Vascular access in hemodialysis: an ongoing search for improvement

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Vascular access in hemodialysis: an ongoing search for improvement

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(met een samenvatting in het Nederlands)

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Chapter 1

Introduction and outline of thesis

History

"As we did not know at all how our first patient would react to the dialysis we started with repeatedly dialyzing small proportions of blood. In the end we succeeded in keeping the percentage of urea at the same level for 26 days, after that no serviceable veins were available" [1]. The 29-year old female patient suffering from malignant hypertension died 1 week after her last dialysis treatment. This text fragment by the Dutch physician Willem Kolff and co-workers, published in 1944, was not only part of the first report of successful hemodialysis treatment in humans, it also described the crucial importance of an adequate access to the blood circuit that is required for chronic hemodialysis.

It took another 16 years before Quinton and Scribner introduced the first permanent vascular access: the Scribner shunt [2]. This device consisted of 2 Teflon® tubes connecting the patient to the dialyser; one tube was inserted into a suitable peripheral artery and one into a suitable vein. After treatment, the circulatory access was kept open by connecting the two tubes outside the body using a small U-shaped Silastic device over a stainless steel plate. The major disadvantages of Scribner shunts were high thrombosis and infection rates resulting in a limited shunt and hence patient life span.

In 1966, Brescia and Cimino solved the blood access problem with a surgically created arteriovenous fistula (AVF) between the radial artery and a vein [3]. This new vascular access was able to deliver flow rates of 250-300 mL/min for unlimited intervals. Results were satisfactory, 13 AVFs (87%) functioned without any complication and two failed before cannulation. The patients were relatively young (mean 40 years) and all but one had chronic glomerulonephritis as primary diagnosis for renal failure [3]. Nowadays, the Brescia-Cimino (radio-cephalic) AVF is still the preferred type of vascular access [4, 5]. Other common native variations are brachiocephalic, brachiobasilic and perforating vein AVFs in the elbow and upper arm [6-9].

Due to inclusion of overweight and obese end-stage renal disease (ESRD) patients as well as ESRD patients with insufficiently sized or stenotic vessels, AVF creation did not always result in a vascular access with sufficient access blood flow for efficient hemodialysis treatment. Hence, the arteriovenous graft (AVG) was introduced in order to create an artificial conduit for cannulation. Saphenous vein grafts, bovine heterografts, homologous vein grafts and human umbilical vein grafts have all been used for hemodialysis purposes in the past [10-15]. However, the expanded polytetrafluoroethylene (ePTFE) graft, introduced in 1976 [16], is the most widely used graft today. Alternative synthetic materials such as plasma tetrafluoroethylene or polyurethane have not proven to be superior to ePTFE [17-20].

Nowadays, the recommended permanent vascular accesses are, in order of preference: the wrist (radio-cephalic) fistula, the elbow (brachio-cephalic) fistula, the transposed brachial-basilic fistula, followed by forearm loop grafts, upper arm grafts or, if all upper arm sites are exhausted, chest wall or leg grafts [4]. Use of long term central venous catheters is discouraged.

Demographics & current guidelines

During the past three decades a number of striking changes have occurred in the American end-stage renal disease population [21]. The number of incident ESRD patients requiring renal replacement therapy (RRT) had increased more than four fold from 76.4/million population in 1980 to 342.4/million in 2004 [21]. During the same period, mean patient age at start of ESRD therapy had increased from 53 to 63 years, gender distribution did not materially change (approximately 55% males), but the distribution of the primary causes of ESRD altered dramatically [21]. In 1980, 18% of ESRD was caused by hypertension, 16% by glomerulonephritis and 15% by diabetes. In 2004, hypertension had almost doubled to 30% and diabetes had tripled to 44%. In contrast, glomerulonephritis had decreased to 8%. In view of the ongoing epidemic nature of diabetes [22] this development is likely to continue in the future.

The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) started a similar registry in 1998. In 2004, the level of incident ESRD patients in Europe varied from 75.3/million in Iceland to 176.4/million in Greece. In The Netherlands, the number of incident ESRD patients increased from 84.1/million in 1998 to 95.9/million in 2004. Interestingly, the U.S.A. was already at the 2004-Dutch incidence level already in 1982 (95/million).

From 1998 to 2004, hemodialysis has increasingly been used as treatment modality in both incident and prevalent ESRD patients in The Netherlands [23]. Mean age increased from 58 to 61 years and gender distribution remained unchanged (approx. 62% males) [23]. Diabetes and hypertension as primary cause of ESRD had increased (from 13 to 17.5% and from 11 to

14.5%, respectively), whereas glomerulonephritis had decreased from 13 to 9%.

The hemodialysis population is not only getting older and more diabetic, they are also more likely to have co-morbidity such as ischemic heart disease and peripheral vascular disease [24, 25]. As a result, these patients often have poor vessels for native fistula creation with an increased risk of insufficient access blood flow (<350-400 mL/min). As a consequence, the blood pump flow rate exceeds access blood flow and the upstream arterial needle draws downstream returned blood from the access. This phenomenon is called 'recirculation' and leads to inadequate delivery of dialysis. Graft placement seems attractive in such situations [26, 27].

Once functional for dialysis, AVFs have better primary and secondary patency rates than grafts [28]. However, due to high primary AVF failure rates [29], one year secondary patency of forearm fistulas is lower than grafts [30-33], while upper arm fistulas have a somewhat better access survival than grafts [34-36]. Despite more or less comparable access survival rates, the major advantage of fistulas over grafts is the lower frequency of complications and interventions [30, 32, 35-41]. In addition, infections occur much more often in grafts than in fistulas [30, 32, 34, 36, 38]. Therefore, both the guidelines of the National Kidney Foundation (NKF) and the Vascular Access Society recommend the arteriovenous fistula as first choice vascular access in hemodialysis [4, 42].

Practice pattern differences

Since the late 1980's, AVFs are used by 60-65% of the hemodialysis patients in the Netherlands [43, 44]. The Dialysis Outcomes and Practice Pattern Study (DOPPS), in which the Netherlands was not included, reported that an AVF was used by 80% of European (including France, Spain, Italy, Germany and the U.K.) and 24% of the American prevalent hemodialysis patients at the end of the previous decade [25]. The DOPPS study also showed that the percentage of AVF use in these different dialysis units displayed a great range among European (39-100%) and among American units (0-87%) [25]. Such results have also been found by others [45, 46]. Polkinghorne *et al.* recently showed geographical differences in vascular access placement patterns in Australia and New Zealand [47, 48]. There are no such European reports other than DOPPS.

Lower AVF prevalence levels have been related to demographic factors such as age, female gender and black ethnicity, as well as to co-morbid conditions like coronary artery disease (CAD), peripheral vascular disease (PVD), increasing body mass index (BMI) and diabetes as cause of ESRD [25, 45-50]. In addition, practice patterns such as the absence of pre-ESRD care, performance or assistance of access placement procedure by a surgical trainee, seizure of vein puncturing, method of modality choice and timing of referral are also related to the type of permanent vascular access placement [25, 50, 51]. Even after adjustment for the wide variety of risk factors significant variations in national access use still remain [45-49], suggesting an important role for local practice patterns.

Several reports have discussed the importance of AVF placement and provided points for consideration to adjust practice patterns [29, 52-54]. Implementation of guidelines has been shown to result in dramatic changes in access placement policy in American centers that were characterized by low fistula incidence and prevalence levels at baseline [55-59]. Decreased AVF maturation rates may challenge such programs [60], requiring further optimization of pre-operative vessel selection and surgical anastomosing techniques.

Insight in arteriovenous fistula functioning

After fistula creation, a period of 4-8 weeks is generally required to allow AVF development (‘maturation’) into a usable vascular access. Successful maturation is characterized by sufficient blood flow to perform adequate dialysis and by enough vein size to allow repetitive puncturing. The most crucial part in this process is the first 2-4 weeks after creation. In this period the greatest part of access flow increase is generated [61-63]. Current guidelines suggest that usable fistulae can be identified by the Rule of 6’s: access flow greater than 600 mL/min, diameter at least 6 mm, no more than 6 mm deep and discernable margins [4].

Early complications such as thrombosis and failure to mature result in huge AVF losses: 20 to even 50% [29]. Although this wide range is partly due to the fact that a clear definition of primary AVF failure has not yet been accepted [64], reduction of primary AVF failures can be expected to result in a significant increase in functional AVF use and consequently reduction of healthcare cost. Non-modifiable factors such as patient age, presence of cardiovascular disease and dependence on dialysis at time of access creation have been associated with lower probabilities of maturation [65]. Of the modifiable factors internal diameters of the artery and the vein [61, 63, 65-67], mean arterial pressure (MAP) and intraoperative doses of heparin have been associated with successful maturation [65].

After first cannulation, late thrombosis rate should be kept below 0.25 events per patientyear [5]. Access flow measurement is the method of choice to monitor fistula function and predict access failure [27, 68-70]. Tonelli *et al.* showed that access flow was positively associated with systolic blood pressure and overweight status, and inversely with diabetic status [71]. Presence of cardiovascular disease, utilization of catheters at HD initiation, and early cannulation (<15 days) have been found to be related to secondary AVF failure [72]. With regard to practice patterns, a relation between access patency and the operating surgeon has been suggested in a retrospective study, but the differences between surgeons was predominantly generated within the first months after surgery [73].

Further insight in characteristics of functional and dysfunctional AVFs may be valuable to optimize patient selection and vessel choice.

Arteriovenous graft stenosis

When all autogenous options for access placement have been exhausted, synthetic graft insertion is the action of choice [4]. Advantages of grafts over fistulas are the possibility to use the new vascular access within 2 weeks after surgery and low primary failure rates (5-15%, depending on graft configuration). The major disadvantage is the rather disappointing patency rates. One year primary and secondary patency rates are 40% and 65%, respectively [28]. Various graft modifications have been tested: 4-7 mm tapering, polyurethane composition instead of ePTFE, different manufacturers and a venous cuff [74-77]. None of them improved cumulative access survival.

The majority of graft failures are the result of stenosis formation within the first three centimeters of the venous anastomosis [78, 79]. These stenoses are caused by progressive intimal hyperplasia. Intimal hyperplasia (IH) is characterized by vascular smooth muscle cell proliferation, extracellular matrix deposition, and angiogenesis within the neointima and adventitia [80, 81], and develops predominantly in regions of low wall shear stress, so-called blood stagnation regions [82-85].

Arterial geometry is commonly three-dimensional [86]. This causes swirling of the blood flow [87, 88] as well as in-plane mixing and a relatively uniform distribution of wall shear stress, preventing flow stagnation, separation and flow instability [89]. Giordana *et al.* found that lower limb arterial bypass grafts are essentially two-dimensional [90], favouring extremes of wall shear stress and flow stagnation. Hypothetically, the same is applicable to AV grafts. Restoration of physiological-type swirling hemodynamics should then reduce IH formation and improve patency rates.

Treatment of AV graft stenosis

Although there is some controversy on prophylactic stenosis treatment for graft survival [91], abundant evidence is available that graft thrombosis will be reduced [92-96] and is therefore recommended by K/DOQI standards [4]. Percutaneous transluminal angioplasty (PTA) is a preferred method for graft salvaging. However, 6 month unassisted post-PTA patency varies from only 25 to 63% [79, 97-101].

Novel endovascular treatments have been developed to reduce the formation or recurrence of intimal hyperplasia. In a pilot study endovascular brachytherapy improved post-intervention primary patency but not 6 month secondary patency [102]. Use of a peripheral cutting balloon for stenotic or thrombosed grafts did not improve primary patency in comparison to standard PTA [103]. Stent placement may improve patency after acute PTA failure or in case of rapid restenosis or recoil [104, 105]. In a porcine model, no intimal hyperplasia was present at the venous anastomosis at 4 weeks after sirolimus-eluting stent deployment [106]. Further elaboration of this promising technique is required.

Cryoplasty is a novel therapy that combines conventional balloon angioplasty with cold thermal energy. Effects of cold therapy include a reduced elastic recoil, apoptosis of smooth muscle cells [107-109], and, in atherosclerotic arteries, an altered plaque response. In 5 arteriovenous grafts with rapidly recurring stenosis at the venous anastomosis, cryoplasty increased the intervention-free interval [110]. However, cryoplasty in AV grafts has not yet been tested in preclinical (animal) studies. An adequate treatment indication for cryoplasty use is not available. Further research on this technique is warranted.

Outline of the thesis

Since the end of the previous decade the K/DOQI guidelines and since 2003 also the guidelines of the Vascular Access Society, recommend AVF creation as first choice vascular access for hemodialysis treatment [4, 42, 111, 112]. Despite numerous reports on the importance of AVF use, the DOPPS study showed great international differences in vascular access placement patterns with low AVF prevalence rates in the U.S.A. and Europe [25]. Therefore, we described in **chapter 2** how current guidelines can be applied in practice and which actions should lead to increased AVF use and improved fistula survival.

In the Netherlands, prevalent AVF use in 2002-2003 was lower than in surrounding countries (59% vs. 74%) [113]. In order to increase native vascular access use we introduced the CIMINO (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment) program in 11 Dutch hemodialysis centers. In **chapter 3** we describe the introduction and outcomes of the CIMINO initiative. In a 22 dialysis centers control group the program was not presented.

Greatest improvements in AVF survival are to be obtained during the peri-operative phase. To get more insight in factors determining primary AVF failure, we conducted a large prospective study among 395 ESRD patients. Results are described in **chapter 4**.

The vascular access placement recommendations of the National Kidney Foundation Work Group are predominantly based on single center studies from the 1980’s and early 1990’s, and on studies that have excluded the phase between AVF creation and cannulation from patency calculations [4]. In **chapter 5** we describe current patency rates and factors associated with patency and access blood flow as obtained in a prospective, multicenter setting. Both patency rates and functional patency rates are included. **Chapter 6** describes the value of baseline access flow measurement (Qa) in relation to AVF function, the natural history of Qa after first successful cannulation and to what extent Qa is affected by patient characteristics and cardiovascular risk factors.

In **chapter 7** we tested a standard PTFE graft with a novel geometry for the first time in humans. The hypothesis was that the helical graft improved hemodynamics at the venous anastomosis reducing the trigger for intimal hyperplasia formation. Ultimately the new prosthesis should lead to improved patency rates.

Chapter 8 describes the results of a pilot study in 5 pigs testing preventative cryoplasty as treatment modality for intimal hyperplasia at the graft-vein anastomosis.

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Chapter 2

Dialysis access - guidelines for current practice

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Abstract

Current guidelines promote the use of the native arteriovenous fistula (AVF) as first choice access over grafts and central venous catheters. However, the prevalence of AVF use shows enormous differences of national, regional and local practice surveys, even after adjusting for demographics. In this review, we will briefly discuss these differences and present actions potentially improving outcome of vascular access care.

Introduction

The ideal vascular access for haemodialysis enables the dialysis staff to deliver adequate dialysis, has excellent patency with low complication rates, and is easy to create. In every day clinical practice 300-400 mL blood per min is required for the extracorporeal circuit in order to provide 'adequate' dialysis. This is only possible when the access blood flow is at least 400-500 mL/min. It is well accepted that the native arteriovenous fistula (AVF) meets best with these expectations.

In 1997, the K/DOQI Work Group issued evidence and opinion based guidelines as well as strategies for implementation to improve quality of life and overall outcome for haemodialysis patients [1]. The primary objectives of these guidelines are increasing the placement of native AV fistulae and detecting access dysfunction prior to access thrombosis. The Vascular Access Society (www.vascularaccesssociety.com) recently published clinical algorithms on access care. They show many similarities with earlier guidelines, but they emphasize the value of the preoperative duplex and the role of the interventional radiologist for fistula salvage [2].

Several studies have demonstrated striking regional differences in vascular access care practice [3-6]. The DOPPS study [6], which compared vascular access use at 145 dialysis units in the United States and 101 units in five European countries, reported that an AVF was used by 80% of European and 24% of the American prevalent haemodialysis patients. After adjusting for age, gender, body mass index, diabetic status, peripheral vascular disease, and angina, AVF versus graft use was still much higher in Europe than the United States [6]. Furthermore, the percentage of AVF use in these different dialysis units displayed a great range, varying from 39% to 100% in Europe (median 83%), and rates as low as 0% AVF use in some American dialysis units but as high as 87% in other facilities, (median 21%) [6] (Figure 1). These findings strongly suggest that a facility's practice is predominantly determined by local preferences and approaches.

In this review we will discuss factors affecting outcome of vascular access care and actions potentially improving outcome.

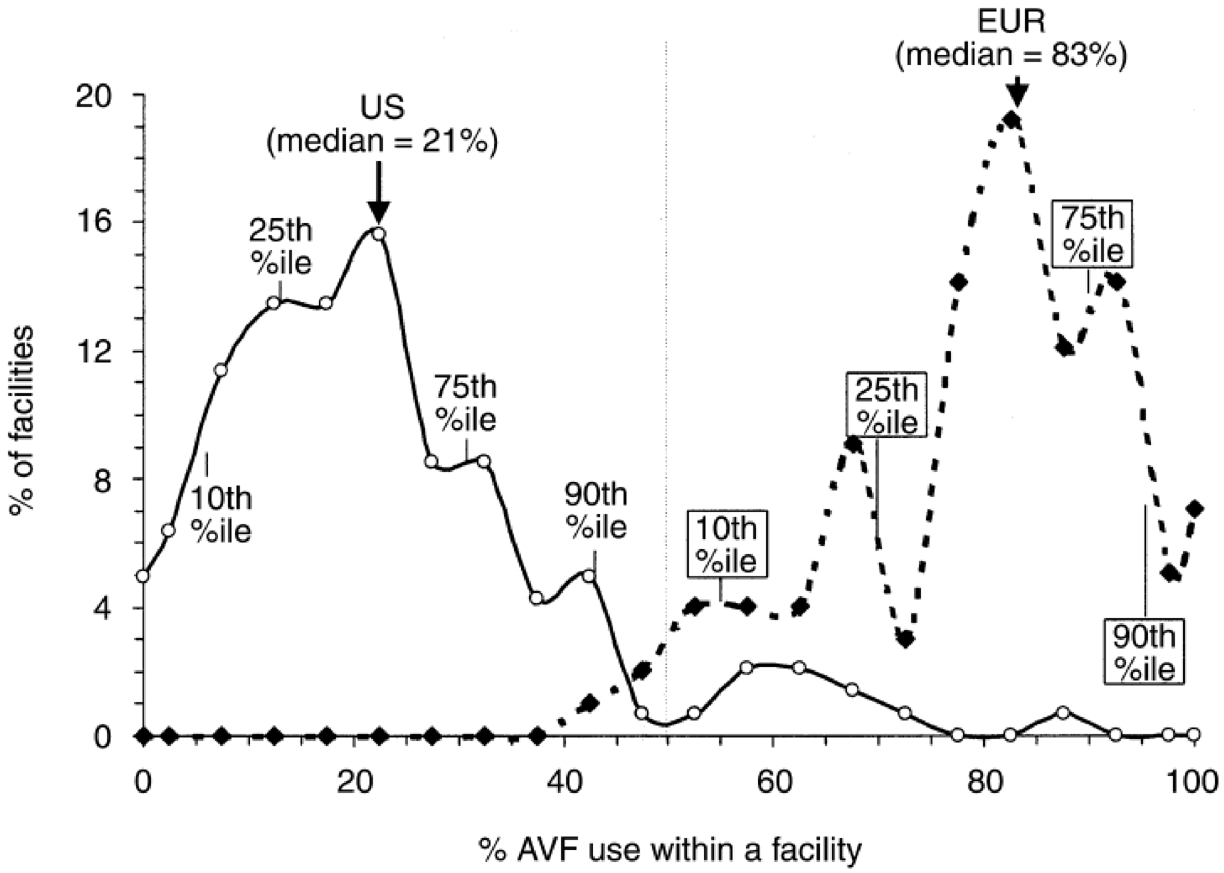

Fig. 1. Distribution of arteriovenous fistula (AVF) use among facilities within Europe (EUR) and the United States (US). The percent of patients using an AVF was determined for a cross-sectional sample of patients within each DOPPS dialysis unit in EUR and the US. The distribution of AVF use within facilities is shown separately for the US (—) and EUR (- - -), and is shown in increments of 5%. The following percentiles of each distribution are provided for the 10^{th}, 25^{th}, 50^{th} (median), 75^{th}, and 90^{th} percentiles (with permission from ref. 6, Blackwell Publishing, UK).

The need for change

Factors affecting quality and outcome of access care can be divided into non-modifiable and modifiable influences. The non-modifiable factors are patient characteristics such as age, diabetes mellitus and peripheral vascular disease. The modifiable factors, on the contrary, appear to be dependent on the willingness and motivation of decision makers and include the implementation of protocols, communication and strategies to meet quality of care standards (Table 1). Recently, recommendations have been presented on how to increase the percentage of prevalent AVFs and optimise surveillance and patency [7, 8].

Factors involved in vascular access care	
Non-modifiable	**Modifiable**
Sex	Local protocol different from DOQI/European guidelines
Peripheral vascular disease	Absence of a multidisciplinary team
Diabetes mellitus	CRF-patients starting dialysis over CVC or graft
Age	Absence of standard pre-operative duplex examination
Body Mass Index	AVF number and patency different from quality of care standards
	Absence of AVF quality control program
	No radiological interventions to assist patency in case of failure
	No secondary AVF creation in graft or catheter patients
	No feedback on outcome

Table. 1

Vascular access care is a classical example of multidisciplinary teamwork between nephrologists, vascular surgeons, interventional radiologists, ultrasound technicians, and dialysis nurses. To achieve the best outcome the team needs to agree on a set of goals, collaborate closely and maintain good mutual communication. A key player in this multidisciplinary approach is a dedicated access coordinator who acts as a liaison officer between the disciplines and schedules the meetings [9]. This person, who may be a member of the nursing staff, prospectively monitors vascular access outcomes and complications, and evaluates on practice patterns. During meetings he/she provides feedback to all decision-makers enabling them to adjust practice if necessary.

Timely referral may increase the percentage of patients starting haemodialysis treatment with AVFs instead of grafts or central venous catheters (CVC) [10]. Referral for access surgery should be within 6-12 months of anticipated start of dialysis, *i.e.* when glomerular filtration rate (GFR) drops below 25-20 mL/min. This allows ample time for access maturation or for additional procedures in case of primary failure.

Finding the best location for fistula placement starts with the selection of the appropriate vessels. Physical examination by an experienced vascular surgeon is indispensable but the addition of preoperative duplex examination has been proven to influence the choice of access placement and provides the vascular surgeon with valuable information [11]. A standardised examination of arteries should record internal diameters, Doppler waveform analysis and the sites of stenosis and occlusion. Veins are assessed for compressibility and internal diameters measured. Cut-off thresholds for internal diameters are still debated so that internal diameter alone cannot fully predict adequate remodelling but internal diameters of ≥ 2.0 mm for artery and vein for radiocephalic AVFs, and 3-4 mm for the vein for brachiocephalic or brachiobasilic AVFs are associated with adequate maturation, whereas smaller diameters may predict non-maturation [2].

Placement of a fistula can be a technically difficult and challenging procedure. It has been demonstrated that the type of access placement is associated with individual surgeon practice patterns [12]. The DOPPS study showed that AVF use was significantly less likely if surgery trainees assisted or performed vascular access placements [6]. Moreover, the odds ratio of AVF placement is more than three times greater in high volume centres (>30 access procedures per year) than in low volume centres (<10 access procedures per year) [12]. Thus, only experienced vascular surgeons who are willing to primarily place AVFs should construct new accesses.

