc Surg. 2020 Jul 1;60(1):98–106.
28. Lee T, Thamer M, Zhang Y, Zhang Q, Allon M. Outcomes of Elderly Patients after Predialysis Vascular Access Creation. J Am Soc Nephrol. 2015 Dec 1;26(12):3133–40.
29. Farrington C, Lee TC. The New Age of Vascular Access: Choosing the Right Access for the Right Reason in Older Hemodialysis Patients [Internet]. Vol. 76, American Journal of Kidney Diseases. W.B. Saunders; 2020. p. 457–9.
30. Link DK, Saxena R. The right patient, the right treatment, the right access and the right time [Internet]. Vol. 21, Advances in Chronic Kidney Disease. W.B. Saunders; 2014. p. 360–4.
31. Hicks CW, Bae S, Pozo ME, DiBrito SR, Abularrage CJ, Segev DL, et al. Practice patterns in arteriovenous fistula ligation among kidney transplant recipients in the United States Renal Data Systems. J Vasc Surg. 2019 Sep 1;70(3):842-852.e1.

32. Bardowska K, Letachowicz K, Kamińska D, Kusztal M, Gołębiowski T, Królicki T, et al. The attitude of kidney transplant recipients towards elective arteriovenous fistula ligation. Dor FJ, editor. PLoS One. 2020 Jul 2;15(7):e0234931.
33. Rao NN, Stokes MB, Rajwani A, Ullah S, Williams K, King D, et al. Effects of Arteriovenous Fistula Ligation on Cardiac Structure and Function in Kidney Transplant Recipients. Circulation. 2019 Jun 18;139(25):2809–18.
34. Lok C, Rajan DK, Clement J, Kiaii M, Sidhu R, Thomson K, et al. Endovascular Proximal Forearm Arteriovenous Fistula for Hemodialysis Access: Results of the Prospective, Multicenter Novel Endovascular Access Trial (NEAT). Am J Kidney Dis. 2017 Oct 1;70(4):486–97.
35. Arnold RJG, Han Y, Balakrishnan R, Layton A, Lok CE, Glickman M, et al. Comparison between Surgical and Endovascular Hemodialysis Arteriovenous Fistula Interventions and Associated Costs. J Vasc Interv Radiol. 2018 Nov 1;29(11):1558-1566.e2.
36. Gage SM, Lawson JH. Bioengineered hemodialysis access grafts [Internet]. Vol. 18, Journal of Vascular Access. Wichtig Publishing Srl; 2017. p. S56–63.
37. Lawson JH, Glickman MH, Ilzecki M, Jakimowicz T, Jaroszynski A, Peden EK, et al. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: Two phase 2 single-arm trials. Lancet. 2016 May 14;387(10032):2026–34.
38. Geelhoed WJ, Moroni L, Rotmans JI. Utilizing the Foreign Body Response to Grow Tissue Engineered Blood Vessels in Vivo. J Cardiovasc Transl Res. 2017 Apr 1;10(2):167–79.
39. Geelhoed WJ, van der Bogt KEA, Rothuizen TC, Damanik FFR, Hamming JF, Mota CD, et al. A novel method for engineering autologous non-thrombogenic in situ tissue-engineered blood vessels for arteriovenous grafting. Biomaterials. 2020 Jan 1;229:119577.
40. Lok CE, Huber TS, Lee T, Shenoy S, Yevzlin AS, Abreo K, et al. KDOQI Clinical Practice Guideline for Vascular Access: 2019 Update. Am J Kidney Dis. 2020 Apr 1;75(4):S1–164.

Chapter 9

Samenvatting in het Nederlands

Curriculum vitae

List of publications

Dankwoord

Samenvatting in het Nederlands

De nieren zijn onmisbaar voor het uitscheiden van vocht en afvalstoffen en reguleren veel processen in het lichaam, zoals wordt beschreven in **hoofdstuk 1**. Veel voorkomende aandoeningen zoals diabetes en hoge bloeddruk kunnen de nierfunctie onherstelbaar beschadigen. Als de nieren falen, kunnen patiënten aangewezen zijn op nierfunctie-vervangende behandelingen, zoals hemodialyse. Bij hemodialyse wordt het bloed van de patiënt gereinigd door een dialyse-apparaat. Voor deze behandeling is een betrouwbare toegang tot de bloedbaan absoluut noodzakelijk.