A fistula is generally ready to be used within 4-6 weeks after placement but primary failure, *i.e*. early thrombosis and lack of maturation, occurs in 20-50% of AVFs [7]. Reported patency rates can be misleading because some investigators have specifically excluded AVFs that never matured, whereas others have included these primary failures, leading to comparable 1-year cumulative patency rates for AVFs and grafts. Despite these figures the major advantage of fistulas over grafts is a better long-term patency with lower incidences of complications and interventions once fully matured. The role of the interventional radiologist in salvaging the failing AVF is very important. Accessory vein ligation and angioplasty (PTA) of primary failures can result in a 68-79% 1-year assisted primary patency [13, 14]. Such additional interventions can convert a considerable proportion of primary non-functioning AVFs to functioning AVFs.

Patients with a functioning fistula (or graft) should have their access monitored regularly in order to predict complications. In grafts, access flow measurement seems to be the best method. A graft flow below 600 mL/min is associated with an increased risk of thrombosis [15]. Trend analysis by sequential access flow measurements has been proven to be even more effective [16, 17]. In AVFs, access flow below 600 mL/min does not necessarily predict thrombosis. The inability to provide a flow of 300-400 mL/min to the extracorporeal circuit, or the finding of poor dialysis adequacy, for instance quantified as urea reduction rates, may help to identify the AVF with insufficient flow.

Every patient with an AV graft or central venous catheter should be evaluated for secondary placement of an AVF. In a recent study, a considerable proportion of such patients were able to have a functioning secondary AVF created allowing the removal of a central venous catheter [18].

The outcome of surgical and radiological interventions should be reported using standard definitions [19], in order to compare results with quality of care standards and modify clinical practice if necessary. Actions potentially improving vascular access care are summarised in table 2.

Actions potentially improving AVF care
Commitment to adherence to K/DOQI/Vascular Access Society guidelines
Multidisciplinary and motivated access team
Dedicated vascular access coordinator
Timely referral to nephrologist and vascular surgeon
Vessel mapping prior to surgery referral
Experienced vascular surgeon willing to meet 'AVF only' expectations
Monitoring and surveillance programs
Acceptance that primary failures occur and need additional AVF interventions
Interventional radiologist performing patency assistance procedures
Secondary AVF creation in AV graft or catheter patients
Outcomes feedback and willingness to adapt to meet care standards

Table 2.

Initiatives for Improvement

The assimilation of recommendations and guidelines into clinical practice is only possible if all parties involved are willing and motivated to cooperate. Single centre experiences have shown that major improvements in practice patterns can be achieved [20] but large scale implementation projects are scarce so that vascular access distribution has remained roughly the same since appearance of the K/DOQI guidelines. In 2003, the United States National Vascular Access Improvement Initiative (NVAII) launched Fistula First (http://www.fistulafirst.org). This is a large national initiative that offers a set of tools for physicians and dialysis facilities in order to accelerate increasing AVF use in haemodialysis patients. Eleven change concepts guide the target groups step-by-step to best practice. In the Netherlands, the CIMINO-project (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment) was initiated as an effort to increase AVF use [21]. In this program vascular access teams are encouraged to adhere to current guidelines. A vascular access coordinator registers practice patterns in a newly developed database. In-centre outcome analysis may then show the need to improve access care in order to meet quality of care standards.

Summary

- Guidelines provide clear evidence based quality of care standards.
- Practice patterns show great variations.
- Modifiable factors affecting outcome of vascular access care are identified. (Table 1).
- Actions potentially improving outcome of care are identified (Table 2).
- Success is only possible if not only dialysis staff, but also surgeons and radiologists regard access care as their concern.

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Chapter 3

Accelerated increase of arteriovenous fistula use in hemodialysis centres: results of the multicentre CIMINO initiative

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Abstract

Background

In the Netherlands, arteriovenous fistulas (AVFs) are used in 60-65% of the haemodialysis patients and this compares poorly with the European average. A multicentre guidelines implementation programme, CIMINO, was initiated aiming at increasing the use of AVFs.

Methods

Physicians and dialysis staff in 11 participating centres (N = 1092 vascular accesses) were strongly and repeatedly advised to adhere to current guidelines with extra attention for pre-operative duplex examination and salvaging of failing and failed fistulae. Specially appointed access nurses prospectively registered all created vascular accesses using an internet-linked database. In 22 other centres (N = 1566 accesses) the CIMINO programme was not offered and they were considered the control group.

Results

On 1 January 2006, average follow up time of the CIMINO group and the control group were 13.3 months and 34.1 months, respectively. A total of 598 new vascular accesses (77% AVFs) were created in the CIMINO group. Prevalent AVF use increased from 58.5% (range: 31-79%) to 62.7% (range: 45-83%) in the CIMINO group and from 65.5% (range: 31-91%) to 67.3% (range: 42-91%) in the control group. The increase in AVF use per year was significantly quicker than in the control group ($P < 0.05$). Use of untunnelled catheters decreased whereas that of tunnelled catheters increased.

Conclusions

This initiative shows that a multicentre guidelines implementation programme results in an accelerated increase of AVF use in comparison to a time control group. These data suggest that the choice of access placement depends predominantly on centre specific factors.

Introduction

An ideal vascular access for haemodialysis allows repetitive puncturing at an access blood flow of at least 400-500 mL per min, and has excellent patency with low complication rates. It is well accepted that the native arteriovenous fistula (AVF) meets best with these expectations and therefore, it is the preferred type of vascular access according to the current guidelines [1, 2]. Numerous articles have emphasized the importance of AVF use and several reviews have addressed points for consideration how to increase AVF placement [3-5]. The Dialysis Outcomes and Practice Pattern Study (DOPPS), in which the Netherlands was not included, reported that an AVF was used by 80% of European and 24% of the American prevalent haemodialysis patients at the end of the previous decade [6]. Furthermore, the percentage of AVF use in these different dialysis units displayed a great range among European (39-100%) and among American units (0-87%) [6].

Since the late 1980’s, AVFs are used by 60-65% of the haemodialysis patients in the Netherlands [7, 8]. Moreover, a national survey we held in 2002-2003 displayed not only an unchanged percentage of AVF use (59%), but also a great range in both type of vascular access use (AVFs: 31-91% and grafts: 3-57%) and anatomical location. As an effort to increase AVF use, we initiated and implemented a multicentre guidelines implementation programme, CIMINO (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment), in 11 access centres in the Netherlands. Our goal was to achieve an increase of AVF use in the prevalent haemodialysis population. As a control group, we analyzed vascular access use in a large sample of dialysis centres in which our programme was not presented.

Subjects and methods

On 1 January 2003, a total of 3552 patients were on haemodialysis in the Netherlands (www.renine.nl). Information on the prevalent number of AVFs, (bio)grafts, tunnelled and untunnelled catheters was obtained in late 2002 and 2003, and included 2701 vascular accesses in 35 centres representing 76% of the entire Dutch haemodialysis population.

For logistical reasons, 12 of these centres were approached for participation in the CIMINO-programme in the central part of the Netherlands in 2004. Three centres were not interested in participation. Two centres, which did not contribute to the baseline data, volunteered resulting in 11 participating centres (two academic, 8 general hospitals and 1 other dialysis institution; total: N = 1092 accesses). The remaining 26 centres served as a control group.

Assessment of AVF use

In the control group, prevalent vascular access use as obtained at baseline in 2002 and 2003 was used for analysis. In the CIMINO group, access use was determined at each centre's individual programme starting date, the first centre on 1 May 2004 and the last on 1 July 2005.

In January 2006, nephrologists of the 26 non-CIMINO dialysis centres (four academic centres, 19 centres in general hospitals and 3 other dialysis institutions) were sent a questionnaire on prevalent haemodialysis access use. If this mailing remained unanswered for 1 month, a second mail was sent to the nursing staff of the dialysis units.

Guidelines implementation programme

In 2003, the Vascular Access Society presented the most recently updated guidelines on vascular access care by means of clearly structured flow charts supported by literature based evidence and expert opinions (www.vascularaccesssociety.org) [2]. Before the start of our programme, the investigators (H.J.H. and P.J.B.) visited all participating vascular access teams (VAT's) and presented a lecture on these 'European guidelines'. Furthermore, translated summaries were provided and the VAT's were encouraged to adhere to these guidelines during the CIMINO programme. All haemodialysis patients or patients with chronic renal failure (CRF) requiring a new permanent vascular access during this follow up period were included. The order of preference of access placement was 1) distal arm AVF, 2) proximal arm AVF, 3) basilic vein transposition or graft insertion, and 4) central venous catheter. It was advised to always perform a standard additional preoperative duplex examination. Furthermore, the caretakers were encouraged to attempt salvaging procedures for the failing and the failed fistula. In each centre a dedicated vascular access coordinator was appointed, 0.1 nurse full time equivalent, to register practice patterns in a newly developed internet-linked database. In-centre analysis allowed participating physicians to evaluate their own practice patterns during the entire project. Aggregate data were only available to the coordinating centre at the University Medical Centre Utrecht in Utrecht. Newsletters were sent regularly to update physicians and nurses on proceedings and progress.

Statistical analysis

Statistical analysis was carried out using SPSS 12.0 for Windows® (SPSS Inc., Chicago, IL, USA). The rate of change in AVF use was determined by subtraction of two time percentages divided by the follow up duration and expressed as annual changes. Linear regression, weighted by the prevalent number of haemodialysis patients at baseline, was used to estimate the slope of annual changes in AVF use in the CIMINO and control group. Ninety-five percent confidence intervals (95% CI) were calculated around estimates. When the slope estimate of the CIMINO group was outside the 95% CI around the estimate of the control group, the rates were considered statistically significantly different.

Results

Twenty-two non-CIMINO access centres (85%) responded to the 2nd questionnaire sent in early 2006, and were considered as control group. Baseline demographics of the entire Dutch haemodialysis population, the CIMINO group (*N* = 11 centres) and the control group (*N* = 22 centres) are shown in table 1.

	Netherlands	CIMINO	Control
Age [yrs]	62.1 ± 15.7	62.1 ± 15.2	62.0 ± 15.7
Male gender [%]	57.7	59.2	57.1
Primary diagnosis ESRD			
Glomerulonephritis [%]	13.6	14.2	13.8
Interstitial nephritis [%]	11.4	12.3	11.7
Cystic kidney disease [%]	9.8	10.3	9.9
Other congenital / hereditary [%]	2.1	2.0	2.2
Other multisystem diseases [%]	6.3	4.2	7.1
Renal vascular disease [%]	21.9	24.6	18.3
Diabetes mellitus [%]	15.6	15.3	14.0
Others [%]	4.9	3.7	5.4
Unknown [%]	14.4	13.5	17.7
Total no. of patients	3605	1034	1568

Table 1. Demographics and primary diagnoses of end-stage renal disease in the entire Dutch haemodialysis population, the CIMINO group (*N* = 11 centres) and the control group (*N* = 22 centres) on 1 January 2004

Prevalent AVF use increased from 65.5% to 67.3% in the control group, and from 58.5% to 62.7% in the CIMINO group (Table 2). Graft use decreased 4% in the CIMINO group but did not change in the control group. In both groups untunnelled catheter use decreased, from 11.4% to 5.3% in CIMINO and from 8.6% to 4.8% in the control group. Tunnelled catheter use increased 5.9% in CIMINO and 2.2% in the control group.
During this observation period, 598 new vascular accesses were created and included in the CIMINO group. Of these, 77% were fistulas, 14% were grafts and 9% catheters. Patient characteristics of incident patients in CIMINO are shown in table 3.

CIMINO	**Baseline**		**2006**	
	N	**[%]**	***N***	**[%]**
AVF	639	58.5	721	62.7
Graft	263	24.1	231	20.1
TC	66	6.0	137	11.9
UC	124	11.4	61	5.3
Total	1092	100	1150	100
Control	**Baseline**		**2006**	
	N	**[%]**	***N***	**[%]**
AVF	1026	65.5	1174	67.3
Graft	284	18.1	313	17.9
TC	122	7.8	175	10.0
UC	134	8.6	83	4.8
Total	1566	100	1745	100

Table 2. Prevalent distribution of types of vascular accesses in the CIMINO group and the control group at baseline and on 1 January 2006
N = absolute number of accesses. AVF = arteriovenous fistula, TC = tunnelled catheter, UC = untunnelled catheter

Further analysis of the CIMINO group showed that the range in prevalent AVF use varied from 31% to 79% at baseline (median: 64%) and from 45% to 83% in January 2006 (median: 66%). In the control group, the range of AVF use varied from 31% to 91% (median: 72%) at baseline and from 42% to 91% (median: 70%) in January 2006.

Interval corrected prevalence changes

On 1 January 2006, average follow up time of CIMINO and the control group were 13.3 months and 34.1 months respectively. In the CIMINO group, prevalent AVF use increased by 3.5% per year (range: -6.6% / yr. to 10.9% / yr.). During the implementation programme, graft use decreased 3.4% per year, tunnelled catheters increased 4.2% per year and untunnelled catheters decreased 4.3% per year. In the control group, fistula use increased by 1.2% per year (range: -5.7% / yr. to 12.4% / yr.), graft use decreased 0.2% per year, tunnelled catheter use increased 0.9% per year, and untunnelled catheter use decreased 1.9% per year.

Characteristic	
No. of permanent vascular accesses	598
No. of patients	461
Age [yrs]	64.6 ± 14.4
Male gender [%]	58
Previous RRT [%]	59
Duration of RRT prior to access placement [months]	14 ± 34
Previous coronary artery disease [%]	23
Previous peripheral vascular disease [%]	11
Previous cerebrovascular disease [%]	13
Caucasian ethnicity [%]	80
Current smoker [%]	20
BMI [kg/m²]	25.1 ± 4.5
Diabetes mellitus [%]	31
Diabetes as primary cause ESRD [%]	12

Table 3. Patient characteristics of incident patients in CIMINO

Means are depicted ± standard deviation. RRT = renal replacement therapy, BMI = body mass index, ESRD = end-stage renal disease.

Relation between AVF use at baseline and annual change in AVF use

Figure 1 shows the relation between prevalent AVF use at baseline and the annual change of AVF use in the CIMINO group (open circles; dashed line) and the control group (solid circles; solid line). The slope of the weighted regression line of the CIMINO group (β = -0.25) was outside of the 95% confidence interval of the slope the control group [-0.16 to -0.01], indicating an accelerated increase of AVF use in the CIMINO group.

Both lines pass the line of unchanged fistula use at ~75% at baseline. The CIMINO group showed an estimate increase in AVF use of 3.9% per year and the control group of 1.2% per year.

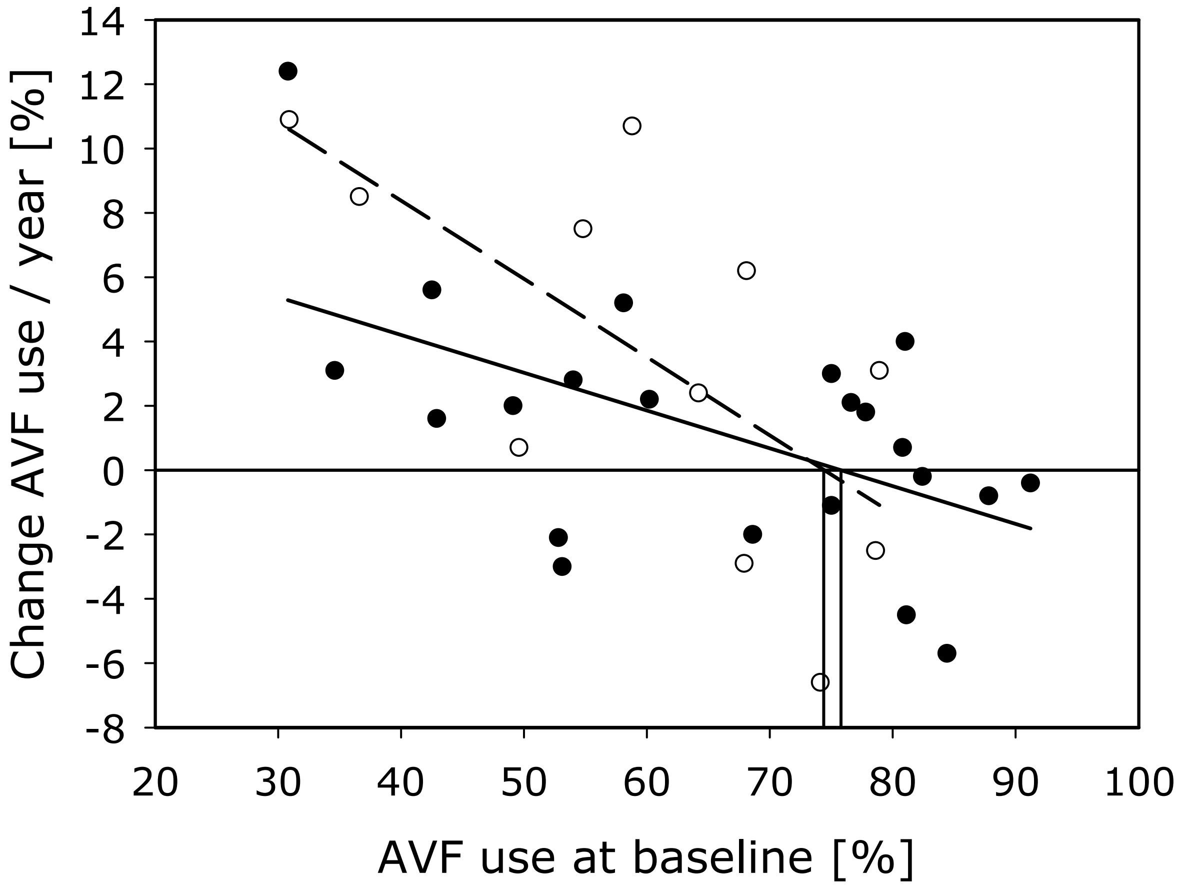

Figure 1. Relation between the percentage of prevalent AVF use at baseline and change of the percentage of AVF use per year. The solid circles and the solid line represent the individual results and the regression line of the centres in the control group. The open circles and the dashed line represent the individual results and the regression line of the centres in the CIMINO-group. Slopes of the regression lines differ significantly ($P < 0.05$) indicating an accelerated increase of AVF use within the CIMINO group.

Discussion

This prospective, multicentre, multidisciplinary guidelines implementation programme demonstrated an accelerated prevalent AVF use in comparison to a large control group. This was predominantly observed in clinics where AVF use was <75% at the start of the observation period. Furthermore, AVF use displayed a wide range among the participating centres but these ranges narrowed during the project. The third major observation was a clear switch from untunnelled to tunnelled catheter use.

Change in time

Since the appearance of the first Dialysis Outcomes Quality Initiative (DOQI) guidelines in 1997, several reports have shown that dramatic changes in access placement can be achieved in a short period of time [9-13]. However, those studies were performed in centres that were characterized by low fistula incidence and prevalence levels at baseline. Our intervention group and the control group started at 58.5% and 65.5% prevalent AVF use, respectively.

Higher baseline fistula levels can be expected to yield smaller annual increments in AVF use when guidelines are implemented, which is indeed seen in our initiative (Figure 1). The CIMINO programme, however, shows that an increase in AVF use can be performed quicker than in general practice. The variability of differences in AVF use per year also suggests an important role for centre specific aspects. Furthermore, figure 1 shows that when a clinic is already using AVFs in 75% of the eligible subjects, increase in use is not easy achievable. This is in line with data from DOPPS II which showed that 74% of the prevalent accesses in countries surrounding the Netherlands are fistulas [14].

Range & demographics

Wide ranges of fistula use in the CIMINO group (45-83%) and the control group (42-91%) are a remarkable observation in a small country like the Netherlands. In addition, high and low fistula prevalence centres were randomly spread over the country. For instance, the centre with the lowest percentage of fistulas (42%) and the one with the second highest percentage (90%) in 2006 were <60 km apart (data not shown). Similar findings have been reported before [15, 16] and such differences are not likely to be explained solely by demographics (Table 1).

Four out of 5 of the centres of the CIMINO group with <60% AVFs at baseline showed great improvements in fistula use, in 2 centres up to almost 11% increase per year. These centre specific results outnumber other single centre achievements [9, 10]. Two centres that already had high AVF baseline levels managed to increase the use even more. This is an interesting observation because the closer a haemodialysis population gets to 100% fistula use the more patients with compromised vessels have to be included. Indeed, registry data reported averages up to 86% prevalent AVF use [17, 18].

Demographics and patient characteristics such as race, presence of peripheral vascular disease and body mass index (BMI) are known to differ between the US and Europe [6], and have been associated with lower fistula prevalence levels [15, 19]. This may partially explain (inter)national differences in practice patterns [6]. However, in conformity with our findings, the HEMO study found substantial variations in AVF use among dialysis units in single metropolitan areas [15]. Moreover, access surgery performed by a surgical trainee is thought to result in more graft placement instead of fistulas [6]. O'hare *et al.* demonstrated that the choice of vascular access placement also depends on differences between individual surgeons [20].

Our results strongly suggest that centre specific characteristics are of paramount importance in vascular access placement and give further support to the idea that access surgery should only be performed by experienced and skilled surgeons willing to meet the 'AVF only' standards.

Catheters

Central venous catheters (CVC) are known to have much higher risks of complications than fistulas. In our initiative CVC use decreased from 17.2% to 14.8% and was lower than European average [14]. A comparison between DOPPS I and II, however, showed an increase in CVC use in both Western Europe and the United States in the recent years [6, 14, 21]. Mendelssohn *et al.* showed that average time from referral to vascular surgeon and actual surgery is commonly 2-4 weeks [14]. Maturation generally takes at least 4-6 weeks [2]. Therefore, it is striking that typical timing for creating a permanent vascular access is <8 weeks in 67% of the European facilities and in 77% of the American facilities [14]. In order to prevent catheter placement in end-stage renal disease patients awaiting AVF use, nephrologists should start to prepare chronic renal failure patients for haemodialysis well in advance, *i.e.* at least 6 months prior to expected haemodialysis [1, 2].

Another interesting observation is the clear switch of untunnelled catheter (UC) to tunnelled catheter (TC) use in both the CIMINO and the control group. Tunnelled cuffed catheter use is thought to be beneficial to UC's when needed for dialysis for more than 14 days [22]. The K/DOQI guidelines advise to insert tunnelled cuffed catheter (TCC) when haemodialysis duration is expected to be longer than 1 week [1].

Limitations

Many aspects of our implementation plan may have contributed to the accelerated increase of AVF prevalence and it remains difficult to determine which was, or were, particularly helpful. It may have been the availability of (translated) outlines of guidelines, the repeated mentioning of the necessity to adhere to the guidelines, the presence of the vascular access coordinator or the availability of the easily accessible database for evaluation of centre specific results. For logistical reasons we approached the centres on geographical basis, *i.e.* primarily located in the middle part of the Netherlands. As can be seen in table 1, both the CIMINO group and the control group were an adequate reflection of the entire Dutch haemodialysis population. These aspects give further support to the idea that current findings are the result of the programme.

Due to higher early thrombosis rates and longer maturation time than grafts, fistulae require extra effort on the short term to become functional. On the long term however, AVFs are accompanied by prolonged patency and less vascular access related morbidity. So, increasing prevalent AVF use should ultimately lead to improved access care for haemodialysis patients.

A cost-effectiveness analysis was not included in our implementation programme. However, extra costs which come with the programme, *i.e.* 0.1 nurse full time equivalent are limited and cost limitation resulting from increased AVF use is likely to be substantial [23]. Furthermore, catheter and graft use have been associated with decreased patient survival [24-26], so an increase in AVF placement might even affect mortality rates.

Conclusion

Initiatives like CIMINO and the large scale 'Fistula First' (www.fistulafirst.org) are meant to provide the vascular access team with tools to achieve vascular access care improvement. Although awareness seems to increase in the recent years, extra effort is still needed to promote implementation of access guidelines in the field of nephrology and, maybe even more important, in vascular surgery and radiology. We have shown that an accelerated increase in AVF use is possible in an average group of access centres. These data also strongly suggest that centre specific factors are of paramount importance for vascular access care.