Er zijn drie vormen van vaattoegang. De centraal-veneuze catheter is een kunststof slang die in de halsader wordt ingebracht en een permanente verbinding tussen de patiënt en 'de buitenwereld' vormt. Infecties zijn hierbij een regelmatig geziene complicatie. De arterioveneuze graft is een kunststof slang die onderhuids tussen een slagader en een ader wordt ingebracht en vervolgens bij elke dialysebehandeling kan worden aangeprikt. Ook hierbij treden infecties op en worden vaker bloedstolsels in de graft gezien, waarvoor heroperaties nodig kunnen zijn.

De focus van dit proefschrift is de arterio-veneuze shunt, een vorm van vaattoegang waarbij de slagader en ader direct aan elkaar worden verbonden, waarna een grote hoeveelheid bloed door de shunt stroomt. De ader kan vervolgens veelvuldig worden aangeprikt voor de dialysebehandelingen. Bij het aanleggen van een shunt wordt, afgezien van enkele hechtdraden, geen kunstmateriaal gebruikt, wat de kans op infecties kleiner maakt. Ook blijft een shunt vaak lang functioneren. Een shunt wordt meestal aangelegd op de onderarm of de bovenarm. Een voordeel van de shunt op de onderarm is een veelal niet te hoge bloedstroom en het bewaren van de mogelijkheid om een toekomstige shunt alsnog op de bovenarm aan te leggen.

Een nadeel van de shunt is echter de fase van maturatie. Na het aanleggen van de shunt, moet deze 'rijpen'. De ader moet in diameter groeien, waarbij ook de bloedstroom toeneemt. Dit proces vindt niet altijd ongehinderd plaats en aanvullende chirurgische ingrepen of radiologische behandelingen via de bloedbaan kunnen nodig zijn. We spreken dan van nonmaturatie. Ondanks alle inspanningen faalt een deel van de shunts alsnog, voordat deze ooit kon worden gebruikt voor hemodialyse.

In **hoofdstuk 2** beschrijven we een retrospectieve cohortstudie waarin patiënten zijn onderzocht bij wie een shunt of graft werd aangelegd. We namen waar dat van de shunts op de onderarm, 24% faalde alvorens voor dialyse te kunnen worden gebruikt. Voor de shunts op de bovenarm

was dit 11% en voor de grafts slechts 6%. Omdat en shunt op de onderarm de hierboven genoemde nadelen van een graft of shunt op de bovenarm niet heeft, is het nuttig te kunnen voorspellen of een shunt op de onderarm zal falen, nog voordat deze wordt aangelegd. We ontwikkelden een statistisch model waarbij een kleine diameter van de ader, vrouwelijk geslacht, perifeer vaatlijden en hersenvaatlijden voorspellers waren voor nonmaturatie van een shunt op de onderarm. Helaas bleek dit model niet nauwkeurig genoeg om voor een individuele patiënt te voorspellen dat een dergelijke shunt zeker zal falen.

In **hoofdstuk 3** bekeken we de uitkomsten in dit cohort op de lange termijn. Hier bleek dat shunts op zowel de boven- als onderarm, als ze niet gefaald zijn door nonmaturatie, inderdaad langer functioneren. Als we alleen kijken naar de vaattoegangen die bruikbaar werden voor dialyse, was drie jaar was 83% van de shunts en 72% van de grafts nog bruikbaar. Als we echter ook de direct gefaalde vaattoegangen meenemen, is dit na 1 jaar voor shunts aan de onderarm met 62% beduidend lager dan voor shunts aan de bovenarm (74%) en grafts (69%). Ook in dit onderzoek stelden we vast dat er bij grafts meer infecties optraden en meer aanvullende behandelingen nodig waren om de graft bruikbaar te houden.