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Chapter 4

Hospital specific aspects predominantly determine primary failure of hemodialysis arteriovenous fistulas

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Abstract

Introduction

Primary failure of the arteriovenous fistula (AVF) is a major problem affecting native hemodialysis access use. A multicenter guideline implementation program, Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment (CIMINO), was designed to identify modifiable and non-modifiable factors involved in the early functionality of the AVF.

Patients & Methods

Physicians and dialysis staff in 11 centers in the Netherlands (N = 1092 prevalent vascular accesses) were strongly and repeatedly advised to adhere to current guidelines. It was advised to always perform a standard preoperative duplex examination and physicians were encouraged to attempt salvaging procedures for failing and failed fistulae. Specially appointed access nurses prospectively registered all created vascular accesses in an internet-linked database. Primary failure (PF) was defined as a complication of the AVF before the first successful cannulation for hemodialysis treatment. Modifiable and non-modifiable factors were related to risk of primary failure using logistic regression models. We restricted the analyses to the first AVF of each patient that was placed during the observation period.

Results

Between May 2004 and May 2006, an AVF was created in 395 patients. Primary failure occurred in one third (131 cases). Factors related to an increased risk of primary failure were female gender (odds ratio (OR): 1.73, 95% confidence interval (CI): 1.01 – 2.94), renal replacement therapy prior to AVF placement (OR: 1.19 per year on RRT, CI: 1.05 – 1.34), diabetes mellitus (OR: 3.08, CI: 1.53 – 6.20), and AVF placement at the wrist (compared with elbow) (OR: 1.86, CI: 1.03 - 3.36). Primary failure rate among the participating centers varied from 8% to 50%. Compared to the 2 centers with the lowest primary failure rates, 6 centers had a significantly higher primary failure rate. Adjustment for risk factors and surgery-related factors did not materially change the center-related findings.

Discussion

In conclusion, we have identified location of AVF placement as a modifiable factor influencing primary failure risk. More importantly, this study shows

that the probability of primary failure is strongly related to the center of access creation, suggesting an important role for the vascular surgeon’s skills and decisions.

Introduction

The current guidelines on hemodialysis recommend the native arteriovenous fistula (AVF) as first choice vascular access [1, 2]. After creation, a period of 4-8 weeks is generally required to allow an AVF to develop ('mature') into a usable vascular access. Successful maturation is characterized by sufficient blood flow to perform adequate dialysis and by enough size of the vein to allow repetitive puncturing.

Early thrombosis and failure to mature are significant problems occurring in 20% to 50% of AVFs [3]. This wide range may be due to the absence of a clear definition of primary or early failure. Beathard *et al.* defines early failure as those cases in which the fistula fails within the first 3 months of usage [4], and the Committee on Reporting Standards for Arterio-Venous Accesses regards an access non-functional when it is not being successfully used for hemodialysis whether it is patent or not [5]. Despite these differences, non-modifiable factors such as age of the patient, presence of cardiovascular disease and dependence on dialysis at time of access creation have been associated with lower probabilities of maturation [6]. Of the modifiable factors internal diameters of the artery and the vein [6-9], mean arterial pressure (MAP) > 85 mmHg, and greater intraoperative doses of heparin have been associated with successful maturation [6].

The Dialysis Outcomes and Practice Patterns Study (DOPPS), in which The Netherlands was not included, showed great differences in both national and regional vascular access placement policies [10, 11]. Therefore, a multicenter guidelines implementation program, CIMINO (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment), was designed to increase AVF use in the hemodialysis population and to identify modifiable and non-modifiable factors involved in both early and late failure of the AVF. The purpose of this analysis was to determine risk factors for primary AVF failure, and to what extent local practice patterns are responsible for such primary failure.

Patients & Methods

Guidelines implementation program

At the start of our program in 2003, the Vascular Access Society (www.vascularaccesssociety.org) presented the most recently updated guidelines on vascular access care by means of 26 algorithms consisting of clearly structured flow charts supported by literature-based evidence and expert opinions [2]. The recommendations of these 'European guidelines' included 1) for nephrologists: vein preservation, patient referral to vascular surgeon at least 6 months prior to expected hemodialysis, performance of a standard preoperative duplex examination and referral to ultrasound technician, surgeon or radiologist in case of suspected inadequate maturation at 4-6 weeks; 2) for vascular surgeons: order of preference of access placement is i) distal arm AVF, ii) proximal arm AVF and iii) basilic vein transposition or graft insertion. Artery and vein internal diameters should both be at least 2.0 mm, and end-to-side anastomosis is preferred over side-to-side; 3) for radiologists: aggressive treatment of the failing and failed fistula; 4) for dialysis unit: a surveillance program including access flow measurements. Summaries of these guidelines (translated into Dutch) were provided to the centers and vascular access teams were encouraged to adhere to these guidelines during the CIMINO program. In each center a dedicated vascular access coordinator was appointed to register practice patterns in a newly developed internet-linked database. This database contained information on medical history, medication use, preoperative duplex examination, surgery and records of complications and interventions. In-center analysis of the database allowed participating physicians to evaluate their own practice patterns during the entire project. Aggregated data were only available to the coordinating center, the University Medical Center Utrecht. Newsletters went out regularly to update participants on progress of the CIMINO initiative.

Patients

Between May 2004 and July 2005, eleven vascular access centers in the middle part of the Netherlands, representing 1092 prevalent access sites, started participation in this prospective observational study. All hemodialysis patients or patients with chronic renal failure (CRF) requiring a new permanent vascular access during this follow up period were included. Only the first AVF created in each subject was considered eligible for the present analysis.

Definitions

Duration of previous renal replacement therapy (RRT) was defined as the period from first hemodialysis / peritoneal dialysis treatment or kidney transplantation date to the date of access creation in this study. *Coronary artery disease (CAD)* was defined as a history of coronary angioplasty, coronary bypass surgery, endovascular stenting, or myocardial infarction. *Peripheral vascular disease (PVD)* was defined as a history of angioplasty, surgical endarterectomy, endovascular stenting or bypass surgery of the iliac and/or femoral arteries, but also amputation due to peripheral artery occlusive disease. *Carotid artery disease* was defined as the same interventions in the carotids, and also included previous cerebrovascular accidents (CVA). *Body Mass Index (BMI)* was expressed as [kg/m²] and its odds ratio reflects the increase of the primary failure risk for every unit of BMI increase. *Diabetes mellitus (DM)* was defined as current use of hypoglycemic medication or use of insulin, or when the diagnosis was recorded in a medical status. Concomitant medication use was subdivided into the following groups, 1) angiotensin converting enzyme inhibitors (ACEi) and angiotensin-2 receptor blockers, 2) calcium channel blockers, 3) HMG-CoA reductase inhibitors (statins), 4) oral anticoagulants (coumarins), and 5) platelet aggregation inhibitors (including acetylsalicylic acid, clopidogrel and dipyridamole), and were recorded positive when used within one week prior to access surgery. Performance of pre-operative duplex examination was recorded. Surgical access placement data contains identification of the surgeon, as well as type, anatomical location and configuration of the vascular access.

A *functional AVF* is an access that is able to deliver a flow rate of 350-400 mL/min without recirculation for the total duration of dialysis. A nonfunctional AVF is an access that is not being successfully used for hemodialysis whether it is patent or not [5].

Inadequate maturation was defined as insufficient access flow to maintain dialysis or the unavailability to cannulate an AVF, if required, at 6 weeks after surgery.

Primary failure (PF) was defined as an AVF that did not develop to sustain dialysis or thrombosed before the first successful cannulation for hemodialysis treatment, regardless of eventual AVF abandonment or not. This definition includes 1) inadequate maturation, 2) early thrombosis, 3) failure of first cannulation, and 4) other complications such as ischemia or infection.

Statistical analysis

The relation between modifiable and non-modifiable parameters with risk of primary failure was studied using univariable and multivariable regression models.

Results are presented as means ± SEM and odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical significance was assumed when two-sided *P*-value was < 0.05. Analyses were carried out using SPSS for Windows® (SPSS Inc., Chicago, IL).

For analyses on the relation between risk of primary failure and hospitals, the two hospitals with the lowest primary failure rates were combined and served as reference group for the other hospitals.

Results

On May 1, 2006, a total of 395 patients had received an AVF between May 2004 and May 2006. Fifty-five per cent were on renal replacement therapy at time of access placement. The mean age was 65 ± 14 (SD) (range 18 - 87) years, and 62% were men. Baseline characteristics are shown in table 1.

Characteristic	**Primary AVF failure**		***P*-value***
	yes	**no**	
No. of patients	131	264	-
Age [yrs]	64.9±15.6	64.4±13.4	0.73
Female gender [%]	43.5	34.8	0.10
Previous RRT [%]	61.1	51.9	0.05
Months on dialysis prior to AVF placement	13.8±35.1	8.4±20.3	0.07
Previous coronary artery disease [%]	22.1	23.9	0.70
Previous peripheral vascular disease [%]	11.5	9.5	0.55
Previous cerebrovascular disease [%]	10.7	12.5	0.60
Caucasian ethnicity [%]	77.9	77.3	0.79
Current smoking [%]	22.1	19.7	0.43
BMI [kg/m^2]	25.7±4.7	24.8±4.3	0.05
Diabetes [%]	37.4	29.9	0.14
Diabetes as primary cause ESRD [%]	11.5	18.9	0.07
Use of ACEi/ARB [%]	35.1	43.6	0.09
Use of calcium antagonist [%]	38.9	33.7	0.33
Use of statin [%]	38.2	42	0.46
Use of coumarin [%]	22.9	18.6	0.30
Use of platelet aggregation inhibitor [%]	38.9	41.3	0.61
Pre-operative duplex [%]	77.1	63.3	0.01
AVF at wrist [%]	72.5	62.1	0.04

Table 1. Baseline characteristics of the patients with and without primary AVF failure; results of a univariable analyis.

Values are depicted as percentages or as means with standard deviation (SD); RRT = renal replacement therapy; BMI = body mass index; ESRD = end-stage renal disease; ACEi = angiotensin converting enzyme inhibitor, ARB= angiotensin-2 receptor blocker.

* *P*-value reflects difference between groups. If *P*-value was ≤ 0.15, covariate was entered in the multivariable regression model.

Causes of primary failure

Primary AVF failure occurred in 131 patients (33.2%). Thrombosis and stenosis were diagnosed in 40% and 33%, respectively (Table 2). Inadequate maturation was the underlying problem in 19% of the cases (*N* = 29), six of which as a result of accessory vein(s).

Thirty-four AVFs (26%) were salvaged and successfully cannulated. In 17 (13%) patients, the AVF was not abandoned but cannulation was not performed at the end of the study; 14 were preparing for dialysis, 1 patient died, 1 was transplanted and 1 was lost-to-follow up. Eventually, 80 (61%) of the primary failed AVFs were abandoned before first cannulation.

Complication		***N***	
Thrombosis		61	39.6%
Stenosis		51	33.1%
Inadequate maturation		29	18.8%
Accessory vein	6		
Ischemia		10	6.5%
Infection		2	1.3%
Venous hypertension		1	0.6%
Total		154	100%
No. of complications per AVF		1.2	

Table 2. Causes of primary AVF failure

Time to first cannulation

In the non-primary failure group (*N* = 264), a total of 213 (81%) AVFs were used for hemodialysis. Thirty of these (14%) were used for the first time later than 120 days after creation. Of this group, 29 patients (97%) were so-called 'pre-dialysis patients' and were in anticipated need of hemodialysis treatment. Of the other 51 patients (19%), 29 were preparing for dialysis, 15 patients died, 3 were transplanted and 4 were lost-to-follow up before hemodialysis commencement. Median time to first successful cannulation was 50 days (range: 0 - 463).

Risk factors for primary failure

Patients with primary failure (PF), compared to those without PF, were more often women, diabetic, overweight (increased body mass index), had longer RRT history, and ACE inhibitor use was less common (Table 1). Concomitant use of platelet aggregation inhibitors and use of coumarins did not reduce the risk of thrombosis, OR = 0.66 (CI: 0.32 – 1.35) and OR = 0.82 (CI: 0.36 – 1.87), respectively. Pre-operative duplex examination was performed in 77% of the patients in the PF-group, and in 63% of the non-PF-group (P < 0.05). In the PF-group, a higher percentage of the AVFs were created at the wrist (P < 0.05) (Table 1).

Multivariable analysis revealed that female gender, duration of RRT prior to access placement and diabetes mellitus were independent risk factors for PF (Table 3).

Of the surgery related factors, only AVF placement at the wrist was a risk factor for PF (Table 4).

Characteristic	OR	95% CI	*P*-value
Female gender	1.73	1.01 – 2.94	0.05
Each year on RRT prior to access placement	1.19	1.05 – 1.34	0.01
BMI per kg/m2	1.03	0.97 - 1.09	0.39
Diabetes	3.08	1.53 – 6.20	<0.01
Diabetes as primary cause ESRD	0.15	0.06 - 0.37	<0.01
Use of ACEi /ARB	0.65	0.38 – 1.11	0.11

Table 3. Results from a multivariable logistic regression model on the relation of potential risk factors for primary AVF failure, adjusted for surgery-related factors and for centers.

OR = odds ratio; CI = confidence interval; RRT = renal replacement therapy; BMI = body mass index; ESRD = end-stage renal disease; ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin-2 receptor blocker.

Characteristic	**OR**	**95% CI**	***P*-value**
Preoperative duplex	1.88	0.90 – 3.91	0.09
AVF at wrist	1.86	1.03 – 3.36	0.04
S-S vs. E-S anastomosis	0.97	0.43 – 2.20	0.94
General vs. regional anaesthesia	0.93	0.39 – 2.21	0.86
Local vs. regional anaesthesia	1.21	0.45 - 3.27	0.71
Surgical resident	0.84	0.27 – 2.60	0.77

Table 4. Results from a multivariable logistic regression model on the relation of surgery-related factors and the risk of primary AVF failure, adjusted for potential risk factors and for centers.

OR = odds ratio; CI = confidence interval; AVF = arteriovenous fistula; S-S = side-to-side anastomosis; E-S = end-to-side anastomosis

Difference between participating centers

Figure 1 displays the primary failure rate per participating center. The range varies from 8 to 50%. When compared to the 2 centers with the lowest primary failure rates (center 6 and 9), six centers had a significantly higher risk of primary AVF failure (Table 5). These findings remained after adjustment for potential risk factors and surgery-related factors (Tables 3 and 4).

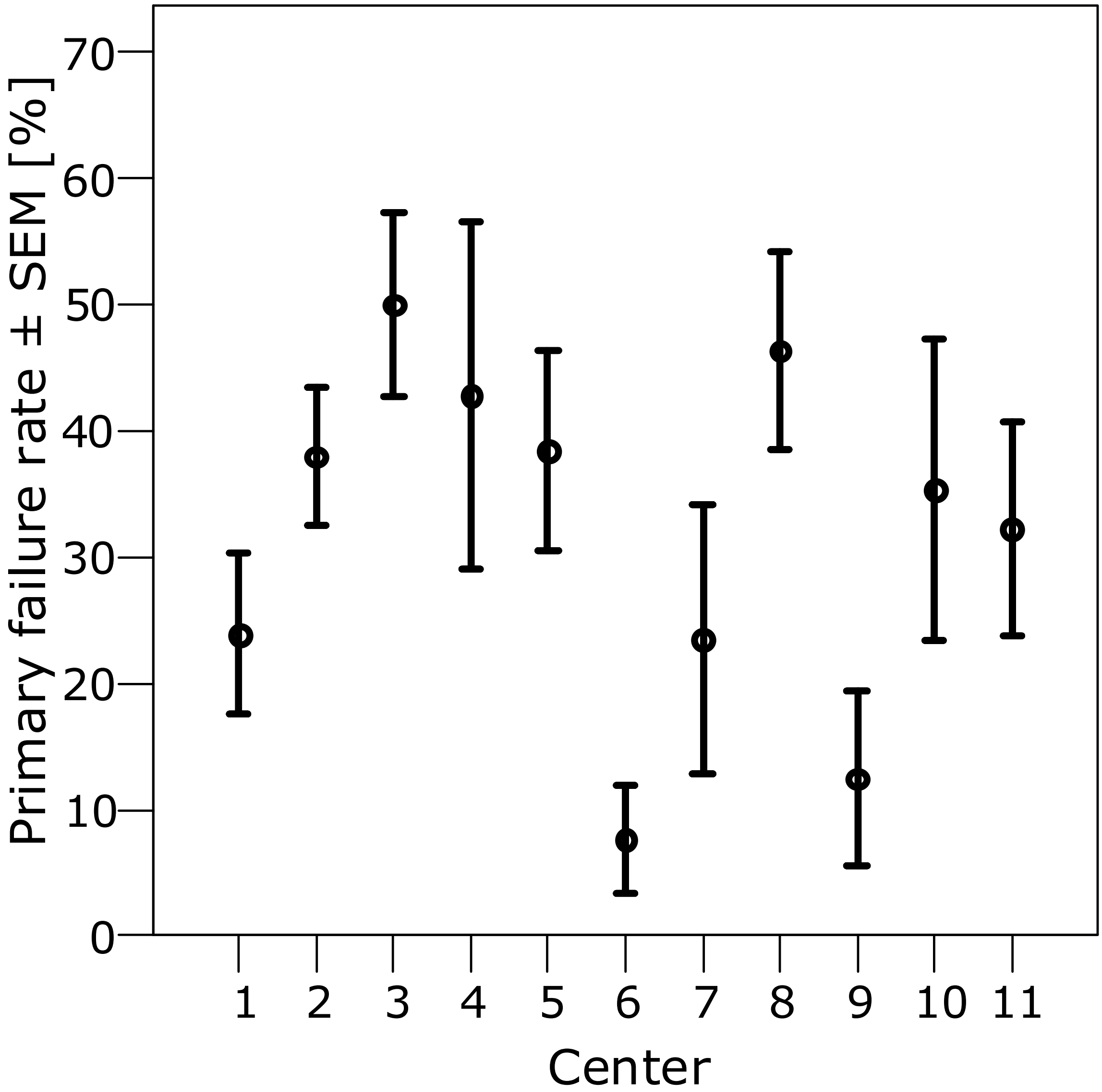

Figure 1. Primary failure rate per center
SEM = standard error of the mean

Results of pre-operative duplex examination

Pre-operative duplex examination was performed in 68% of the cases. In the wrist AVF group, mean cephalic vein diameter was 2.34 ± 0.07 mm in the non-PF group, and 2.51 ± 0.09 mm in the PF group (*P* = 0.15). In centers 6 and 9 combined, mean wrist cephalic vein diameter (2.58 ± 0.17 mm) was not significantly different from any of the other centers. In the elbow AVF group, mean cephalic vein diameter was 3.44 ± 0.18 mm in the non-PF group, and 3.06 ± 0.28 mm in the PF group (*P* = 0.25). In centers 6 and 9 combined, mean elbow cephalic vein diameter was 3.39 ± 0.47 mm and did not differ significantly from any of the other centers.

Center	*N*	OR	95% CI	*P*-value
1	46	3.43	0.73 – 16.11	0.12
2	79	7.38	2.46 – 22.16	<0.01
3	48	8.69	2.29 – 33.05	<0.01
4	14	7.24	1.01 – 52.03	0.05
5	39	5.53	1.68 – 18.17	0.01
6	39	1.00	reference	-
7	17	1.62	0.26 – 10.14	0.61
8	41	9.38	2.42 – 36.30	<0.01
9	24	1.00	reference	-
10	17	3.84	0.82 – 18.12	0.09
11	31	5.96	1.35 – 26.34	0.02

Table 5. Relation between center and risk of primary AVF failure, adjusted for potential risk factors and for surgery-related factors. Centers 6 and 9 combined were regarded as reference group.

N = number of AVFs included in CIMINO; OR = odds ratio; CI = confidence interval

Discussion

In this prospective multicenter initiative, we observed a primary arteriovenous fistula (AVF) failure rate of 33%. Factors associated with the risk of primary failure (PF) were female gender, duration of previous renal replacement therapy, diabetes mellitus, and AVF placement at the wrist (in comparison to the elbow). Importantly, PF rates varied considerably between participating hospitals, even after adjustment for the potential risk factors and surgery-related factors.

An overview of current literature shows that PF occurs in 20-50% of the AVFs [3]. This wide range may partially be explained by the absence of an accepted clear definition of PF. Great differences in (inter)national access placement policies [10] may also contribute to these large differences. In our initiative, CIMINO, a uniform protocol on hemodialysis access management was used [2], and standardized definitions assured objective comparison of PF rates [5]. The median time to first successful cannulation of 50 days for uncomplicated fistulas is in line with the recommended maturation time in the recent K/DOQI guidelines [1]. Furthermore, observations were performed in a relatively small geographical area limiting possible effects of ethnic differences on placement pattern [12] and PF rate [13].

A wide range in PF-rates was observed among the participating centers in CIMINO (Figure 1). After adjustment for all other risk factors, a strong relation was found between the risk of primary failure and the center of access creation (Table 5). Similarly, a retrospective survey on newly created radial-cephalic AVFs displayed a wide distribution of PF among 23 dialysis facilities [14]. These center specific aspects may include pre-operative evaluation (physical examination, duplex ultrasound) [9, 15-17], optimal vessel choice, technical skills required for anastomosing [18], and surgical experience. In this perspective, it is noteworthy that AVF creation was done by a surgical resident in 7% of the cases but, in contrast to international access placement patterns [10], an association with PF was not found. Our results however, may implicate that the vascular surgeon not only plays an important role in type of access placement [10, 19-21] but also in early AVF functionality.

Adequate fistula maturation has been found to depend on non-modifiable factors like age, RRT prior to access creation and the presence of cardiovascular disease [6], but also on diabetes (Table 3). The only potential modifiable risk factor of PF we identified was AVF placement at the wrist (versus the elbow). Interestingly, the remodeling capacity of a calcified radial artery, especially in diabetics, can be severely diminished, thus preventing the substantial dilation required for successful maturation [22]. By creating significantly more elbow and perforating vein (Gracz) [23] fistulas, similar primary patency rates for diabetics and non-diabetics have been observed in a single center experience [24]. Moreover, Hakaim *et al.* have found better survival rates for brachio-cephalic and brachio-basilic AVFs than radial-cephalic AVFs in diabetic hemodialysis patients [25].

In terms of pharmacological prevention of primary AVF failure, we did not observe protective effects within any of the medication groups. ACEi use has been related to an improved secondary patency in AVFs [26]. In grafts, dipyridamole three times a day reduced the risk of thrombosis [27] but clopidogrel in combination with aspirin failed to reduce thrombosis rate [28]. Currently, a trial is being conducted investigating whether clopidogrel has beneficial effects on early fistula thrombosis [29]. Our study was insufficiently powered to effectively study such drug effects.

The CIMINO program was initiated as an effort to improve vascular access care and increase the use of AVFs in the hemodialysis population. We stimulated the creation of distal arm AVFs, even in case of suboptimal but non-stenotic vessels [1]. Such programs have been found to be accompanied by decreased maturation rates [30]. However, distal AVF placement results in less cases of steal syndrome, especially in diabetics [31], with future opportunities to perform a secondary procedure more proximally in the arm. In the CIMINO initiative, the two centers with lowest PF rates had a slightly higher percentage of wrist AVF placement (71%) than the other 9 centers (65%). This combination of low PF-rate and a high percentage of wrist AVFs are more likely the result of superior technical skills and surgical decisions.

Fifty-one per cent of the diabetic patients in this study had diabetes as primary cause of end-stage renal disease (ESRD). In this subgroup of patients, only 23% had a primary AVF failure. Of interest may be that 43% were female, 48% had RRT before access placement (duration: 0.78 ± 0.29 yr.) and only 55% had a wrist AVF. Thus, all but one of the risk factors were less represented in this subgroup contributing to the decreased risk of PF for patients with diabetes as primary cause of ESRD. One could conclude that only a selection of these diabetic patients with the best vessels received an AVF and that a significant part started dialyzing using a graft. However, further explanation of this finding remains unclear.

Limitations

Different aspects of vascular access care are important in early AVF outcome. Experience in AVF surgery expressed as the total number of performed procedures by a surgeon may be relevant. However, the number of years a surgeon performs access surgery did not reveal an obvious relation with early AVF function in a retrospective study [32]. Interestingly, AVF creation by a surgical resident was not related to primary failure in this analysis but those operations could have been limited to less complex cases. Additional data on the surgeons was not available in this initiative. Technical skills and the surgeon’s personal interest in access surgery remain difficult to measure objectively but our findings warrant further analysis of surgical aspects in a next study.

Although we analyzed and identified most possible risk factors for primary AVF failure, other center specific factors, such as nephrological aspects (vein preservation, timely referral) or in-patient characteristics, may have contributed to our results. Such data were not available in our initiative and thus, possible impact on AVF outcome remains speculative.

Conclusion

In this analysis we demonstrated a strong relation between vascular access center and risk of primary failure. These results justify further analysis of local practice patterns. Identification and adjustment of local aspects involved in decreased AVF functionality should be able to improve vascular access outcomes.

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Chapter 5

Hemodialysis arteriovenous fistula patency revisited; results of a prospective, multicenter initiative

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Abstract

The K/DOQI vascular access placement standards are predominantly based on older single center reports and exclude the maturation period. However, hemodialysis population characteristics have changed dramatically and primary AVF failure is a significant problem. In this prospective, multicenter study we used standardized definitions to analyze patency rates and risk factors for patency reduction.

Eleven centers participated in a guidelines implementation program. All new permanent vascular accesses during this follow up period were included. Patency rates were calculated using Kaplan Meier analysis and life table method. Risk factors for patency loss were determined using regression models.

A total of 491 AVFs (76% of all inclusions) were placed in 395 patients. Mean age was 65 years and 62% were men. Six, 12 and 18 months secondary patency and functional patency were 75 ± 2.0%, 70 ± 2.3%, 67 ± 2.7% and 90 ± 1.9%, 88 ± 2.2%, 86 ± 2.7%, respectively. Primary failure rate was 35%. Thrombosis rate was 0.14 per patientyear. Only diabetes was associated with primary functional patency loss (HR: 1.70 [95%CI: 1.07–2.68]). No factors were related to secondary failure (SF). The SF-rate per hospital varied from 0 to 38%. Compared to the hospitals with low secondary failure rates, three hospitals had higher risks of SF.

We showed a marked difference between patency and functional patency, likely to be explained by high primary failure rates. After adjustment for potential risk factors, secondary failure was more likely in 3 of the 11 hospitals suggesting an important role for practice patterns.

Introduction

The K/DOQI standards promote the increase of native vascular access use because of superior patency rates and lower complication rates than grafts once established [1]. These recommendations are predominantly based on single center studies from the 1980's and early 1990's, and on studies that have excluded the phase between AVF creation and cannulation from patency calculations [2]. However, current hemodialysis patients are older, more often have diabetes [3] and more often have cardiovascular co-morbidity [4, 5]. Moreover, fistulas have high primary failure rates [6] and maturation problems will increasingly challenge vascular access teams in meeting the K/DOQI goals [7]. In patients with compromised forearm vessels graft patency has been shown to be better than AVF patency [8]. Therefore, a renewed analysis of native vascular access patency rates is justified.

The Dialysis Outcomes and Practice Patterns Study (DOPPS), in which the Netherlands was not included, showed large differences in both national and regional vascular access placement policies [5, 9]. At the start of the new millennium prevalent AVF use in the Netherlands was approximately 60% with a wide range [31-91%] [10]. Therefore, a multicenter guidelines implementation program, CIMINO (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment), was initiated to increase AVF use in a proportion of the Dutch hemodialysis population. In addition, this prospective multicenter observational study was designed to learn more about both early and late functionality of the AVF. Recently our group showed that hospital specific aspects predominantly determine primary AVF failure [11].

The purpose of the analysis in the present study was to compare AVF patency rates in 11 dialysis centers with K/DOQI standards using standardized definitions in a methodological favorable study setup. Furthermore, we aimed at obtaining insight in risk factors affecting patency rates and late AVF functionality.

Patients and Methods

At the start of our program in 2003, the Vascular Access Society (www.vascularaccesssociety.org) presented the most recently updated guidelines on vascular access care by means of 26 algorithms consisting of clearly structured flow charts supported by literature-based evidence and expert opinions [12]. The recommendations of these 'European guidelines' included 1) for nephrologists: vein preservation, patient referral to vascular surgeon at least 6 months prior to expected hemodialysis, performance of a standard preoperative duplex examination and referral to ultrasound technician, surgeon or radiologist in case of suspected inadequate maturation at 4-6 weeks; 2) for vascular surgeons: order of preference of access placement is i) distal arm AVF, ii) proximal arm AVF and iii) basilic vein transposition or graft insertion. Artery and vein internal diameters should both be at least 2.0 mm, and end-to-side anastomosis is preferred over side-to-side; 3) for radiologists: aggressive treatment of the failing and failed fistula; 4) for dialysis unit: a surveillance program including access flow measurements. Summaries of these guidelines (translated into Dutch) were provided to the centers and vascular access teams were encouraged to adhere to these guidelines during the CIMINO program. In each center a dedicated vascular access coordinator was appointed to register practice patterns in a newly developed internet-linked database. This database contained information on medical history, medication use, preoperative duplex examination, surgery and records of complications and interventions. In-center analysis of the database allowed participating physicians to evaluate their own practice patterns during the entire project. Aggregated data were only available to the coordinating center, the University Medical Center Utrecht. Newsletters went out regularly to update participants on progress of the CIMINO initiative.

Patients

Between May 2004 and July 2005, eleven vascular access centers in the middle part of the Netherlands, representing 1092 prevalent access sites, started participation in this prospective observational study. All hemodialysis patients or patients with chronic renal failure (CRF) requiring a new permanent vascular access during this follow up period were included.

Definitions

Coronary artery disease (CAD) was defined as a history of coronary angioplasty, coronary bypass surgery, endovascular stenting or myocardial infarction. *Peripheral vascular disease* (PVD) was defined as a history of angioplasty, surgical endarterectomy, endovascular stenting or bypass surgery of the iliac and/or femoral arteries, but also amputation due to peripheral artery occlusive disease. *Cerebrovascular disease* was defined as the same interventions in the carotids, and also included previous cerebrovascular accidents (CVA). *Diabetes mellitus* (DM) was defined as current use of hypoglycemic medication or use of insulin, or when the diagnosis was recorded in a medical status.

Primary patency was defined as the interval from time of access placement to any intervention designed to maintain or reestablish patency, access thrombosis, or the time of measurement of patency [13]. *Assisted primary patency* was defined as the interval from time of access placement to access thrombosis or time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to maintain the functionality of a patent access [13]. *Secondary patency* was defined as the interval from time of access placement to access abandonment, access thrombosis or time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to reestablish the functionality of thrombosed access [13]. The word 'functional' was added to patency to indicate that patency interval started at date of first successful cannulation for hemodialysis treatment instead of date of placement.

A *functional AVF* is an access that is able to deliver a flow rate of 350-400 mL/min without recirculation for the total duration of dialysis. A *nonfunctional AVF* is an access that is not being successfully used for hemodialysis whether it is patent or not [13].

Inadequate maturation was defined as insufficient access flow to maintain dialysis or the unavailability to cannulate an AVF, if required, at 6 weeks after surgery.

Primary failure (PF) was defined as an AVF that did not develop to maintain dialysis or thrombosed before the first successful cannulation for hemodialysis treatment, regardless of eventual AVF abandonment or not. This definition includes 1) inadequate maturation, 2) early thrombosis, 3) failure of first cannulation, and 4) other complications such as ischemia or infection. *Secondary failure (SF)* was defined as permanent failure of the AVF, after it had achieved adequacy for hemodialysis.

Statistical analysis

Means are depicted ± SEM unless otherwise described. Kaplan–Meier survival analysis and the life table method were used to calculate patency rates, and the log-rank test was used to compare patency rates.

Only the first created AVF per patient in this dataset was used to determine relations between possible risk factors and AVF outcome. Risk factors for loss of primary functional patency and for secondary failure were determined using multivariate Cox proportional-hazards models. Hazard ratios (HR) are expressed with 95% confidence intervals (CI). Statistical significance was assumed when two-sided P-value was < 0.05. Analyses were carried out using SPSS 12.0 (SPSS Inc., Chicago, Ill) and SigmaStat 3.11 (Systat Software Inc., San Jose, CA) for Windows®.

Results

From 1 May 2004 to 1 May 2006, a total of 649 permanent vascular accesses, representing all inclusions of CIMINO, were recorded in the database. This included 491 AVFs (76%) in 395 patients. Of these patients, 80 received 2 AVFs during this observation period, 13 patients had 3 AVFs, and 3 patients had 4 AVFs. A total of 291 AVFs were created in the forearm, 198 in the upper arm and 2 in the leg. Mean age was 64.6 ± 14.2 years and 62% were males. Baseline characteristics are shown in table 1.

Total follow up time from access placement to lost-to-follow up, secondary AVF failure or study end was 343.3 patientyears. Follow up time from first successful cannulation to lost-to-follow up, secondary AVF failure or study end was 204.8 patientyears.

Baseline characteristics of CIMINO patients	
No. of AVFs	491
No. of patients	395
Age [yrs]	64.6 ± 14.2
Male sex [%]	62
RRT prior to AVF placement [%]	55
Coronary artery disease [%]	23
Peripheral vascular disease [%]	10
Cerebrovascular disease [%]	12
Caucasian ethnicity [%]	78
Current smoker [%]	21
BMI [kg/m^2]	25.1 ± 4.5
Body height [m]	1.70 (1.45 – 2.07)
Diabetes [%]	33
Diabetes as primary cause ESRD [%]	17

Table 1. Baseline characteristics

Values are depicted as percentages, as mean ± SD or as median with range. RRT = renal replacement therapy; BMI = body mass index; ESRD = end-stage renal disease.

	Patency rate from surgical AVF creation											
Patency	**3 mo**	**95% CI**	***N***	**6 mo**	**95% CI**	***N***	**12 mo**	**95% CI**	***N***	**18 mo**	**95% CI**	***N***
Primary	71%	[67 - 75]	319	57%	[52 - 62]	212	49%	[44 - 54]	102	39%	[32 - 46]	25
Assisted primary	77%	[73 - 81]	349	69%	[65 - 73]	262	64%	[59 - 69]	232	59%	[53 - 65]	38
Secondary	81%	[77 - 85]	366	75%	[71 - 79]	284	70%	[65 - 75]	147	67%	[62 - 72]	42

	Patency rate from 1st cannulation											
Patency	**3 mo**	**95% CI**	***N***	**6 mo**	**95% CI**	***N***	**12 mo**	**95% CI**	***N***	**18 mo**	**95% CI**	***N***
Primary functional	83%	[78 - 88]	212	70%	[64 - 76]	137	61%	[54 - 68]	54	57%	[49 - 65]	12
Assisted primary functional	92%	[89 - 95]	238	85%	[80 - 90]	171	83%	[78 - 88]	74	77%	[70 - 84]	15
Secondary functional	96%	[94 - 98]	248	90%	[86 - 94]	184	88%	[84 - 92]	80	86%	[81 - 91]	15

Table 2. Primary, assisted primary and secondary patency rates at 3, 6, 12 and 18 months (mo) with 95% confidence interval (CI) and number of patients at risk at the end of the interval (*N*).

Patency

Three, 6, 12 and 18 months patency rates and functional patency rates are depicted in table 2.

Primary AVF function

In the non-primary failure group (*N* = 321), a total of 258 AVFs (80%) had been successfully used for hemodialysis (Figure 1). Of these, 36 (16%) were not used until more than 120 days after placement; 34 (89%) of which were pre-dialysis patients.

Of the 63 patients whose AVF was not cannulated (20%), 16 patients had died, 3 were transplanted and 4 were lost-to-follow up before AVF use. The remaining 40 were preparing for dialysis at study end.

Median time to first cannulation was 49 days (interquartile range (IQR): 41 - 77 days). Of the salvaged AVFs (*N* = 44), median time to cannulation was 81 days (IQR: 51 - 115 days).

Before first cannulation, 205 complications occurred in 170 fistulas resulting in a primary failure rate of 35% and 1.2 complications per failing AVF. Forty-four fistulas (26%) were salvaged and successfully cannulated. In 26 (15%) patients, the AVF was not abandoned but cannulation was not performed yet at study end. Of these, 23 were preparing for dialysis, 1 patient died, 1 was transplanted and 1 was lost-to-follow up. Eventually, 100 (59%) AVFs were abandoned before first successful cannulation; primary AVF abandonment rate was 25% (lost-to-follow ups and predialysis patients excluded).

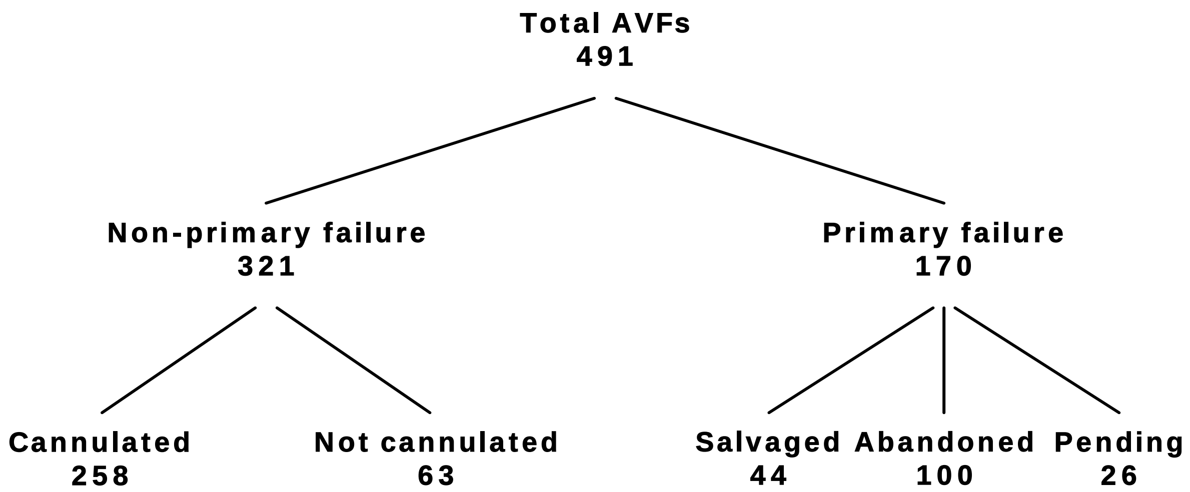

Figure 1. Diagram of primary AVF function

Complications

At the end of the follow up period, 302 AVFs had been used in 285 patients. Thrombosis occurred 29 times (0.14 per patientyear). Eight patients received antibiotics for AVF infection. Two ischemic events required surgical intervention, 1 in a forearm AVF and 1 in an upper arm AVF. A total of 49 PTA-procedures and 40 surgical revisions (including the 2 procedures for ischemia) were performed in order to salvage fistulas. Eventually, 31 AVFs were abandoned in 27 patients.

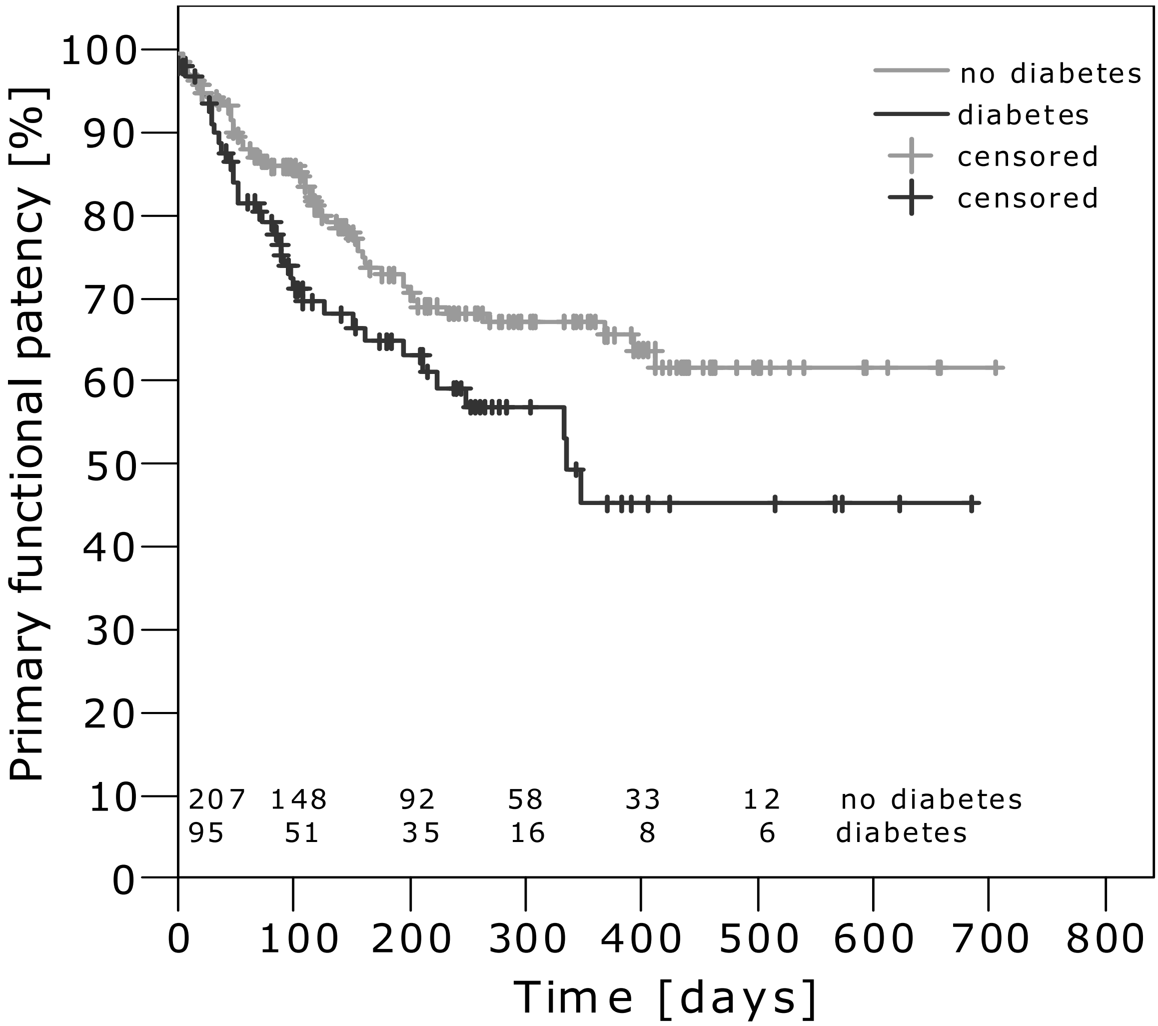

Figure 2. Primary functional patency in diabetics (black line) and non-diabetics (grey line) with numbers of patients at risk

Primary functional patency rates are significantly different (Log rank test: P = 0.03). After adjustment for age ≥ 65 yrs, gender, coronary artery disease, peripheral vascular disease, renal replacement therapy prior to access cannulation, BMI ≥ 30 kg/m^2 and AVF location in the forearm, diabetics had a higher risk of loss of primary functional patency then non-diabetics (HR: 1.70 [95% CI: 1.07 to 2.68]).

Risk factors for loss of patency

In univariate analyses male gender (HR: 0.72, P = 0.14), age ≥ 65 years (HR: 1.53, P = 0.06), presence of peripheral vascular disease (HR: 0.39, P = 0.07) and diabetes (HR: 1.69, P = 0.02) were related to loss of primary functional patency. No characteristics were associated with secondary failure.

On multivariable survival analysis with age ≥ 65 yrs, gender, coronary artery disease, peripheral vascular disease, fistula location, BMI ≥ 30 kg/m^2 and RRT prior to access cannulation, diabetes was the only factor significantly associated with loss of primary functional patency (HR: 1.70 [CI: 1.07 – 2.68]) (Figure 2). None of these factors were significantly related to secondary failure (Table 3).

Characteristic	**Loss PFP (*N* = 87)**		**Secondary failure (*N* = 27)**	
	HR	**95% CI**	**HR**	**95% CI**
Male gender (yes vs no)	0.69	0.44 – 1.09	1.11	0.48 – 2.57
Age ≥ 65 yrs (yes vs no)	1.52	0.97 – 2.39	1.00	0.45 – 2.21
CAD (yes vs no)	1.07	0.63 – 1.84	0.84	0.32 – 2.25
PVD (yes vs no)	0.38	0.14 – 1.10	1.54	0.42 – 5.63
Diabetes mellitus (yes vs no)	1.70	1.07 – 2.68	0.94	0.38 – 2.30
BMI ≥ 30 kg/m^2 (yes vs no)	1.03	0.53 – 1.98	1.38	0.45 – 4.26
RRT prior to cannulation (yes vs no)	1.08	0.66 – 1.77	1.74	0.64 – 4.73
Forearm AVF (vs upper arm)	1.19	0.75 – 1.89	1.37	0.59 – 3.18

Table 3. Results of a multivariate Cox proportional hazard model for loss of primary functional patency and for secondary AVF failure.

AVF = arteriovenous fistula, CAD = coronary artery disease, PVD = peripheral vascular disease, BMI = body mass index, RRT = renal replacement therapy.

PFP = primary functional patency, HR = hazard ratio, CI = confidence interval.

Hospital specific aspects

The secondary failure rate per hospital varied from 0 to 38% (Table 4), and secondary functional patency rates were different among the 11 hospitals (P < 0.01).

Because of the relatively small number of events that occurred, the hospitals were divided in 2 subgroups; secondary failure rate greater (N = 3) and less (N = 8) than the mean (9.5%). The risk of secondary failure was significantly greater in the 3 high rate hospitals in comparison to the low rate group: HR: 3.03 [95% CI: 1.12 – 8.24], HR: 6.80 [95% CI: 2.36 – 19.57] and HR: 4.86 [95% CI: 1.68 – 14.10] for hospitals 1, 4 and 11, respectively.

Characteristic	**Hospital**											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total**
No. of patients	35	53	27	13	22	37	10	34	21	11	22	285
Male gender [%]	69	59	63	69	59	68	50	77	57	82	59	65
Age ≥ 65 yrs [%]	51	55	59	54	73	62	70	56	52	27	41	55
CAD [%]	33	23	15	31	14	22	40	29	33	27	18	25
PVD [%]	6	8	7	23	9	3	30	9	10	18	5	9
Diabetes [%]	20	43	44	46	36	27	50	21	33	9	14	31
BMI ≥ 30 kg/m^2 [%]	3	17	8	0	19	11	20	24	15	0	14	13
RRT prior to cannulation [%]	69	74	82	69	59	51	80	85	76	91	73	72
Forearm AVF [%]	66	42	33	85	46	76	50	62	62	36	64	56
SF-rate per hospital [%] [*N*=27]	17.1	5.7	7.4	38.5	4.5	2.7	0	8.8	0	9.1	22.7	9.5

Table 4. Patient characteristics and secondary failure rate per hospital

Results are presented as percentages.

CAD = coronary artery disease, PVD = peripheral vascular disease, BMI = body mass index, RRT = renal replacement therapy, AVF = arteriovenous fistula, SF-rate = secondary failure rate.

Discussion

In the present prospective multicenter study we have shown that AVF patency and functional patency are markedly different. This difference appears to be caused by high primary failure rates. After adjustment for potential risk factors, primary functional patency was only decreased in diabetics. Secondary failure rate among participating hospitals varied from 0-38% and was not related to patient characteristics or cardiovascular risk factors. Compared to the hospitals with a low secondary failure rate combined, 3 hospitals had a significantly higher risk for secondary AVF failure.

The thrombosis rate at 0.14 episodes per patientyear at risk was well below current outcome goals (0.25 per py) [1]. Regarding the multicenter character of this study, the K/DOQI goal seems to be more than reasonable.