Hoofdstuk 4 beschrijft de opzet van de LIPMAT-studie, een vergelijkend onderzoek waarin patiënten deelnemen die een nieuwe shunt op de onderarm kregen. We veronderstelden dat ontsteking de shuntrijping tegenhoudt en dat het remmen van deze ontsteking de shuntrijping ten goede komt. De helft van de patiënten behandelden we daarom met een ontstekingsremmer, liposomaal prednisolon. De andere helft van de patiënten werd behandeld met placebo, een onwerkzaam infuus. Het resultaat beoordeelden we met een echografisch onderzoek en we registreerden of de shunt uiteindelijk bruikbaar bleek voor dialyse.

De resultaten van de LIPMAT-studie worden in **hoofdstuk 5** gepresenteerd. De patiënten bleken de behandeling met liposomaal prednisolon goed te verdragen. De uitkomsten van de shunts waren in beide groepen vergelijkbaar. Na zes weken was de diameter van de shunt 3.9 mm in de placebo-groep en 3.7 mm in de behandelde groep. Ook de bloedstroom verschilde niet significant, evenals de uiteindelijke bruikbaarheid: functionele nonmaturatie trad op in 23% in de placebo-groep en 13% in de behandelde groep.

Een nadeel van shunts en grafts wordt besproken in **hoofdstuk 6**. Aangezien bij deze vaattoegangen een verbinding tussen een slagader en een ander wordt gemaakt, stroomt er dagelijks vaak meer dan 1000 liter bloed door de shunt. Deze bloedstroom moet door het hart

worden opgebracht, terwijl veel dialysepatiënten lijden aan hart- en vaatziekten. Deze combinatie kan leiden tot hartfalen, een ongunstig verhoogde bloeddruk in de longen en een ongunstige verdikking van de hartspier. In dit hoofdstuk is een literatuuronderzoek verricht, waaruit we concluderen dat het opheffen van een shunt mogelijk leidt tot een verbetering van de hartspierdikte en de longbloeddruk. Dit is echter nog niet onomstotelijk vastgesteld in gerandomiseerde onderzoeken.

Als een patiënt een succesvolle niertransplantatie heeft ondergaan, is de shunt voor lange tijd niet meer nodig. In **hoofdstuk 7** onderzoeken we met een vragenlijstonderzoek of artsen een shunt dan liever opheffen of behouden. We ontvingen 585 reacties, waaruit bleek dat artsen een verminderde hartfunctie en een hogere bloedstroom door de shunt beschouwen als redenen om de shunt op te heffen. Er waren echter veel verschillende meningen. Hieruit blijkt dat er meer onderzoek nodig is om duidelijkheid te krijgen over de werkelijke voordelen van het opheffen van deze shunts.

Tenslotte vatten we in **hoofdstuk 8** de bevindingen uit dit proefschrift samen en bespreken recent en lopend onderzoek op het gebied van vaattoegang. We concluderen dat de perfecte vaattoegang niet bestaat en dat samen met elke patiënt een individuele beslissing moet worden genomen, waarbij voor- en nadelen worden afgewogen. Met de vergrijzing van de samenleving en de nieuwe ontwikkelingen op het gebied van hemodialyse, wordt de betrouwbaarheid van de vaattoegang alleen nog maar relevanter en is er een belangrijke rol voor innovatief onderzoek op dit gebied.

Curriculum vitae

Bram Mattijs Voorzaat was born on November 29th, 1984 in Nieuwegein, the Netherlands. In 2004 he began his Medicine studies at the Leiden University, attending part of the curriculum at the Karolinska Institute in Stockholm, Sweden. During his studies he was active in AEGEE, an international student's association. With a keen interest in information technology, he coordinated projects in an ICT-company. In 2011, he graduated with honours and started his training to become a medical specialist in the Haga Hospital, The Hague, where he worked for four years as a medical doctor.