Patency rates

A significant proportion of the AVFs suffer from primary failure during the first weeks after surgery [6, 11, 14]. However, when patency rates are calculated starting at the day of first cannulation, primary failed AVFs are not included. In order to prevent confusion and incorrect comparisons we discriminated patency from functional patency as reported by Sidawy *et al.* [13]. Functional patency started when a vascular access had been successfully used for hemodialysis treatment for the first time; patency started at the day of surgical AVF creation. Whereas primary AVF failure was extensively studied and reported earlier by our group [11], we focused on aspects of functional patency in the present study.

Primary functional patency was similar to rates in current literature [15]. Our 18-months secondary functional patency was somewhat higher at 86% (median: 690+ days). The difference may be explained by the fact that more than half of the reports used in Huber’s review were published before the appearance of the first K/DOQI guidelines [15], and surveillance programs and preventative stenosis correction were not common practice yet. In contrast, 18-months secondary patency (from creation date) was 67%. The long-term difference of approximately 20% appears to be caused by a significant primary failure rate. Thus, after adequate maturation resulting in successful initiation of HD treatment, only little fistulas are abandoned (table 2). Consequently, reduction of primary failures is likely to result in greatest patency improvements.

Diabetes was identified as risk factor associated with loss of primary functional patency (HR: 1.70), but not with secondary failure [16]. These results indicate that diabetics may encounter more complications during fistula life but if treated adequately, functionality can be maintained as long as in non-diabetics, regardless of the anatomical location of the anastomosis [17]. Similar results were observed for primary functional patency in elderly, albeit that the hazard ratios did not reach significance [18]. In contrast to a report by Kats *et al.*, we did not observe any effects of obesity on secondary failure [19]. Similarly, BMI was not related to an increased risk of primary failure either [11]. All other factors including gender, coronary artery disease, peripheral vascular disease, fistula location and renal replacement therapy prior to cannulation did not reduce AVF survival [20].

Hospital specific aspects

Secondary failure rate varied from 0-38% between the hospitals participating in CIMINO resulting in significant difference of secondary functional patency rates (log rank test: $P < 0.01$). The limited number of patients and secondary failures hindered analysis of individual hospital effects. However, the 3 hospitals in the high secondary failure-rate subgroup each had a significant higher risk of secondary failure compared to the other hospitals combined. Since none of the cardiovascular risk factors were related to secondary failure, local practice patterns may have played an important role. Similarly, practice patterns have been shown to be involved in vascular access placement [21-23] and in the risk of primary failure [11]. Although this study was not designed to identify aspects of secondary failure in detail, surgical aspects are less likely to be involved. Indeed, Prischl *et al.* suggested that the surgeon creating the fistula was involved in patency but these differences were predominantly generated during the first months after fistula creation [24]. In the present study, only successfully used AVFs were analyzed.

Practice aspects such as negligent shunt surveillance (dialysis unit), delayed action to detected stenoses (nephrologists) or inadequate PTA / surgery procedures (radiologist / vascular surgeon) may have contributed to the current findings. Further in-center analysis can be useful to improve secondary functional patency rates but obviously the multidisciplinary character of complication handling requires a well functioning vascular access team [25].

Patient selection and future improvements

The greatest improvements in fistula patency are to be achieved during the peri-operative period [6, 11]. Diabetics in particular, bus also elderly and women can be expected to encounter early complications and require extra attention. In these risk groups, upper arm AVFs may be more appropriate resulting in less complications [17]. Next to careful physical examination and pre-operative duplex scanning, additional 'vascular wall-quality' tests such as the arterial resistance index at reactive hyperemia [26] may be useful in determining the best location for creation of the anastomosis. Optimal anastomosing techniques [27], alternative locations for anastomosing [28, 29], and aggressive treatment of primary failing fistulas [30, 31] should also further increase the proportion of functional AVFs.

The clear relation between the hospital of access placement and AVF survival in 3 participating hospitals further support the idea that the most important prerequisite for optimal vascular access care is a motivated vascular access team that is willing to meet current standards and adjusts practice patterns to AVF outcomes [25].

Limitations

Fistulae are preferred over grafts because of superior long-term patency. Follow up time in our study was limited to 18 months. In ePTFE grafts, six, 12 and 18 month secondary functional patencies are approximately 76%, 65% and 55% [15]. When primary graft failures (approximately 10%) are also included, secondary graft patency from date of creation is likely to decrease slightly, expecting fistula survival to be superior from 12 month on (Table 2).

However, extra follow up time is required to obtain further insight in long-term AVF patency.

Conclusion

A total of 76% of the vascular accesses in our prospective database were native AVFs. Using recently suggested standardized definitions we showed a marked difference between patency and functional patency that can be explained by high primary failure rates. Furthermore, after adjustment for potential risk factors, secondary AVF failure was more likely in 3 of the 11 participating hospitals suggesting an important role for local practice patterns.

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Chapter 6

Access blood flow in mature arteriovenous fistulas is related to the risk of secondary failure

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Abstract

Background: A functional vascular access is able to deliver a flow rate of 350-400 mL/min without recirculation. Once clinically matured a proportion of the arteriovenous fistulas (AVFs) fail during follow up (secondary failure).

Study design: Prospective, multicenter observational study.

Setting & participants: 175 Dutch hemodialysis patients with a new arteriovenous fistula.

Predictor: First access blood flow measurement after cannulation for HD (baseline Qa) and patient characteristics.

Outcomes & measurements: A failed AVF was defined as a permanently failed AVF or an AVF that required at least one surgical or endovascular intervention, after achievement of adequacy for hemodialysis. Factors associated with secondary AVF failure and mean Qa were determined using Cox proportional-hazards and linear regression models. Primary AVF failures were excluded from analyses.

Results: Baseline Qa of non-failed and failed forearm AVFs was 757 ± 52 (SE) mL/min and 544 ± 57 mL/min, respectively (P = 0.03), and 1322 ± 103 mL/min and 898 ± 157 mL/min in non-failed and failed upper arm AVFs, respectively (P = 0.05). The risk of forearm AVF failure was graded and decreased with 15% (95% confidence interval (CI): 2-26%) by each 100 mL/min increase in baseline Qa. Diabetics had a significantly increased risk of upper arm AVF failure (HR: 3.32, 95% CI: 1.11–9.95). Qa did not change from approximately 4-5 months after creation. In non-failed forearm AVFs, diabetes mellitus was related to a lower Qa (β = -314 ± 122, P = 0.01) and BMI was related to a higher Qa (β = 36 ± 13; P = 0.01). For non-failed upper arm AVFs no relations with risk factors were found.

Limitations: Unequal timing and number of Qa measurements.

Conclusions: In adequately matured AVFs, access blood flow measured shortly after first cannulation is related to the risk of secondary failure but the time to failure is not related to baseline Qa. Furthermore, diabetics and underweight HD patients can be expected to have lower Qa.

Introduction

Adequate hemodialysis treatment in end-stage renal disease (ESRD) patients requires a functional vascular access that is able to deliver a flow rate of 350-400 mL/min without recirculation for the total duration of hemodialysis (HD) [1, 2]. This requires an access blood flow (Qa) rate of at least 500 mL/min. In order to meet current outcome goals in the 'AVF only' era [3], more patients with compromised vessels will receive native vascular accesses and possibly jeopardize functional AVF obtainment [4]. Primary AVF failure occurs in a substantial proportion of HD patients [5]. We have recently reported on risk factors of primary failure [6]. However, once an AVF has matured to a condition ready to be cannulated, some fail during follow up. Little is known on factors that are associated with this secondary failure and whether access flow measurements, which are accepted as the preferred method for arteriovenous access function monitoring [7], are related to failure.

A multicenter guidelines implementation program, CIMINO (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment), was initiated to increase AVF use in a proportion of the Dutch hemodialysis facilities [8]. In addition, this prospective multicenter observational study was designed to learn more about both early and late functionality of the AVF.

The aim of the present study was to evaluate in patients with adequately matured AVFs, whether access flow measured shortly after first cannulation was related to secondary failure, and which factors were associated with access blood flow.

Methods

As part of the guidelines implementation program CIMINO (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment), vascular access coordinators in 11 Dutch dialysis facilities included all hemodialysis patients or patients with chronic renal failure (CRF) requiring a new permanent vascular access in a computerized database [8]. During the program Transonic® access blood flow measurements were performed and recorded. Primary AVF failures were excluded from current analyses.

Definitions

Duration of previous renal replacement therapy (RRT) was defined as the period from first hemodialysis / peritoneal dialysis treatment or kidney transplantation date to the date of AVF cannulation in this study. *Coronary artery disease (CAD)* was defined as a history of coronary angioplasty, coronary bypass surgery, endovascular stenting, or myocardial infarction. *Peripheral vascular disease (PVD)* was defined as a history of angioplasty, surgical endarterectomy, endovascular stenting or bypass surgery of the iliac and/or femoral arteries, but also amputation due to peripheral artery occlusive disease. *Cerebrovascular disease* was defined as the same interventions in the carotid arteries, and also included previous cerebrovascular accidents (CVA). *Diabetes mellitus (DM)* was defined as current use of hypoglycemic medication or use of insulin, or when the diagnosis was recorded in a medical record. *Primary failure (PF)* was defined as an AVF that did not develop to maintain dialysis or thrombosed before the first successful cannulation for hemodialysis treatment, regardless of eventual AVF abandonment or not. This definition includes 1) inadequate maturation, 2) early thrombosis, 3) failure of first cannulation, and 4) other complications such as ischemia or infection. *Access blood flow (Qa)* value was calculated as the mean of 3 consecutive access flow measurements during one hemodialysis session performed at approximately 30 minutes after starting HD treatment. *Baseline Qa* was defined as the first Qa measurement during follow up. A *failed AVF* was defined as an AVF that permanently failed, or an AVF that required at least one surgical or endovascular intervention after it had achieved adequacy for hemodialysis. *Mean access blood flow* was determined using all Qa measurements per non-failed AVF during follow up.

Statistical analysis

Data are presented as means ± SE. The T-test was used to compare baseline Qa and duplex measurements of failed and non-failed AVFs. Spearman's rank correlation test was used to study the relation of baseline Qa and time to AVF failure. The risk of AVF failure was studied in multivariate Cox proportional-hazards models for forearm and upper arm AVFs, separately. One way repeated measures ANOVA with Student-Newman-Keuls post-hoc test was used to study Qa changes in time. Patient characteristics possibly related to mean Qa were studied using univariate and multivariate linear regression models for forearm and upper arm AVFs separately. Analyses were carried out using SPSS 12.0 for Windows® (SPSS Inc., Chicago, IL) and SigmaStat 3.11 (Systat Software Inc., San Jose, CA).

Results

Patients

From 1 May 2004 to 1 May 2006, a total of 649 permanent vascular accesses, representing all inclusions of CIMINO, were recorded in the database. This included 491 AVFs (76%) in 395 patients. Access flow measurements were available from 103 forearm AVFs and 75 upper arm AVFs in 175 patients.

Relation of baseline Qa with AVF failure

On 1 May 2006, median follow up time was 283 days (interquartile range (IQR): 150-431 days) and 105 days (IQR: 35-199 days) in non-failed and failed forearm AVFs, respectively. In non-failed and failed upper arm AVFs, median follow up time was 233 days (IQR: 137-382 days) and 87 days (IQR: 34-145 days), respectively. Baseline characteristics of 100 forearm AVF patients and 75 upper arm AVF patients are shown in table 1.

	Forearm AVF		**Upper arm AVF**	
	failure	**no failure**	**failure**	**no failure**
No. of patients	26	74	16	59
Age [yrs]	63.5±13.1	65.7±12.9	59.8±13.1	59.8±15.5
Male gender [%]	61.5*	77.0	37.5	55.9
RRT prior to cannulation [%]	65.4	58.1	75.0	81.4
Duration RRT [months]	3.7±9.8	24.1±154.4	9.9±15.9	39.2±172.6
Coronary artery disease [%]	19.2	25.7	18.8	16.9
Cerebrovascular disease [%]	11.5	5.4	6.3	15.3
Peripheral Vascular Disease [%]	0.0	8.1	0.0	11.9
Diabetes mellitus [%]	30.8	21.6	68.8*	33.9
Diabetes as primary cause ESRD [%]	19.2	12.2	37.5	20.3
Body height [m]	1.71±0.11*	1.75±0.09	1.68±0.11	1.69±0.09
Body mass index [kg/m²]	24.7±4.3	25.3±4.1	26.2±4.0	24.0±4.3
Caucasian ethnicity [%]	92.3	81.1	50.0*	69.5

Table 1. Baseline characteristics of patients with and without AVF failure during follow up. * *P*-values were ≤ 0.15 on univariate analysis and introduced in a multivariate Cox regression model. Means are presented ± SD. RRT = renal replacement therapy, ESRD = end-stage renal disease

In the forearm AVF group, baseline Qa of non-failed and failed AVFs was 757 ± 52 mL/min and 544 ± 57 mL/min, respectively (*P* = 0.03). In the upper arm AVF group, baseline Qa of non-failed and failed AVFs was 1322 ± 103 mL/min and 898 ± 157 mL/min, respectively (*P* = 0.05) (Figure 1).

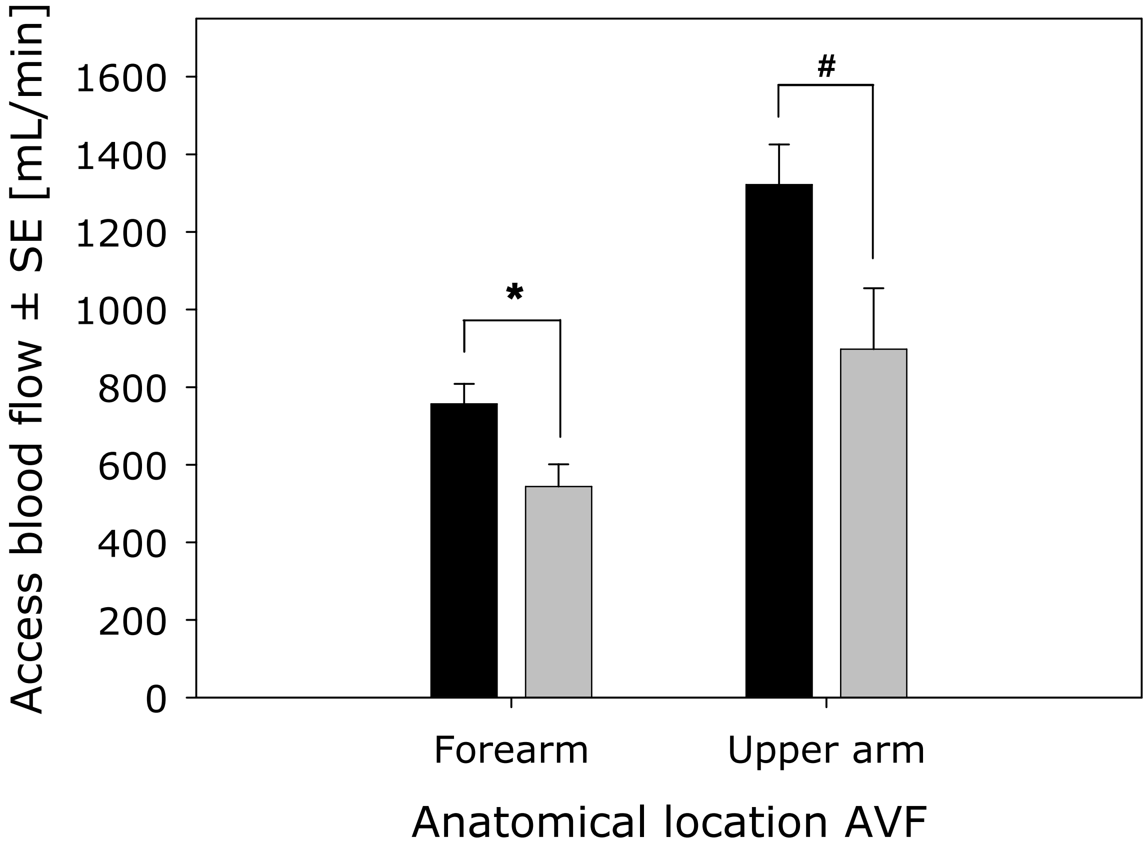

Figure 1. Baseline access blood flow (± SE) in forearm and upper arm AVFs. The black bars represent the baseline Qa measurement of the AVFs that did not require any interventions during follow up. The grey bars represent the baseline Qa measurement of the AVFs that permanently failed or required ≥1 intervention during follow up.
***** *P* = 0.03; # *P* = 0.05

Baseline Qa was different between the failed forearm and upper arm AVFs (*P* = 0.02), and between the non-failed forearm and upper arm AVFs (*P* < 0.001). Time from access placement to baseline Qa measurement was 84 ± 10 days and 55 ± 8 days in the non-failed and failed forearm AVFs (*P* =

0.10), and 60 ± 8 days and 65 ± 13 days in the non-failed and failed upper arm AVF group (*P* = 0.72).

There was no significant relation between baseline Qa and time to AVF failure in the forearm AVF group (ρ = 0.01, *P* = 0.97), nor in the upper arm AVF group (ρ = -0.02, *P* = 0.94). The risk of forearm AVF failure was graded and decreased with 15% (95% confidence interval (CI): 2-26%) by each 100 mL/min increase in baseline Qa (Table 2). Diabetics had a significantly increased risk of upper arm AVF failure (HR: 3.32, 95% CI: 1.11 – 9.95).

Forearm AVFs	**H.R.**	**95% C.I.**	***P*-value**
Qa per 100 mL/min	0.85	0.74 – 0.98	0.03
Female gender	1.03	0.38 – 2.83	0.95
Body height per cm	0.97	0.93 – 1.02	0.23
Upper arm AVFs	**H.R.**	**95% C.I.**	***P*-value**
Qa per 100 mL/min	0.90	0.81 – 1.01	0.06
Diabetes mellitus	3.32	1.11 – 9.95	0.03
Non-caucasian ethnicity	1.76	0.64 – 4.84	0.28

Table 2. Results of multivariate Cox proportional hazards model on potential risk factors for AVF failure. Only characteristics that had a *P*-value of ≤ 0.15 in univariate analysis were included the multivariate analysis with Qa.
H.R. = hazard ratio; C.I. = confidence interval

In 66% of the forearm AVFs and approximately 70% of the upper arm AVFs, preoperative duplex examinations with internal vessel diameters were available (Table 3). The arterial diameter of failed forearm AVFs was smaller than of non-failed forearm AVFs (*P* = 0.02). Venous diameters were not different between failed and non-failed groups.

AVF	Vessel	*N*	Failure		*P*-value
			yes	no	
Forearm	artery	66 (66%)	2.29 ± 0.11	2.67 ± 0.09	0.02
	vein	66 (66%)	2.26 ± 0.13	2.44 ± 0.12	0.39
Upper arm	artery	52 (69%)	4.45 ± 0.21	4.42 ± 0.16	0.92
	vein	53 (71%)	2.88 ± 0.38	3.53 ± 0.27	0.74

Table 3. Preoperative internal diameters [millimeters ± SE] of failed and non-failed AVFs as measured by duplex ultrasound

N represents the total number vessels that were examined.

Access blood flow characteristics

A total of 21 non-failed forearm AVFs and 15 non-failed upper arm AVFs had Qa measurements at ≥ 3 consecutive time points. In the forearm AVF group, median time to first cannulation was 49 days (IQR: 44-77 days) and Qa did not change significantly from approximately 5 months after creation onward (699 ± 63 mL/min at 148 ± 18 days, 771 ± 54 mL/min at 243 ± 26 days and 792 ± 61 mL/min at 339 ± 30 days; P = 0.54) (Figure 2). In the upper arm AVF group, median time to first cannulation was 50 days (IQR: 42-84 days) and Qa did not change significantly from approximately 4 months after creation onward (1483 ± 174 mL/min at 119 ± 15 days, 1549 ± 215 mL/min at 250 ± 19 days and 1572 ± 241 mL/min at 343 ± 17 days; P = 0.82) (Figure 2).

In non-failed AVFs, mean forearm access blood flow was significantly lower than mean upper arm Qa (788 ± 50 vs. 1310 ± 171 mL/min, $P < 0.01$). Patient characteristics or cardiovascular risk factors that were related to Qa in univariate analysis are shown in table 4. Diabetes mellitus and BMI entered multivariate analysis in forearm AVFs, and age ≥ 65 years, coronary artery disease and cerebrovascular disease entered multivariate analysis in upper arm AVFs. In multivariate analysis, diabetes mellitus (β = -314 ± 122, P = 0.01) and BMI (β = 36 ± 13; P = 0.01) were significantly associated with mean Qa in forearm AVFs. No factors were significantly related to mean Qa in upper arm AVFs.

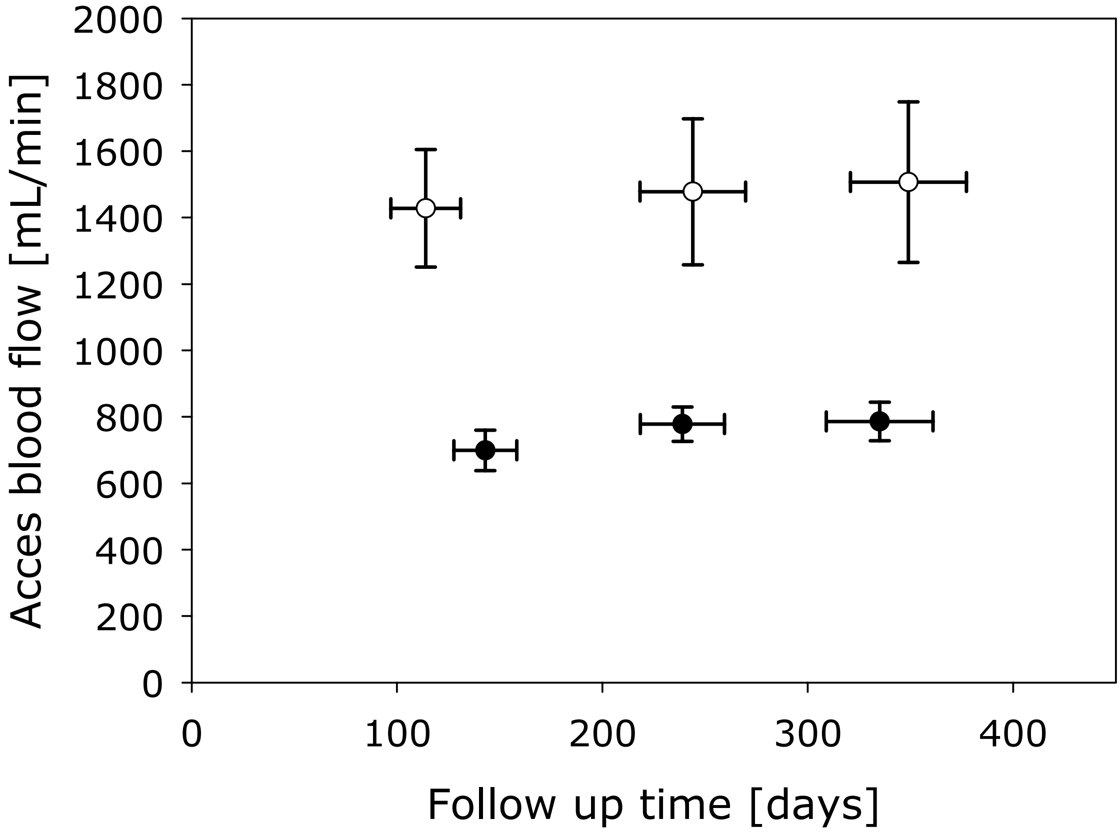

Figure 2. Access flow (± SE) in 21 non-failed forearm AVFs (solid circles) and 15 non-failed upper arm AVFs (open circles).

Qa did not significantly change in time in the forearm AVFs: $P = 0.54$. Friedman repeated measures ANOVA on ranks for upper arm AVFs: $P = 0.82$

Characteristic	**Mean access flow [mL/min] ± SE**	
	Lower arm [N=74]	**Upper arm [N=59]**
Mean	788 ± 50	1310 ± 171
Female	832 ± 154	1221 ± 122
Male	775 ± 48	1380 ± 164
Age ≥ 65 yr.	737 ± 71	1047 ± 105*
Age < 65 yr.	851 ± 71	1503 ± 160
Coronary artery disease	705 ± 96	877 ± 122*
No coronary artery disease	817 ± 59	1398 ± 122
Cerebrovascular disease	741 ± 156	949 ± 174*
No cerebrovascular disease	791 ± 53	1375 ± 119
Peripheral vascular disease	608 ± 95	917 ± 169
No peripheral vascular disease	804 ± 54	1363 ± 116
Diabetes	624 ± 72*	1106 ± 101
No diabetes	833 ± 60	1414 ± 150
BMI ≥ 24 kg/m²	868 ± 84	1280 ± 126
BMI < 24 kg/m²	705 ± 50*	1334 ± 163
Body height ≥ 1.70 m	797 ± 51	1210 ± 136
Body height < 1.70 m	783 ± 141	1420 ± 165

Table 4. Mean access flow (± SE) per potential risk factor for decreased Qa in non-failed AVFs

***** *P*-values were ≤ 0.15 on univariate analysis and introduced in a multivariate linear regression model. Median BMI was used for the current table.

Discussion

After achievement of adequacy for hemodialysis, a proportion of the AVFs fail during follow up. The relation of access flow measurement shortly after first cannulation and secondary failure has not been investigated. In the present prospective multicenter study, we showed that baseline access blood flow (Qa) of failed AVFs was significantly lower then in non-failed AVFs. Qa was also different within failed and non-failed groups. Interestingly, the risk of forearm AVF failure was graded and decreased with 15% by each 100 mL/min increase in baseline Qa. The risk of upper arm AVF failure borderline significantly decreased with 10% by each 100 mL/min. Although AVFs can be regarded as clinically adequate for hemodialysis treatment, our findings suggest that low Qa AVFs are more likely to encounter complications during follow up than high flow AVFs.

Furthermore, Qa did not change from approximately 5 months postoperative onward and in forearm AVFs lower mean Qa was positively associated with the presence of diabetes mellitus and inversely with BMI. No factors were significantly associated with decreased mean upper arm AVF Qa.

Relation of baseline Qa with AVF failure

Arteriovenous fistula placement causes dramatic changes of hemodynamics and results in wall shear stress differences within the outflow vein [9]. Intimal hyperplasia, and subsequent stenosis formation, develops preferentially in regions of low wall shear stress [10-13]. Whereas shear stress is positively related with blood velocity and inversely with internal diameter [14-16], it might explain why reduced baseline Qa at approximately 9 weeks after creation was indicative for AVF failure during follow up (Figure 1). Interestingly, this also explains why upper arm AVFs, using larger vessels, encounter complications starting at higher blood flow rates than forearm AVFs.

However, the absence of a relation between baseline Qa and the time to AVF failure suggests involvement of additional aspects such as vessel wall characteristics or surgical techniques. Increased anastomosis angles cause increased flow separation regions near the toe of the anastomosis [17-19], and more extreme variations in time-averaged wall shear stress and oscillatory shear along the bed of the anastomosis [20]. To what extent these aspects are involved remains speculative and require further investigation.

The lower baseline Qa of failed forearm AVFs is likely to be related to a smaller preoperative inflow artery diameter (Table 3). However, in upper arm AVFs arterial diameters were not different between failed and non-failed AVFs. The optimal arterial diameter for achievement of HD adequacy in forearm AVFs has recently been suggested to be 2.1-2.5 mm [21]. In larger arteries, more significant roles for systemic aspects such as cardiac output and blood pressure can be expected [22]. Venous diameters were not different between failed and non-failed AVFs suggesting that the preoperative vein size is less important for Qa then inflow artery size.

Access blood flow characteristics

In non-failed AVFs, mean Qa at 788 ± 50 mL/min was slightly less then reported by others [23], but upper arm Qa (1310 ± 171 mL/min) was comparable [24, 25]. Interestingly, no significant changes in Qa were observed during follow up in both groups (Figure 2). Similar results were observed in a group of patients with radio-cephalic wrist AVFs [23]. However, the patients in the present study were observed from date of AVF creation, while mean time from AVF placement to study start in the Italian study was more than 5 years [23]. Moreover, a significant part of that study population had been treated for AVF failure before, thereby introducing post-interventional hemodynamic effects that affect Qa. In the present study we have explicitly selected non-failed AVFs to obtain unbiased insight in the follow up of Qa.

Fistula outflow vein diameter increases during the first weeks after surgery [26, 27] and is accompanied by a great blood flow rise [27, 28]. It is unknown whether venous dilation proceeds afterwards. Regarding the stabilization of Qa in both forearm and upper arm fistulas one would expect the natural outward remodeling process of the vein to seize. This is physiologically supported by the fact that flow depends on the radius to the fourth power in Poiseuille's law for laminar flow. Moreover, after initial post-operative dilation the radial artery proximal to a wrist AVF seizes to increase in diameter furthermore [29]. The brachial artery diameter has been shown to increase until 1 year after wrist AVF creation without reduction of wall shear stress [29]. Whereas cardiac output (CO) and mean arterial pressure

(MAP) determine the magnitude of Qa [22], those functions are likely to limit Qa, predominantly in elderly [30].

Radial artery media calcification, atherosclerosis and increased intima media thickness are more often present in elderly and diabetics [31, 32]. These injurious wall changes cause impaired dilation and reduced vascular remodeling capacity leading to early AVF failure [33]. Increased use of upper arm AVFs in diabetics and elderly has been shown to equal primary failure and patency rates compared to non-diabetics and younger ESRD patients [34, 35]. In addition to underweight ESRD patients, diabetics and elderly can be expected to have a lower Qa. These findings may have consequences for optimization of preoperative vessel selection in order to obtain high flow AVFs. Preoperative examination should be directed towards an individual patient evaluation model. Demographics, (cardiovascular) risk factors, physiological and morphological vessel parameters combined will then result in a score that predicts AVF function leading to a reduction of failure rates.

Limitations

In contrast to results by others [36], figure 2 may suggest a limited additional flow increase between 3 and 6-8 months after forearm AVF creation. Our study was not sufficiently powered to achieve significance. A next study is required to address that question. To obtain more insight in fistula physiology, it can be interesting to determine internal vessel diameters from 6 weeks after AVF creation onward. However, the most important conclusion drawn from figure 2 is that the initial flow increase during maturation is pivotal for achieving adequacy for hemodialysis.

We were not able to discriminate between various upper arm AVF configurations. Brachial-median cubital and perforating vein AVFs may have been included in the current group. Nevertheless, mean upper arm Qa was comparable to others [24, 25]. This observation suggests that the inflow artery size is more determining for long term Qa then the size of the outflow vein.

Cardiac output and blood pressure are very important for Qa [22]. These parameters were not recorded in the present study. Despite this omission we can confirm that the found factors are related to decreased Qa [37]. To what extent demographics and cardiovascular risk factors are specifically related to decreased Qa remains to be investigated in a study including both CO and blood pressure.

Conclusion

After achievement of adequacy for hemodialysis, baseline Qa is lower in AVFs that fail during follow up. However, these baseline Qa values differed significantly for forearm and upper arm AVFs. Qa in non-failed AVFs remained unaltered after first cannulation for hemodialysis. This finding underscores the importance of an adequate flow increase during maturation. Furthermore, Qa was lower in diabetic and underweight hemodialysis patients implying extra attention to preoperative vessels selection in various patient subgroups.

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Chapter 7

A helical PTFE arteriovenous access graft to swirl flow across the distal anastomosis; results of a preliminary clinical study

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Abstract

Intimal hyperplasia develops preferentially in regions where the blood flow is stagnant and wall shear stress low. The small amplitude helical geometry of the SwirlGraft™ was designed to ensure physiological-type swirling flow, and thus suppress the triggers. We report the first conceptual testing of the SwirlGraft™. Primary, assisted primary and secondary patency rates at 6 months in 20 patients were 57.9 ± 11.4%, 84.4 ± 8.3% and 100 ± 0.0%. There was angiographic evidence of reduction of helical geometry in a proportion of the grafts.

The helical graft is associated with high assisted primary and secondary patency. Elaboration of the surgical implantation techniques and an improved SwirlGraft™ design can be expected to exploit the advantages of the helical concept.

Introduction

Failure of ePTFE vascular access grafts is predominantly caused by progressive intimal hyperplasia at the graft/vein anastomosis. Intimal hyperplasia (IH) develops preferentially in regions where flow is stagnant and wall shear stress is low [1-4], causing endothelial gene regulatory responses [5].

Native arterial geometry is three-dimensional, causing blood swirling and the expectation of relatively uniform wall shear stress and inhibition of flow stagnation [4, 6]. However, arterial bypass grafts are essentially two-dimensional [7], and hence associated with adverse fluid dynamics.

The Small Amplitude Helical Technology (SMAHT) prosthesis, SwirlGraft™, was developed to achieve physiological-type swirling in and downstream of vascular access grafts. We report the first test in patients.

Report

Between December 2004 and November 2005, eleven men and 9 women (median age 72, range 24 - 86 yrs.) requiring PTFE vascular access grafts were recruited in 6 centers (Table 1). Patients were treated according NKF-K/DOQI guidelines [8], with institutional review board approval. Graft patency rates were calculated by life table method using SPSS 12.0 (Chicago, USA) for statistical analysis. Antibiotic, anticoagulation and anesthetic regimes were as per unit protocol.

The 20 Swirlgraft™ implantations were uneventful. Mean suture line blood loss duration was 2.9 minutes (0 to 10 min), procedure duration was 78 minutes (45 to 105 min), and technical success rate at 1 month was 90%.

On 1 June 2006, the mean follow-up was 9.5 months (range 1.6 - 15.6), and the total follow up time 15.9 patient-years (py). One patient was transplanted and 3 patients died of non graft related causes (2 stopped dialysis treatment, 1 myocardial infarction).

Demographics & co-morbidities	***N* = 20**
Male gender	55%
Age [yr]	72 (24-86)
BMI [kg/m2]	25.3 ± 4.5
Prior VA surgery [%]	65
Smoking [%]	25
Diabetes [%]	30
Hypertension [%]	50
Ischemic heart disease [%]	20
Peripheral vascular disease [%]	15
Diagnosis renal failure	
glomerulonephritis [%]	10
interstitial nephritis [%]	5
cystic kidney disease [%]	5
congenital disease [%]	5
renal vascular disease [%]	25
diabetes [%]	10
other (multisystemic) diseases [%]	15
unknown aetiology [%]	25

Table 1. Baseline demographics and co-morbidities.
BMI = body mass index; VA = vascular access; median (range); mean ± SD

The 6-month primary patency rate was 57.9% ± 11.4 (SE) (Figure 1). Nine patients developed 18 stenoses. Six (33%) were identified in the outflow vein and 4 (22%) at the graft/vein anastomosis. Seven stenoses were located in the graft and at the proximal anastomosis. One patient had an unrelated stenosis of the brachiocephalic vein for which he was observed. The thrombosis-incidence was 0.69/py. Ten out of the 11 thromboses occurred in 2 patients.

Twenty interventions were required for graft salvage: 11 PTA procedures (0.69/py), 7 surgical revisions (0.44/py) and in 2 cases mechanical thrombolysis (0.13/py). The 6-month assisted primary and secondary patency were 84.4% ± 8.3 and 100% ± 0.0 respectively.

Angiograms performed when access flow measurement or duplex suggested a flow problem, revealed reduction of helical geometry in at least 3 of 9 angiograms at a mean of 5.1 months.

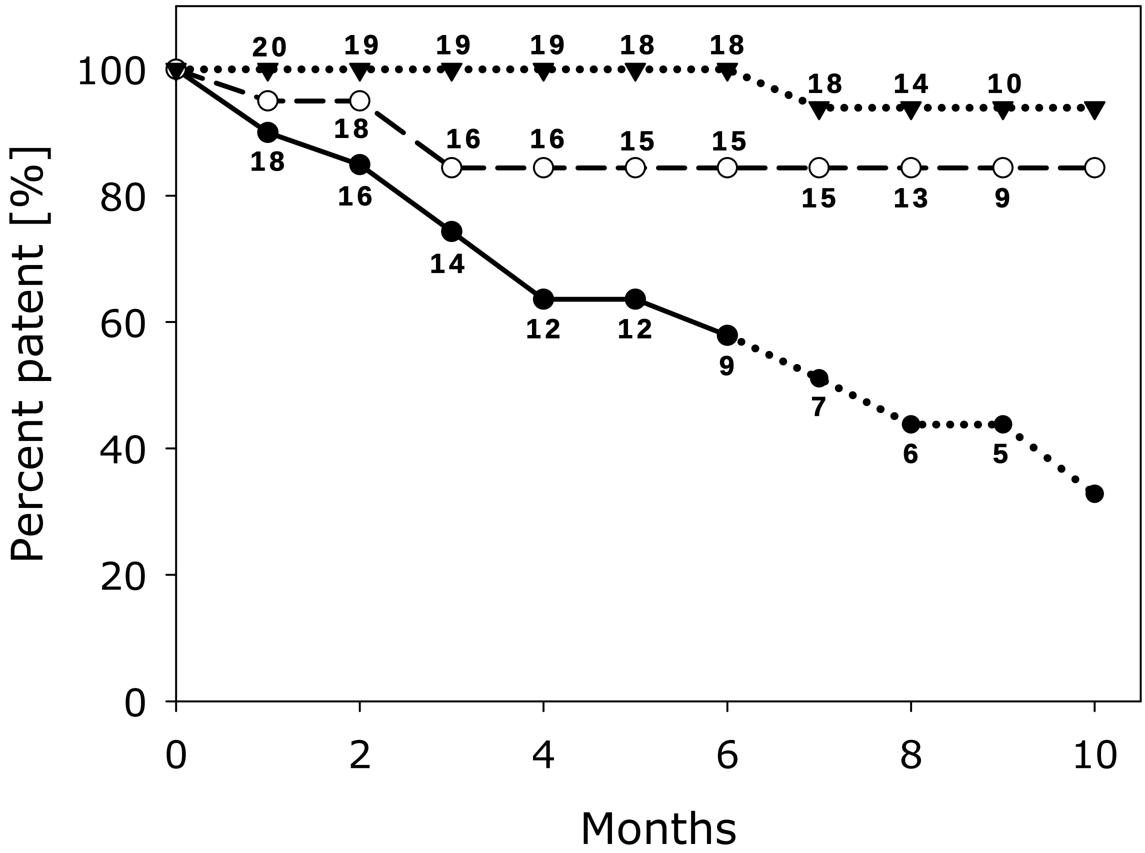

Figure 1. Patency rates of the SwirlGraft™ with number of patients at risk. Solid line = primary patency; Dashed line = assisted primary patency; dotted line = secondary patency.

Discussion

Review of currently available literature suggests that one year primary and secondary patency rates of standard ePTFE hemodialysis grafts are approximately 40% and 65%, respectively [9]. As most failures occur secondary to intimal hyperplasia at the graft/vein anastomosis, inhibition of this process could have a major impact on morbidity and healthcare costs of end-stage renal disease patients. In this prospective, first in-man study, technical success (90% <1 month) is in line with DOQI standards [8]. The 6-month primary patency at 58% is similar to that of standard ePTFE AV-grafts but the assisted primary (84%) and secondary patency (100%) rates are at the highest end of reported series and suggest possible benefit. Angiographic examination in a limited number of grafts suggests that there was reduction of helical geometry at or after implantation, implying function like that of conventional ePTFE prostheses (Figure 2). This may have been due to overstretching during implantation, or by elongation under arterial pressure; these problems have been addressed in subsequent iterations of the graft.

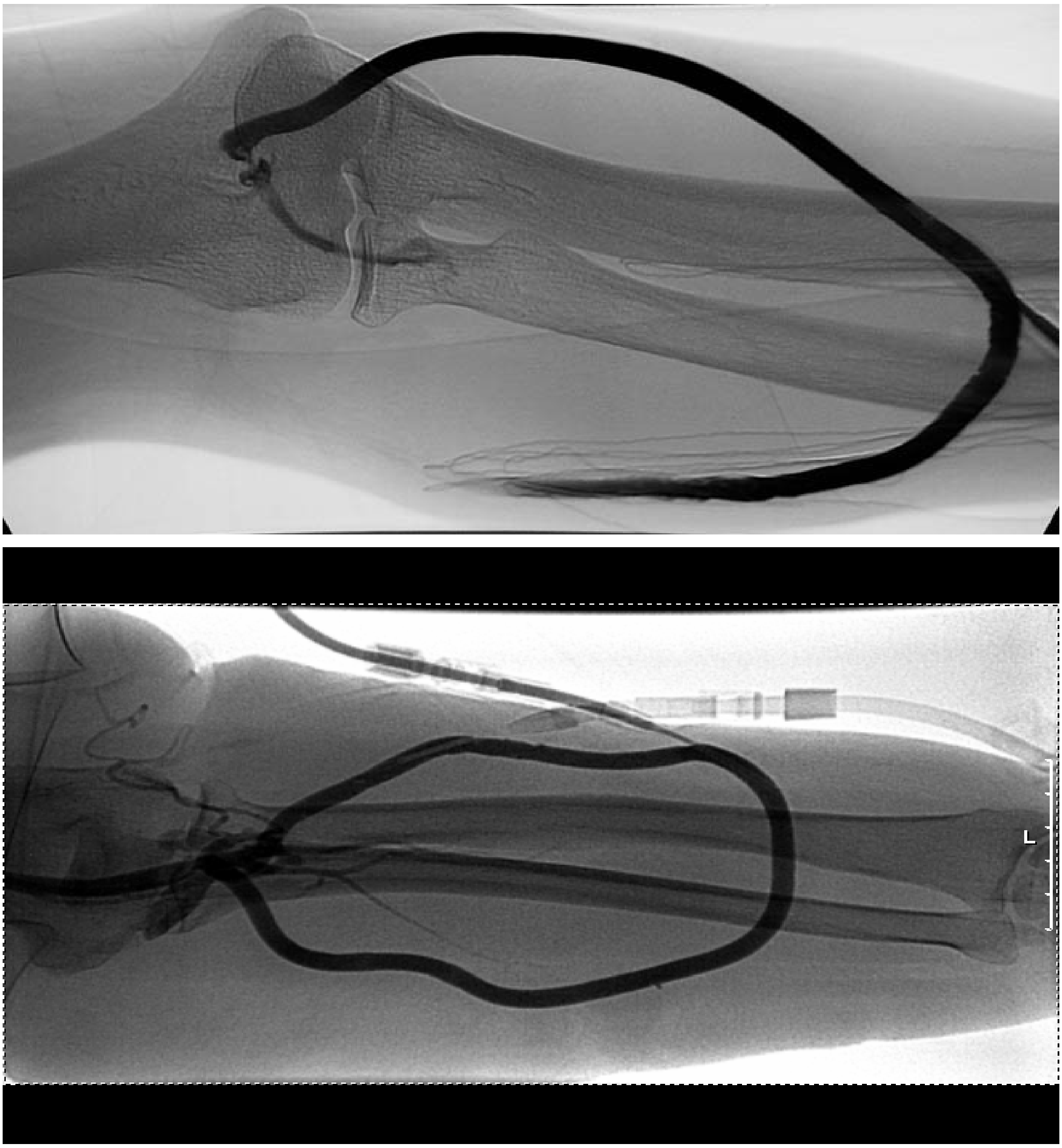

Figure 2. Upper angiogram: possible loss of graft helical geometry. Lower angiogram: intact graft helical geometry

The helical geometry of the SwirlGraft™ produces swirling and mixing of blood flow, in a manner like that believed to be present in native human arteries. Flow model experiments and computational fluid dynamic studies show that such conditions powerfully affect the flow across end-to-side anastomoses. Low wall shear is minimized and stagnation eliminated (Figure 3), reducing the likelihood of IH development [1, 4].

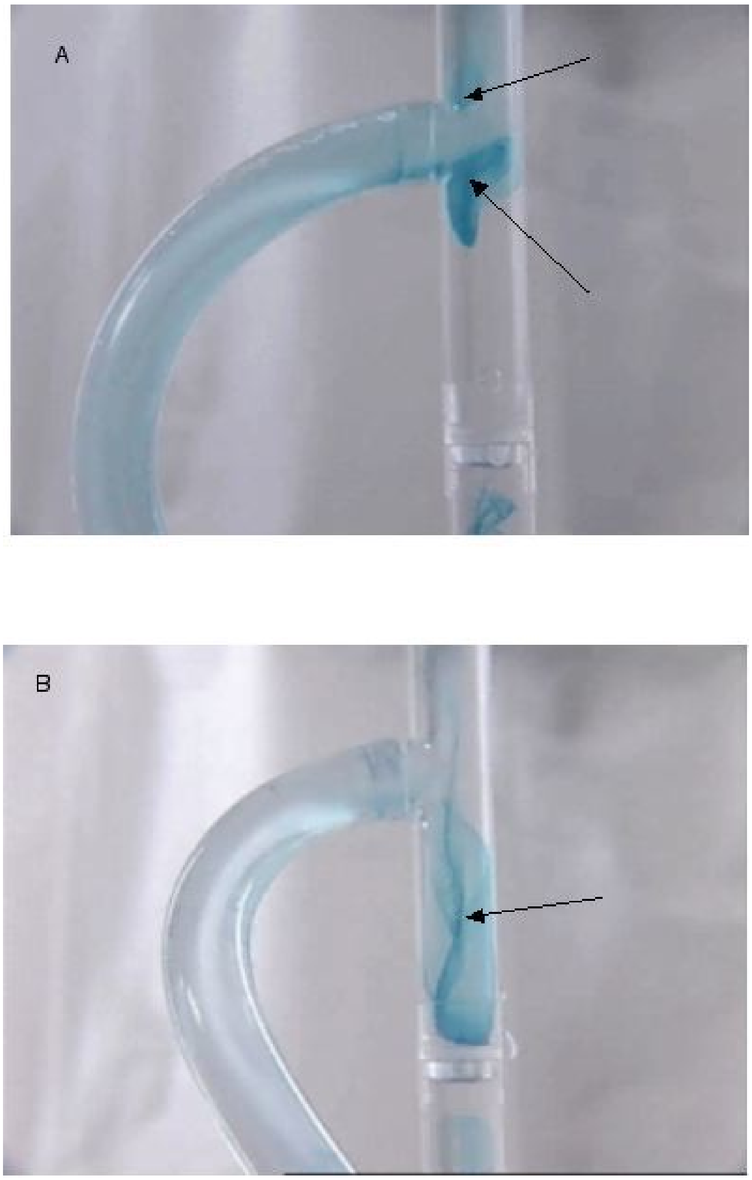

Figure 3. Ink flow studies of the distal anastomosis of simulated bypass grafts. In standard, planar anastomoses (3A, top), tracer remains in stagnant areas around the heel and toe of the anastomosis (arrowed) after the centre of the graft and host vessels has cleared. With non-planar helical-type geometry (3B, bottom), the heel and toe are clear of ink a similar time after tracer injection seen in 3A. Helical flow patterns can be seen in the occluded proximal (lowermost) limb of the model (arrowed). From: Caro *et al*.[4].

In a small porcine carotid artery – to – jugular vein study, there was markedly less intimal hyperplasia and thrombosis in SwirlGrafts™ than conventional ePTFE grafts [10]. In contrast to the present clinical study, the grafts were implanted during open surgical exposure, allowing attention to preservation of helical geometry.

Another potentially important finding of this study is the site of stenosis development; Kanterman *et al.* found that almost 60% of angiographic AV-graft stenoses were located at the distal anastomosis [11]. In our study however, only 22% of the stenoses were confined to this region and 33% were detected in the outflow vein. The explanation remains unclear.