In 2015 he decided to pursue a career in Nephrology and began his PhD at the department of internal medicine at the Leiden University Medical Center, under the supervision of Joris Rotmans and Ton Rabelink. There he designed and conducted a retrospective study on vascular access outcomes. Later he designed and wrote the manuscript of the LIPMAT study, a multi-center randomized controlled trial aiming to improve vascular access maturation with a novel drug. In the following years, he worked on the enrolment and treatment of patients in this study, working closely together with surgeons, nephrologists, trial nurses and ultrasound technicians in the participating hospitals. During his PhD, he presented his research at several medical conferences, including two Vascular Access Society congresses, the Dutch Nephrology Days and the Kidney Week of the American Society of Nephrology.

He expects to finish his training as an internist-nephrologist late 2021. He then aims to work as a clinical physician and work on e-health solutions and the improvement of the healthcare process using information technology. It is his vision that ICT should help patients and healthcare professionals alike.

Bram lives in Berkel en Rodenrijs with his wife Veronique and their son Ben.

List of publications

1. **Voorzaat BM**, van Schaik J, Siebelink HM, Tordoir JH, Rotmans JI.
The pros and cons of preserving a functioning arteriovenous fistula after kidney transplantation.
The Journal of Vascular Access 2016; 17 (Suppl 1): S16-S22.

2. **Voorzaat BM**, van Schaik J, Crobach SL, van Rijswijk CS, Rotmans JI.
Alpha-1 antitrypsin deficiency presenting with MPO-ANCA associated vasculitis and aortic dissection.
Case Reports in Medicine 2017; 8140641.

3. **Voorzaat BM**, van Schaik J, van der Bogt KE, Vogt L, Huisman L, Gabreëls BA, van der Meer IM, Statius van Eps RG, Eefting D, Weijmer MC, Groeneveld HO, van Nieuwenhuizen RC, Boom H, Verburgh CA, van der Putten K, Rotmans JI.
Improvement of radiocephalic fistula maturation: rationale and design of the Liposomal Prednisolone to Improve Hemodialysis Fistula Maturation (LIPMAT) study - a randomized controlled trial
The Journal of Vascular Access 2017; 18 (Suppl 1): S114-S117.

4. **Voorzaat BM**, van der Bogt KEA, Janmaat CJ, van Schaik J, Dekker FW, Rotmans JI; Dutch Vascular Access Study Group.
Arteriovenous fistula maturation failure in a large cohort of hemodialysis patients in the Netherlands.
World Journal of Surgery 2018: 42, 1895–1903

5. Bezhaeva T, de Vries MR, Geelhoed WJ, van der Veer EP, Versteeg S, van Alem CMA, **Voorzaat BM**, Eijkelkamp N, van der Bogt KE, Agoulnik AI, van Zonneveld AJ, Quax PHA, Rotmans JI.
Relaxin receptor deficiency promotes vascular inflammation and impairs outward remodeling in arteriovenous fistulas.
The FASEB Journal 2018; 32 (11): 6293-6304.

6. **Voorzaat BM**, Janmaat CJ, Wilschut ED, van der Bogt KE, Dekker FW, Rotmans JI.
No consensus on physicians' preferences on vascular access management after kidney transplantation: Results of a multi-national survey
The Journal of Vascular Access 2019; 20 (1): 52-59.

7. **Voorzaat BM**, Janmaat CJ, van der Bogt KEA, Dekker FW, Rotmans JI; on behalf of the Vascular Access Study Group.
Patency outcomes of arteriovenous fistulas and grafts for hemodialysis access: a trade-off between nonmaturation and long-term complications
Kidney 360 2020; 1 (9): 916-924.

8. **Voorzaat BM**, van der Bogt KEA, Bezhaeva T, van Schaik J, Eefting D, van der Putten K, van Nieuwenhuizen RC, Groeneveld JO, Hoogeveen EK, van der Meer IM, Statius van Eps RG, Vogt L, Huisman L, Gabreëls BATF, Boom H, Verburgh CA, Boon D, Metselaar JM, Weijmer MC, Rotmans JI.
A randomized trial of liposomal prednisolone (LIPMAT) to enhance radiocephalic fistula maturation: A pilot study
Kidney International Reports 2020; 5: 1327–1332.

9. Nauta L, **Voorzaat BM**, Rotmans JI, Ghariq E, Urlings T, van der Bogt KEA, van der Linden E.
Endovascular salvage of non-maturing autogenous arteriovenous fistulas by using angioplasty and competitive vein embolization
The Journal of Vascular Access 2020; 21 (5): 615-622.

Dankwoord

Vijf jaar geleden begon ik, toen nog zonder enige onderzoekservaring, aan mijn promotieonderzoek in het LUMC. Het was me meteen duidelijk dat onderzoek iets is dat je samen als team doet, niet alleen. Graag wil ik iedereen bedanken die mij tijdens dit onderzoek heeft geholpen.

Allereerst Joris, bedankt voor je eindeloze inzet en geduld tijdens onze samenwerking. Tijdens onze vele overlegmomenten prikkelde je me altijd om dieper over alles na te denken en slaagde je er telkens in me overal het maximale uit te laten halen. Tijdens het onderzoek had ik het niet altijd even makkelijk en dat voelde je haarfijn aan. Bedankt voor het voorbeeld dat je voor me bent, zowel in de kliniek als in het onderzoek. Ik heb enorme bewondering voor hoe je het allemaal klaarspeelt.

Ton, dank je voor je goede commentaar op mijn werk. Het was goed je down-to-earth mening over dingen te horen.

Koen, je bent een werkelijke kunstenaar in je werk. Je hulp en inzichten waren onmisbaar. Bedankt voor de fijne samenwerking!

Cynthia, bedankt voor je tomeloze inzet en alle gezellige overlegjes. Je enthousiasme voor de epidemiologie is aanstekelijk en als geen ander kon je de moeilijke materie goed uitleggen.

Friedo, zonder jouw hulp waren we nergens. Academisch waar het kan, praktisch waar het moet, de ideale combinatie. Ook bleef je altijd geduldig, als we weer eens iets wilden doen dat statistisch eigenlijk niet kon.

Bart, je bent een voorbeeld. Hoe je vanuit het academisch onderzoek je bedrijf hebt opgezet. Hoe veel er ook op je af komt, je houdt alle details piekfijn in de gaten. Bedankt voor al je hulp.

Wouter, wat hebben wij veel nerdy momentjes gehad onder het genot van de C7-koffie! Als echte *gadgeteers* hadden we telkens weer nieuwe ideeën. Bedankt dat je altijd voor me klaarstond.

Carla, jouw droge humor is ongeëvenaard en je hebt je hart op je tong. Ik heb altijd van je aanwezigheid genoten.

Reshma, wat was het leuk om jou na al die jaren opnieuw op de werkvloer te zien, en weer met je samen te werken.

Comrade Taya. I always admire your chill, hippie outlook on life.

Anton Jan, Hetty, Cees en alle anderen bij het Einthoven Lab. Bedankt voor de vele gezellige momenten. De meetings met jullie waren de ideale brug tussen klinisch en preklinisch onderzoek. Altijd leuk en uitdagend.

Carolien en ChunYu, jullie geweldige preklinische werk heeft al het vervolgonderzoek mogelijk gemaakt.

Iedereen op C7, D2, D3 en het eilandjeslab, jullie brengen altijd leven in de brouwerij. Bij elke lunch en elke meeting was er een bijzonder groepsgevoel.

Redouan, Marianne en Arnelle. Zonder jullie zou C7 niet bestaan. Jullie doen fantastisch werk en zijn ontzettend fijne mensen.

Alle verpleegkundigen, studenten, assistenten, nefrologen en chirurgen die hebben meegewerkt met de LIPMAT en retrospectieve studie. Bedankt voor jullie inzet en de warme ontvangst in al jullie ziekenhuizen. We hebben bergen werk verzet en ik ben ieder van jullie even dankbaar.

De patiënten die hebben deelgenomen aan de LIPMAT-studie. We hebben veel van jullie gevraagd en belangeloos hebben jullie je ingezet voor dit belangrijke onderzoek, terwijl er al zo veel op jullie af kwam. Ik weet dat dat niet vanzelfsprekend is en ben jullie allen dankbaar.

Véronique, bedankt voor alles. Lieve Ben, jouw geboorte was het grootste hoogtepunt en ik geniet elke dag van je.