Our thrombosis incidence (0.69 per py) exceeds DOQI standards [8], but only 2 grafts in this relatively small patient group caused 91% of the thromboses. So, salvaging has led to increased longevity at the expense of a higher thrombosis rate.

In conclusion, with the right modifications to implantation techniques and Swirlgraft™ design we believe a randomized controlled trial with this device is justified.

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Chapter 8

Cryoplasty to reduce intimal hyperplasia in a porcine arteriovenous graft model

A pilot study

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Abstract

Introduction

Percutaneous transluminal angioplasty (PTA) is a frequently used method for the treatment of arteriovenous graft stenosis. However, the intervention-free interval after PTA is very disappointing. Cryoplasty is a novel endovascular technique that combines conventional angioplasty with cold thermal energy, aiming at a reduction of intimal hyperplasia at the venous anastomosis.

Methods

In 5 pigs, ten ePTFE grafts were bilaterally inserted between the common carotid artery and internal jugular vein. One venous anastomosis was treated with a single cycle of cryoplasty at -10ºC and the contralateral anastomosis received conventional PTA. At 4 weeks, graft flow was measured and quantitative angiography was performed. Subsequently, the pigs were sacrificed and grafts with adjacent vessels were excised for histological analysis.

Results

Angiographic outflow vein diameter and graft blood flow in the cryoplasty group were not different from the control group (3.04 ± 0.51 versus 3.89 ± 0.70 mm and 703 ± 62 versus 815 ± 87 mL/min). Compared to the control group, intimal hyperplasia at the venous anastomosis was 49% reduced in the cryoplasty group (1.46 ± 0.46 versus 2.86 ± 0.62 mm^2).

Conclusion

The data in this study suggest that cryoplasty reduces intimal hyperplasia at the venous anastomosis of hemodialysis grafts compared to conventional PTA. These results justify additional research on this subject using our validated porcine model.

Introduction

Arteriovenous vascular access grafts are currently used by 42% of the prevalent hemodialysis patients in the United States [1]. One-year primary and secondary patency rates of these grafts are 40% and 60% respectively [2]. Hemodialysis graft failure is predominantly caused by progressive intimal hyperplasia (IH) in the venous outflow tract [3, 4], which is characterized by vascular smooth muscle cell proliferation, extracellular matrix deposition, and angiogenesis within the neointima and adventitia [5, 6]. According to the current guidelines, pre-emptive treatment of the stenosis is mandatory to prevent graft thrombosis [7, 8]. Percutaneous transluminal angioplasty (PTA) is a preferred method for graft salvaging. However, as a result of restenosis the 6 month unassisted post-PTA patency varies from 25 to 63% [3, 9-13].

Cryoplasty is a novel therapy that combines conventional balloon angioplasty with cold thermal energy. Effects of cold therapy include a reduced elastic recoil, apoptosis of smooth muscle cells [14-16], and, in atherosclerotic arteries, an altered plaque response. First clinical studies of cryoplasty in femoropopliteal arterial disease compare favorable to conventional angioplasty [17-20]. However, this effect was not shown for arterial restenosis [21]. In hemodialysis grafts with rapidly recurring stenosis at the venous anastomosis, the intervention-free interval may increase after cryoplasty [22]. So far, there is no evidence that cryoplasty has beneficial effects in preventing arteriovenous grafts restenosis.

In the present pilot study, we tested the hypothesis that cold thermal energy of cryoplasty induces apoptosis of vascular smooth muscle cells and, as a result, reduces intimal hyperplasia at the venous anastomosis in a porcine arteriovenous graft model.

Methods

For the present study we used our validated porcine model which was described in detail before [23-25].

Animals

Five female Landrace pigs weighing 52.2 ± 2.7 kg received bilateral expanded polytetrafluoroethylene (ePTFE) grafts (W.L. Gore and Associates, Flagstaff, AZ) between the carotid artery and the internal jugular vein. In each pig, a cryoplasty procedure was performed at the venous anastomosis of one graft at a randomly selected side. The contralateral graft served as control and received a conventional PTA treatment. At 28 days, the animals were sacrificed after which the grafts and adjacent vessels were excised for analysis. The study protocol was approved by the Institutional Review Board for animal experimentation of the University Medical Center Utrecht and conforms to the *Guidelines for the Care and Use of Laboratory Animals*, published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Anesthesia

Before the operation and termination, the animals were fasted overnight. At day -1 a fentanyl plaster (25 µg release per hr.) was applied to the skin. Animals were pre-medicated with an intramuscular injection containing ketamine 10 mg/kg, midazolam 0.4 mg/kg and atropine 0.5 mg. After cannulation of an ear vein an intravenous injection of thiopental sodium 4 mg/kg was administered. Then, they were intubated and ventilated with a mixture of O_2 and air (1:2). During the operation, the ear vein was used for continuous administration of 0.3 mg/kg/h midazolam, 2.5 µg/kg/h sufentanil and pancuronium 50 µg/kg/h. The pigs were monitored by electrocardiogram and capnography.

Oral antiplatelet therapy

Starting 6 days preoperatively, the pigs received acetylsalicylic acid 80 mg/dd. Clopidogrel (Sanofi-aventis, Gouda, the Netherlands) 225 mg was added 1 day preoperatively and continued at a dose of 75 mg/day until termination. Before graft puncturing for cryoplasty and conventional angioplasty, an intravenous bolus of 10 mg abciximab was administered [24].

Antibiotics

Before operation the animals received intravenous amoxicilline/clavulanic acid 500/125 mg. Intramuscular ampicilline 500 mg/day was administered until 5 days postoperatively.

Operative procedure

Operational procedure was performed as described earlier [23]. In short, through a longitudinal incision in the midline of the neck, the common carotid artery and the internal jugular vein were dissected bilaterally. Baseline flow through the carotid artery was measured using a 4 mm perivascular flow probe (Transonic Systems, Maastricht, The Netherlands). Heparin 100 IU/kg iv was administered before vessel manipulation.

An experienced vascular surgeon (H.J.M.V.) created the end-to-side anastomoses at a 45° angle using a continuous 8-0 polypropylene suture. Sterile, reinforced, thin-walled, ringed, ePTFE grafts were implanted (5 mm in diameter and 7 cm in length). Then, blood flow through the artery and vein was measured and graft flow was calculated as flow of the caudal carotid artery minus the flow of the cranial artery. After administration of abciximab, each graft was punctured separately to perform the radiological procedure. After treatment, the puncture hole was sutured using 6-0 polypropylene.

Cryoplasty

The PolarCath Peripheral Dilatation System (Boston Scientific, Maastricht, The Netherlands) was used for cryoplasty procedure. This system consists of a nitrous oxide expanded dual balloon catheter, a microprocessor-based inflation unit, and a nitrous oxide cylinder. After implantation of bilateral AV grafts, 1 graft was randomly selected for cryoplasty. A 6F sheath was placed in the graft and the PolarCath balloon was advanced to the venous anastomosis over a 0.035-inch guidewire. Upon entering the balloon the pressurized liquid nitrous oxide changes phase, resulting in balloon expansion. The balloon is inflated in 2-atmosphere increments until nominal dilation force of 8 atmospheres is achieved. The temperature on the surface of the balloon is reduced to -10°C. The treatment cycle lasts for 20 seconds, after which the flow of nitrous oxide is automatically halted and the balloon is passively warmed. After a fixed warming delay, the balloon was then deflated and removed. The contralateral site underwent conventional angioplasty treatment using a 6F sheath and a 4 mm balloon.

Tissue preparation and morphometric analysis

After 4 weeks, pigs were anesthetized as described previously. Heparin 100 IU/kg was administered before manipulation of the vessels. After determining graft flow using the perivascular flow probe, the ePTFE grafts were cannulated and angiograms are obtained. Subsequently, the grafts and adjacent vessels were first perfused with saline for 3 min. and then formalin at physiologic pressure (*i.e.* 100 mmHg). After 2 min, both sides of the arteries and veins were ligated, allowing pressure fixation of the vessels. Subsequently, grafts and adjacent vessels were excised and immersed in formalin for at least 24 hrs. The fixated veins were cut in 5-mm blocks and embedded in paraffin. Five-μm thick sections were prepared of the vein 1 cm proximal and distal to the anastomosis, and at the center of the anastomosis. For morphometric analysis, sections were Elastin von Gieson (EvG) stained for general morphology. Area measurements were performed on captured images obtained with a color camera attached to a light microscope by using computer-assisted morphometry. With the highest magnification that allowed visualization of the entire vein section in one field, the intimal and medial areas and the area inside the external elastic lamina (total vessel volume) were manually traced. The circumference of the vein was traced 1 cm proximally to the anastomosis. To distinguish intimal hyperplasia from organized thrombi, sections were stained with hematoxylin and eosin. Collagen was vizualized using picro-sirius red staining and digital image microscopy with circularly polarized light.

Immunohistochemical analysis

Following deparaffinization and hydration, antigenic determinants were unmasked (when necessary) by boiling in 10 mM citrate acid for 15 min. Next, the sections were preincubated with 10% normal horse serum (Vector Laboratories, Peterborough, UK) to block aspecific binding. Serial sections from each graft were then incubated with mouse anti-α-smooth muscle actin at 1:1500 dilution (Sigma, St. Louis, MO). Subsequently, sections were incubated with a biotinylated horse anti-IgG antibody (Vector Laboratories, Peterborough, UK) for 1 hour at room temperature, followed by incubation with streptavidin-horseradish peroxidase. For visualisation of the HRPO we used diaminobenzidine (DAB) in 0.05 M Tris-Cl mixed with 0.01 M imidazole. Endogenous hydrogen peroxidase was blocked by incubating the sections in 1.5% hydrogen peroxide/methanol during deparaffinization.

Statistical analysis

Data are presented as mean ± standard error of the mean. Paired t-test was used for comparison of graft blood flow and angiographic outflow vein diameters. The limited number of pigs supplying morphometric data did not allow statistical analysis. Analyses were carried out using SPSS 12.0 for Windows® (SPSS Inc, Chicago, Ill). A *P*-value <0.05 was considered statistically significant.

Results

Ten ePTFE grafts were successfully implanted in 5 pigs. All angioplasty procedures went uneventful. Grafts and outflow veins remained intact and no bleeding complications occurred during follow up. All grafts were patent at time of termination. One control anastomosis section and 1 cryoplasty outflow vein section were lost during tissue processing.

Baseline carotid artery blood flow in the cryoplasty group and the control group were 271 ± 31.0 mL/min and 236 ± 21.3 mL/min, respectively (P = 0.27). At 28 days graft blood flow was 703 ± 62.4 mL/min in the cryoplasty group, and 815 ± 86.9 mL/min in the control group (P = 0.34).

General histology

No obvious morphological differences were observed between venous anastomosis sections of the cryoplasty group and the control group. At 4 weeks, intimal hyperplasia at the venous anastomosis consisted of vascular smooth muscle cells, extracellular matrix, fibroblasts, inflammatory cells, macrophages and little collagen. Representative sections of the venous anastomosis are shown in figure 1.

External parts of the grafts were lined with 'foreign body' giant cells and macrophages. Inflammatory reactions seen around the venous anastomosis were pig dependent, not treatment dependent. Consistent thin vein media layers were surrounded by adventitia with neo-vascularization.

		Cryoplasty [*N*=4]	Control [*N*=4]	Difference
Anastomosis	intima	1.46 ± 0.46	2.86 ± 0.62	-49%
	media	1.09 ± 0.24	1.20 ± 0.21	-9%
	i/m	1.26 ± 0.14	2.55 ± 0.71	-51%
Vessel volume		11.08 ± 2.35	15.51 ± 3.53	-29%

Table 1. Results of Elastica von Gieson stained morphometric analysis of the venous anastomosis and the outflow vein. Intima, media and vessel volume values are expressed as square millimeters ± SE.

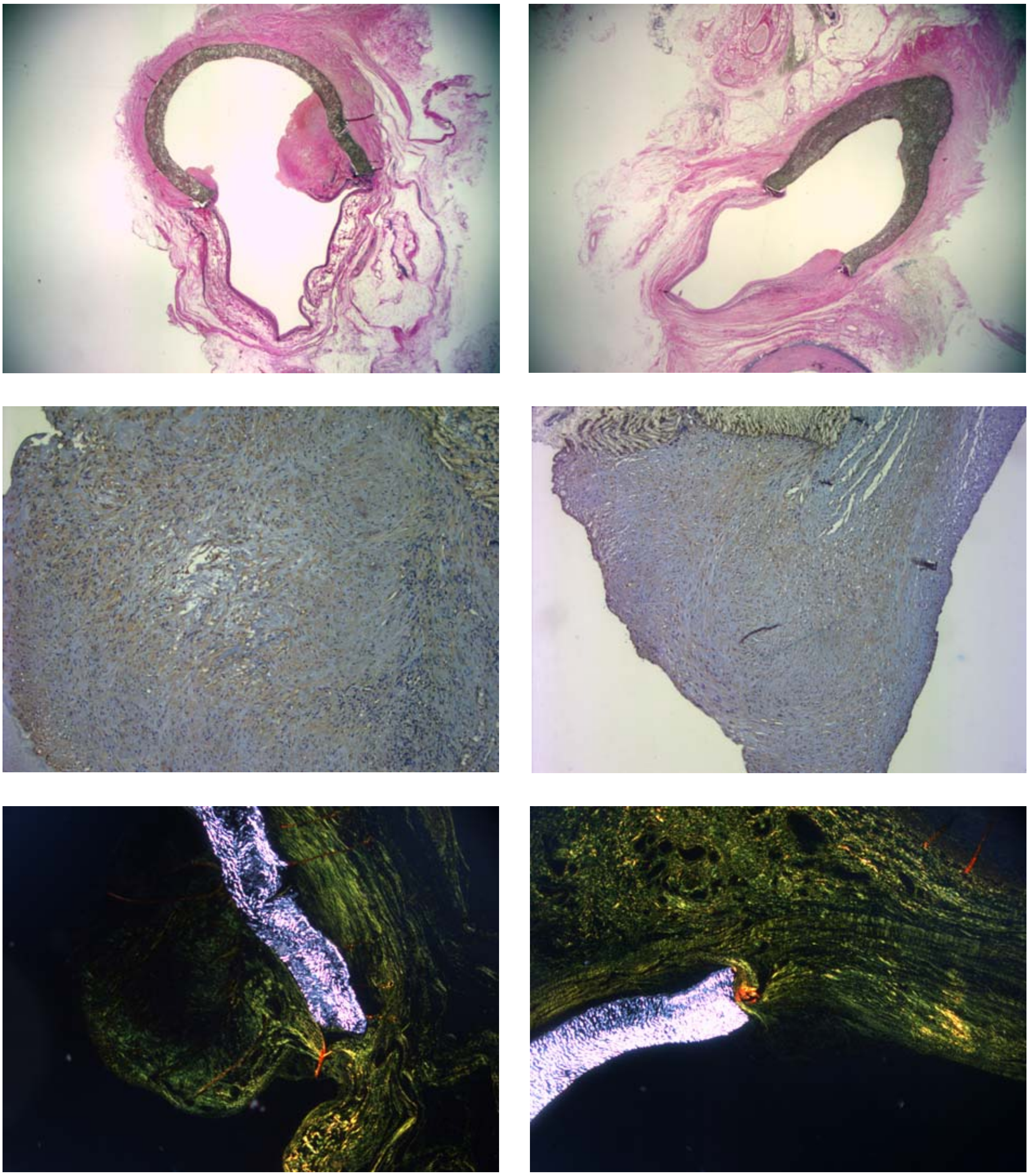

Figure 1. Representative Elastica von Gieson stained sections of the graft vein anastomosis of control animals (upper left panel) and cryoplasty treated animals (upper right panel) (12.5x magnification). Detail of α-SMA stained intimal hyperplasia in the control group (middle left panel) and the cryoplasty group (middle right panel) (100x magnification). Note the extensive brown coloration in both sections. Pico-sirius stained section of the venous anastomosis, visualized with polarized light in the control group (lower left panel) and the cryoplasty group (lower right panel) (40x magnification).

Morphometry

Data from morphometrical analysis are presented in table 1. At 28 days, treatment with cryoplasty resulted in a 49% reduction of intimal area at the venous anastomosis. The media did not differ between the groups. Compared to the control group, the intima-media ratio was 51% reduced in the cryoplasty group (Figure 2). The proximal outflow vein area in the cryoplasty group was not statistically different from the control group.

Angiographic luminal diameter at the toe of the venous anastomosis was 2.93 ± 0.22 mm. in the cryoplasty group and 4.15 ± 0.95 mm. in the control group (P = 0.27). Luminal diameters of the proximal outflow vein were 3.04 ± 0.51 mm in the cryoplasty group and 3.89 ± 0.70 mm. in the control group (P = 0.14) (Figure 3).

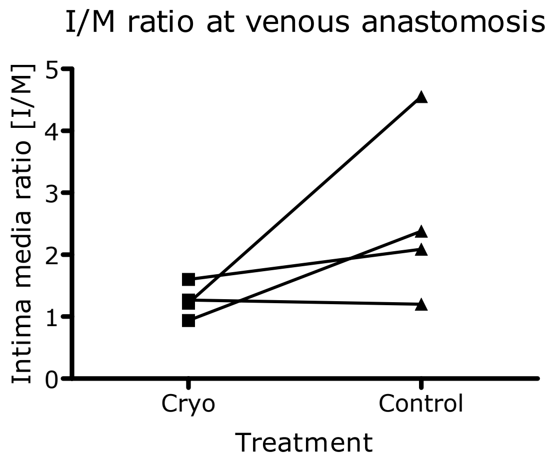

Figure 2. Intima media ratio at the venous anastomosis in 4 pigs. Compared to the control side, all but one animal showed a reduced intima media ratio on the cryoplasty treated side.

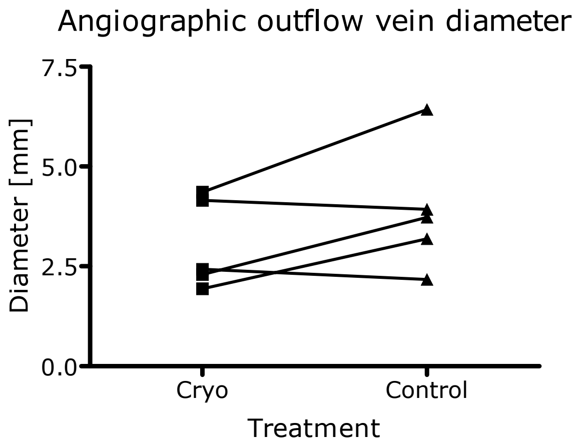

Figure 3. Angiographic luminal diameters of proximal outflow veins in 5 pigs

Discussion

In the present porcine pilot study we have shown that a single treatment with cryoplasty possibly results in a reduction of the intima area and the intima-media ratio at the venous anastomosis of arteriovenous grafts. Furthermore, a 22% reduction of the angiographic outflow vein luminal diameter was observed. Current results justify additional research on this subject with our porcine model.

Intimal hyperplasia and apoptosis

Reacting on mechanical stress, endothelial damage, compliance mismatch, turbulent flow patterns and inflammation [26], proliferation of vascular smooth muscle cells (VSMC) is a key characteristic in the formation of intimal hyperplasia [5, 6], which was also seen in both treatment groups in our pilot study (Figure 1). Vascular smooth muscle cells are thought to react approximately 24 hours after injury by changing from the contractile to synthetic phenotype [27]. In a rabbit study, a maximum of smooth muscle cells were undergoing DNA synthesis within the first 7 days after carotid artery angioplasty [28, 29]. At 28 days a homeostasis between cell proliferation and natural apoptosis had been reached, possibly resulting in growth retardation of the restenotic lesion [29]. In our model, a 51% reduction of intimal hyperplasia was seen at 4 weeks. A 'catch-up phenomenon' has been observed in a balloon injury rabbit iliac artery model. At 10 weeks after reaching an average wall temperature of -26ºC, intima hyperplasia had increased 2-fold in cryotherapy treated arteries and collagen content had increased in all vessels layers [30]. However, a clinical trial in femoropopliteal arteries using a single cycle of -10ºC has shown beneficial effects after 9 months [18].

Cryoplasty is a novel endovascular technique for treatment of (re)stenosis that starts with nucleation of small ice crystals in the extracellular fluid in tissue adjacent to the balloon. Whereas ice does not incorporate solutes, a hypertonic environment is created, leading to osmotic dehydration of cells [31]. When the balloon is removed, the tissue thaws, isotonic conditions are regained and smooth muscle cells rehydrate [31], inducing triggers for apoptosis. The optimal temperature for smooth muscle cell apoptosis is thought to be approximately -10°C [15, 16]. *In vitro*, temperatures closer to

0°C will result in less apoptosis and colder temperatures, as used by Cheema *et al*. [30], increase the likelihood of necrosis [15], which is accompanied by inflammatory reaction. Interestingly, at -11°C the viability of smooth muscle cells embedded in collagen has been shown to be lower than of cells in suspension [14]. In the present study, a single cycle treatment at -10°C was used. Tatsutani *et al.* showed that smooth muscle cell apoptosis did not vary with cold exposure times from 30 to 120 seconds [15]. A single treatment cycle with the current device lasts for 20 seconds. However, residual stenosis has been negatively correlated with the duration of the inflation in hemodialysis grafts [32], so additional treatments may be required in case of resistant stenosis. Whereas angioplasty itself results in an early apoptotic response [33], and vein wall thickness is much thinner compared to arteries, loss of vein wall integrity may possibly result in a higher incidence of complications such as dissection.

Venous remodeling

In the present study, angiographic diameter of the proximal outflow vein was 22% decreased in the cryoplasty group. Whereas outward remodeling accompanies adequate access flow increase required for maturation [34, 35], cold treatment may restrict that process. Prophylactic treatment at the day of access placement may thus be inappropriate to prevent intimal hyperplasia. However, graft flow measurements did not suggest limitations and pico-sirius stained sections did not suggest increased collagen contents.

Translation to clinical practice

Novel endovascular treatments have been developed to reduce the formation or recurrence of intimal hyperplasia at the venous anastomosis of arteriovenous grafts. In a pilot study endovascular brachytherapy improved post-intervention primary patency but not 6 month secondary patency [36]. Compared to standard PTA, the use of a peripheral cutting balloon for stenotic or thrombosed grafts did not improve primary patency [37]. Cryoplasty increased the intervention-free interval of 5 hemodialysis grafts with rapidly recurring stenosis from 3 to 16 weeks [22]. Thus far, no clinical trials have been conducted that have tested the efficacy of this device in AV grafts. Treatment of femoropopliteal arterial disease has been investigated more extensively [17, 18]. The clinical patency, defined as freedom from target lesion revascularization, was favorable with 82% at 9 months after a single 20 seconds cryoplasty treatment [18], and suggests beneficial effects. However, the optimal indication for treatment with this device should be further investigated.

Limitations

The main limitation of the present pilot study is the limited number of pigs. Preliminary statistics cannot be executed yet but current results may provide a first impression on outcomes and mechanism of cryoplasty in arteriovenous grafts. Extrapolation of current results in 3 or 4 additional pigs can be expected to result in significant reduction of intimal hyperplasia.

In a balloon injured rabbit iliac artery model, 'catch-up' of intimal hyperplasia was observed at 10 weeks [30]. However, treatment temperatures were much colder than in our experiments. In the present study no striking differences in cellular composition at the anastomoses was observed. A next study with prolonged follow up time will therefore be required to investigate long term results.

Pigs are favorable animals to study cardiovascular disease because of their analogous vascular anatomy, size an physiology [38, 39]. The rapid intimal hyperplasia formation at the venous anastomosis in our model closely resembles human hemodialysis graft failure [23]. As soon as 8 weeks after surgery a 50% patency loss can be expected in this model [23]. In addition, graft blood flow in our model is similar to the human situation.

We used 4 mm balloons for the angioplasty procedures. Whereas porcine jugular vein are approximately 4 mm. mechanical stress due to overstretch of the anastomosis may have been limited. The observed results should therefore be imputed to effects of cold treatment rather than to PTA itself.

Finally, cardiovascular risk factors and the uremic milieu were not present in this model. Thus, any effects on vascular remodeling and intima hyperplasia were not included. Extrapolation to the human situation should therefore be exerted with caution.

Conclusion

Preliminary data from the present study suggest intimal hyperplasia reduction by cryoplasty at 4 weeks. Therefore, additional research on this subject is justified. Decreasing the number of potentially dividing smooth muscle cells may result in prevention or delay of intima hyperplasia. Ultimately, cryoplasty may be a valuable tool to increase the intervention-free post-PTA period in hemodialysis grafts.

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Chapter 9

General discussion and summary

General discussion

Background

Hemodialysis is often used as renal replacement therapy (RRT) for patients with end-stage renal disease (ESRD). A blood pump usually routes 350-400 mL/min through a dialyzer. When the blood pump flow exceeds the access blood flow, the upstream arterial needle draws downstream returned blood. This phenomenon, called recirculation, will reduce urea reduction rate. In order to achieve sufficient urea reduction rates, adequate vascular access is thus of crucial importance. The definition of a functional access is an access that is able to deliver a flow rate of 350-400 mL/min without recirculation for the total duration of dialysis [1]. The arteriovenous fistula (AVF) is recommended as first choice vascular access [2, 3]. Compared to grafts and central venous catheters, AVFs have lower complication rates and superior patency rates once established [2, 4, 5]. The major disadvantages are relatively high incidence rates of inadequate maturation, *i.e.* sufficient vascular remodelling, and early thrombosis during the first weeks after creation. These primary failures can dramatically decrease patency rates.

Since the introduction of the arteriovenous fistula in 1966 [6], ESRD patients are getting older and more often have diabetes mellitus and cardiovascular co-morbidity [7-9]. As a consequence, more patients requiring vascular access have compromised vessels. These developments are increasingly challenging vascular surgeons to meet current native access standards.

When a patient's vessels do not allows the creation of a fistula, an arteriovenous ePTFE graft will be inserted. However, the 18-months primary patency of such grafts is only 33% [5]. The most important problem is stenosis formation at the venous anastomosis and at the outflow vein [10, 11]. This results in luminal narrowing and decreasing blood flow, ultimately leading to graft thrombosis. No satisfactory therapeutic strategies to reduce stenosis are available at present.

To prevent thrombosis, prophylactic stenosis correction is mandatory. Percutaneous transluminal angioplasty (PTA) is the preferred method for graft salvaging. However, 6-month unassisted post-PTA patency varies from only 25% to a reasonable 63% [11-16]. When stenosis correction is required every 2-3 months, the graft will usually be abandoned, and a new surgical procedure is then required.

Guidelines

Single center studies have shown that saving veins, introduction of preoperative duplex protocols, assignment of vascular access coordinators and increased use of transposed brachio-basilic AVFs can lead to increased AVF use and less interventions [17-20]. However, the most important aspect contributing to such local success seems to be the motivation of the entire vascular access team (VAT) to increase functional AVF use and meet quality of care standards. Hence, we did not aim at emphasizing the importance of native vascular access placement in **chapter 2**. Instead, we suggested VAT actions that potentially increase AVF use and decrease complication rates in common practice.

Arteriovenous fistulas and practice patterns

Despite global consensus about preferred vascular access use, the Dialysis Outcomes and Practice Patterns Studies (DOPPS) have shown great international differences in vascular access incidence and prevalence levels between the USA and Europe [9, 21]. In The Netherlands, AVF use was generally 10-15% lower than other countries in Western Europe. Apart from differences in demographics and co-morbidities that affect blood vessel quality in ESRD patients, recent reports suggest that these differences are to a considerable extent the result of local practice patterns [22-24].

In order to increase native vascular access use we introduced the CIMINO program (Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment) in 11 Dutch hemodialysis facilities. The results are described in **chapter 3**. Before the start of the program, the investigators visited all participating VAT's and presented a lecture on the most recently updated guidelines for vascular access [3]. Furthermore, summaries, translated in Dutch, were provided and during the program VAT's were strongly and repeatedly encouraged to adhere to these guidelines. Extra attention was paid to pre-operative duplex examination and salvaging of failing and failed fistulae. Specially appointed access nurses prospectively registered all created vascular accesses using an internet-linked database. As

a novel control group, 22 other dialysis facilities were assessed for type of vascular access use in 2002-2003 and in January 2006.
In the CIMINO group, prevalent AVF use varied from 6.6% decrease per year to 10.9% increase per year (mean: 3.5% increase). In the control group, AVF use varied from 5.7% decrease per year to 12.4% increase per year (mean: 1.2% increase). Linear regression showed a significantly steeper increase of AVF use in the CIMINO group than in the control group. Baseline demographics between both study groups were similar. Interestingly, higher baseline AVF prevalence levels in the control group (65.5% vs 58.5%) may suggest earlier implementation of guidelines. However, the rate of change was slower than in the CIMINO group. Sample size in this study was not large enough to perform a multivariate analysis with demographics and patient characteristics. Exact reasons for our results remain speculative. However, the small geographical study area in combination with enormous differences in vascular access prevalence, strongly support the idea that local preferences, rather than either demographics or patient characteristics were responsible for regional differences. Two other interesting results were observed. First, increasing AVF when prevalence is already at approximately 75% appeared to be difficult in both groups. Similarly, DOPPS II showed an identical fistula prevalence level in countries surrounding the Netherlands [21]. Although regional registries have reported fistula prevalence up to 86% [25, 26], 75% fistula use is perhaps at top end in Europe. Such percentages might be introduced as quality of care standard for AVF use. Secondly, a clear switch was observed from untunneled catheter (UC) use to tunnelled catheter (TC) use. This is in line with current K/DOQI standards, which recommend TC use instead of UC use when hemodialysis duration is expected to be used more than 1 week [2]. In contrast to our results the total proportion of catheter use has increased in Europe and the U.S.A. despite their known association with numerous detrimental outcomes in HD [21].

Primary AVF failure

Primary failure occurs in 20-50% of the AVFs [4]. Internal diameters of the inflow artery and the outflow vein are very important to this matter [27-30]. In addition, age, cardiovascular disease, lower mean arterial pressure and lower intra-operative doses of heparin have also been associated with decreased maturation [27].

In **chapter 4** we observed primary AVF failure in 131 of 395 patients. Finally, 24% of all AVFs were lost before cannulation, underscoring the magnitude of this problem for vascular access care. Inadequate maturation occurred as a result of stenosis or insufficient arterial or venous remodeling. Together with early thrombosis, inadequate maturation accounted for more than 90% of the primary AVF failures. Female gender, duration of renal replacement therapy prior to access placement and diabetes mellitus were identified as non-modifiable risk factors. Only location of access placement was identified as potentially modifiable factor. Surgery related aspects such as anastomosis configuration and type of anesthesia were not related to primary failure. Moreover, venous diameters in the primary failure group and the non-primary failure group were not significantly different.

Primary failure rates varied widely between the hospitals participating in the CIMINO initiative: 8 to 50%. Compared to the 2 hospitals with lowest PF-rates, the odds for primary failure varied from 1.62 to as high as 9.38 in the other 9 hospitals. Most probably these outcomes are related to the surgeon. Optimal vessel choice, technical skills required for anastomosing [31] and surgical experience are aspects that may have contributed to these findings. In addition, changing practice patterns to creation of more native vascular accesses may result in increased maturation problems [32]. However, when center specific results of chapter 3 and 4 are combined, linear regression does not show a relation between the annual increase in AVF prevalence and the primary failure rate within the hospitals (P = 0.55). On the contrary, hospitals starting at low baseline AVF prevalence levels tended to have higher primary failure rates than hospital starting at high prevalence levels (figure 1). These results may suggest that high PF-rates are not so much explained by inclusion of compromised vessel AVFs but more likely by insufficient native access surgery experience. Consequently, decreasing proportions of early thromboses and inadequate maturation may characterize the learning curve towards higher AVF prevalence.

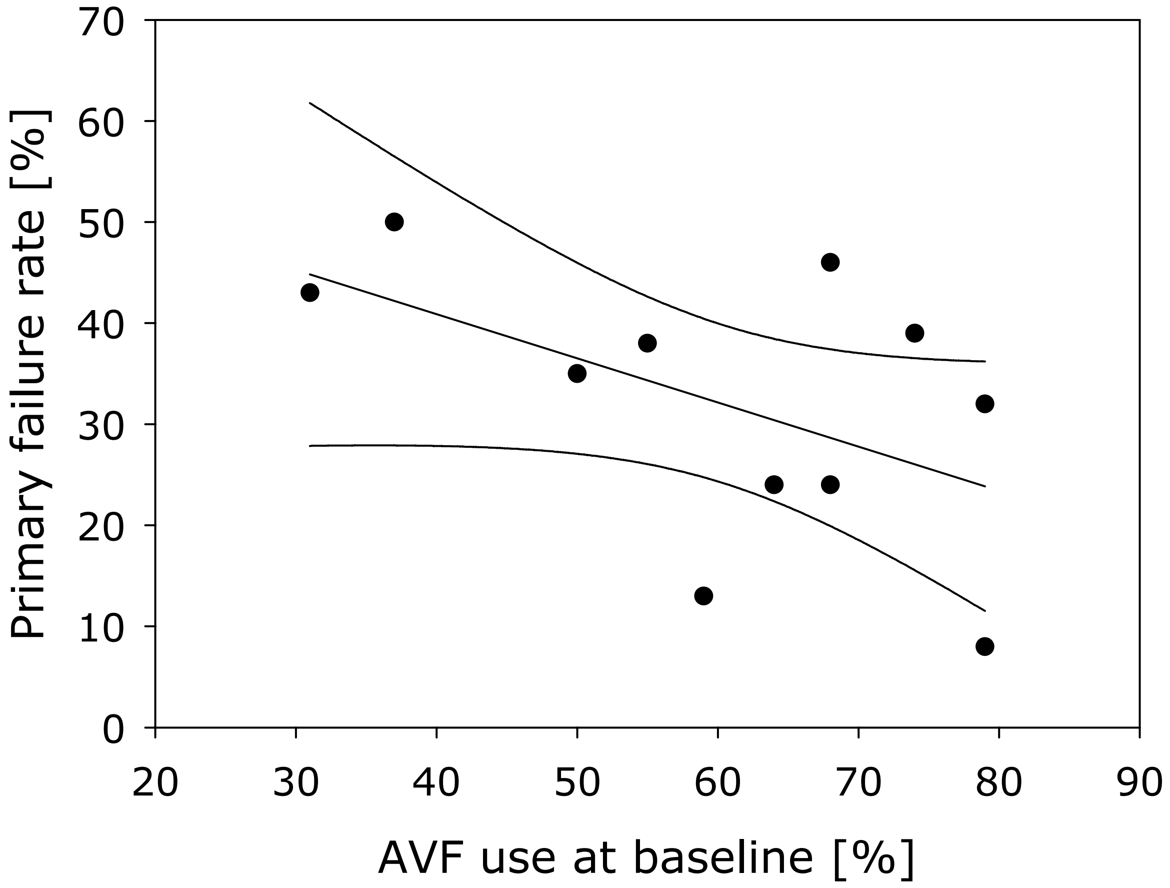

Figure 1. Relation between the prevalent AVF use at baseline versus the primary failure rate in 11 dialysis facilities. Linear regression ± 95% confidence interval was weighted for the number of prevalent AVFs per facility and showed no statistical significance (*P* = 0.14).

Patency rates

The K/DOQI recommendations on vascular access use are predominantly based on reports from the 1980's and early 1990's. Ever since, demographics and co-morbidities of incident ESRD patients have changed [8]. Nowadays, ESRD patients are older, more often have diabetes mellitus and are more likely to have cardiovascular disease; all of which are characteristics that affect blood vessel quality. Moreover, primary failure rates are currently higher [4] and may thus result in significant patency reductions. Recently, graft patency has been shown to be significantly better than fistula patency in patients with compromised vessels [33]. Therefore, a renewed analysis of native vascular access patency rates is justified.

In the 491 fistulae in **chapter 5**, one-year secondary patency and one-year secondary functional patency were 70% and 88%, respectively. This difference was predominantly generated during the first months after fistula creation. Comparing AVF to grafts, a review of available literature showed that secondary functional patency in grafts is approximately 65% [5]. Including primary graft failure rate of approximately 10%, secondary patency will probably decrease slightly, suggesting beneficial patency rates for AVFs from 12 month on.

Source	**Patency**	**6 mo.**	**12 mo.**	**18 mo.**
Chapter 4	secondary AVF	75%	70%	67%
Huber *et al.* [5]	secondary functional graft	76%	65%	55%

Table 1. Comparison of secondary AVF patency in chapter 4 of this thesis and secondary functional graft patency as reported by Huber *et al.* [5].

Comparing patency rates in literature can sometimes be misleading. Some investigators have excluded primary failures and start calculating at the day of the first cannulation (functional patency) whereas others have included primary failures (patency). Given the high primary failure rate conclusions on vascular access performance can be rather different. In chapter 5 we used patency definitions as reported by Sidawy *et al*. [1]. Functional patency started when a vascular access had been successfully used for hemodialysis treatment for the first time, whereas patency started at the day of surgical AVF creation.

Whereas aspects of early patency loss were extensively described in chapter 4, we focussed on functional patency in chapter 5. After adjustment for age, gender, coronary artery disease, peripheral vascular disease, fistula location, body mass index (BMI) and renal replacement therapy prior to access cannulation, primary functional patency was only decreased in diabetics (Hazard Ratio = 1.70). Secondary failure, defined as permanent failure of the AVF, after achieving adequacy for hemodialysis, varied from 0-38% among participating hospitals and was not related to any of the aforementioned patient characteristics or cardiovascular risk factors. Compared to 8 hospitals with a low SF-rate combined, 3 hospitals had a higher risk for secondary AVF failure. Whereas primary failure is probably related to the surgeon's skills and decisions, secondary failure is more likely the result of other factors such as negligent shunt surveillance (dialysis unit), delayed action to detected stenoses (nephrologists) or inadequate PTA / surgery procedures (radiologist / vascular surgeon). Further in-center analysis can be useful to improve secondary functional patency rates but obviously the multidisciplinary character of complication handling requires a well functioning vascular access team.

Access blood flow

In functional fistulae, vascular access blood flow (Qa) increases rapidly during the first weeks after surgical creation [30, 34-36]. Once an AVF has matured to a condition ready to be cannulated, some fail during follow up. However, little is known on factors that are associated with secondary AVF failure and whether access flow measurements, which are accepted as the preferred method for arteriovenous access function monitoring, are related to failure. In **chapter 6**, reduced baseline Qa at approximately nine weeks after surgery was related to AVF failure during follow up. Interestingly, Qa values were different for forearm and upper arm AVFs, and there was no relation between baseline Qa and time to complication. These findings suggest involvement of additional aspects such as vessel wall characteristics or surgical techniques. Arteriovenous fistula placement results in dramatic changes of hemodynamics [37]. Intimal hyperplasia, and subsequent stenosis formation, develops preferentially in regions of low wall shear stress [38-41]. Shear stress is related with blood velocity and inversely with internal diameter [42-44]. This may explain why reduced baseline Qa is more likely to result in AVF failure during follow up. It also explains why upper arm AVFs, using larger vessels, tend to encounter complications at higher blood flow rates than forearm AVFs.

Furthermore, we showed that Qa in non-failed forearm and upper arm AVFs did not increase from 4-5 months after creation. For the forearm AVFs these observations may be explained by an unaltered radial artery diameter from 3 weeks after the operation [45]. A non-significant 14% Qa increase between

4.5 and 8 months might raise the question whether the flow augmentation period extends beyond the 4-8 weeks maturation period. Whereas cardiac output (CO) and mean arterial pressure (MAP) predominantly determine Qa [46], these functions will probably limit the increase in Qa. Importantly, confirming a report by Basile *et al.* showing that radiocephalic AVF Qa maintained a steady level for several years after extensive access usage [47], our findings underscore the crucial importance of the initial Qa increase upon access placement.

Finally, we confirmed findings by Tonelli *et al.* that Qa is inversely associated with diabetes mellitus [48]. In diabetics and elderly, increased radial artery media calcification, atherosclerosis and increased intima media thickness may be related to impaired arterial dilation and reduced remodeling capacity [49, 50]. In contrast, body mass index was positively related to Qa. This was probably not due to larger vessels because body height was not related to Qa. The observations in chapter 6 may have consequences for optimization of preoperative vessel selection in order to obtain high flow AVFs.

Helical geometry

Failure of ePTFE vascular access grafts is predominantly caused by progressive intimal hyperplasia at the graft/vein anastomosis [10, 11]. Intimal hyperplasia develops preferentially in regions where blood flow is stagnant and wall shear stress low [38-40, 51]. The Small Amplitude Helical Technology (SMAHT) prosthesis, SwirlGraft™, was developed to achieve physiological-type swirling in, and downstream, of vascular access grafts in order to prevent adverse fluid dynamics.

In **chapter 7**, 20 Swirlgrafts™ were successfully implanted in 20 ESRD patients. The 6-month primary patency at 58% is similar to that of standard ePTFE AV-grafts but the assisted primary (84%) and secondary patency (100%) rates are at the highest end of reported series [5]. Angiographic examination in a limited number of grafts suggested reduction of helical geometry at or after implantation, implying function similar to that of conventional ePTFE prostheses. This may have been due to overstretching during implantation, or by elongation under arterial pressure. Graft reinforcement, in particular at the distal anastomosis, may be of additive value to maintain geometry.

Kanterman *et al.* found that almost 60% of the stenoses diagnosed on angiograms are located at the venous anastomosis [11]. In our study only 22% of the stenoses were confined to this region and 33% were detected in the outflow vein. During surgery the graft may have accessed the vein from a ventral instead of a lateral direction. When closing the wound, the overlying skin may have moved the graft laterally causing kinking of the vein. Further explanations for this finding remain unclear. With the right modifications of implantation techniques and Swirlgraft™ design a randomized controlled trial with the Swirlgraft™ is justified.

Cryoplasty

Cryoplasty is a novel therapy that combines conventional balloon angioplasty with cold thermal energy. Effects of cold therapy include reduced elastic recoil, apoptosis of smooth muscle cells [52-54], and, in atherosclerotic arteries, an altered plaque response. Whereas vascular smooth muscle cell outgrow is a key characteristic of intimal hyperplasia in hemodialysis grafts [55, 56], we conducted a pilot study to test this device in a porcine model that has previously resulted in rapid intimal hyperplasia formation at the venous anastomosis [57]. Compared to conventional angioplasty, a single 20 seconds cryoplasty treatment at -10ºC resulted in a 51% reduction of intima media ratio at 4 weeks (**chapter 8**). Angiographic outflow vein diameter and graft blood flow were not different between the study groups. Current results suggest possible benefit of cold treatment without the 'catch-up phenomenon' seen using colder temperatures in balloon injured rabbit iliac arteries [58]. Additional research on this subject with the porcine model is justified.

Future perspectives

The challenge in vascular access care is to overcome the great national and international differences in vascular access use and increase AVF prevalence to 65% in the USA and to 75-80% in Europe in the forthcoming years [9, 21, 59]. Major contributions can be expected from reduction of primary failures and salvaging of failing fistulae. This requires highly motivated vascular access teams (VAT's). Vascular surgeons and interventional radiologists in particular, are thought to make the difference. Although an increasing prevalence of cardiovascular risk factors in the hemodialysis population will challenge the VAT's, aspects such as willingness to achieve outcome goals, learning from suboptimal results and adjustment of practice patterns where necessary, will be the key to care improvement. In the USA, the National Vascular Access Improvement Initiative (NVAII) launched the large 'Fistula First' initiative to help VAT's that require outcomes improvement. Eleven change concepts guide the target groups step-by-step to best practice. Some physicians even suggest to return access surgery and radiological interventions to nephrologists [60, 61], but such developments are not likely to occur in the near future. Finally, a large trial is currently being conducted that investigates whether peri-operative administration of a platelet aggregation inhibitor, clopidogrel, can decrease early thrombosis rates [62].

In addition to our findings in chapter 5, sufficiently powered, prospective studies with prolonged follow up time should provide conclusive data on the status of long-term AVF patency. Very important is the use of generally accepted standardized definitions, which allow future reports to act as updates for currently used literature in the K/DOQI standards. However, the studies described in chapters 3-5 can currently be used as quality of care standard for AVF use, primary failure and patency rates. Mid-term follow up studies registering access blood flow can be interesting from a physiological point of view. Future studies should include cardiac output and blood pressure measurements as most important determinants of Qa.

With respect to the ePTFE vascular access graft studies, a prospective randomized trial with the Swirlgraft™ is currently being conducted in the USA. The Swirlgraft™ design has been adapted with extra attention for reinforcement of the distal part of the device. Outcomes of the trial will show whether improved hemodynamics is the solution for disappointing graft patency rates. Regarding our findings in chapter 8, expanding the number of pigs may result in a significantly decreased intima-media ratio after cryoplasty, without adverse effects on graft flow or venous remodeling. Whereas a 50% thrombosis rate can be expected at 8 weeks in our porcine model [57], long term evaluation with this technique in pigs may be problematic. A single case report showed beneficial effects of cryoplasty in 5 hemodialysis grafts in man [63]. A pilot study in humans may provide information of suitability in general practice. However, indications for optimal use still need to be clarified.

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Summary

Current guidelines promote the use of the native arteriovenous fistula (AVF) as first choice access over ePTFE grafts and central venous catheters, because of favourable complication and patency rates. However, the prevalent AVF use shows enormous differences among national, regional and local practice surveys, even after adjustment for demographics. In chapters 3 to 6 we analyzed various aspects of vascular access placement patterns and risk factors for decreased AVF function.

Due to the abundant presence of cardiovascular disease in the ageing hemodialysis population ePTFE grafts are still widely used in the USA and may, regarding the current global diabetes epidemic, play an increasingly important role in the future. In the chapters 7 and 8 we investigated novel devices for prevention and treatment of the single most important complications of hemodialysis grafts: intimal hyperplasia at the venous anastomosis. The first device is a helical ePTFE graft that aims at improvement of hemodynamics, the second includes a combination of conventional balloon angioplasty in combination with cold therapy to reduce restenosis at the venous anastomosis in a porcine model.

In a review in **chapter 2**, we briefly discussed (inter)national practice pattern differences and presented actions that potentially increase AVF use and improve outcomes of vascular access care.

In **chapter 3** the prospective CIMINO study was introduced in 11 dialysis facilities. CIMINO is an acronym for Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment. This guidelines implementation program demonstrated that prevalent AVF use was increased quicker in comparison to a 22 center control group in which the program was not presented. These changes were predominantly observed in clinics where AVF use was less than 75% at the start of the observation period. Furthermore, AVF use displayed a wide range among the participating centers but these ranges narrowed during the project. The third major observation was a clear switch from untunnelled to tunnelled catheter use.

Primary AVF failure is defined as a fistula that does not develop to sustain dialysis or thromboses before the first successful cannulation for hemodialysis treatment, regardless of whether the AVF is finally abandoned or not. In

chapter 4, we observed a primary failure rate of 33% in 395 patients. Factors associated with the risk of primary failure were female gender, duration of previous renal replacement therapy prior to access placement, diabetes mellitus, and AVF placement at the wrist (in comparison to the elbow). Importantly, primary failure rates varied considerably between participating hospitals, even after adjustment for the potential risk factors and surgery-related factors. Whereas vessel selection, anastomosing techniques and surgical experience are definitely surgical aspects, these results may imply that the vascular surgeon not only plays an important role in type of access placement but also in early AVF functionality.

The Vascular Access Work Group of the National Kidney Foundation guidelines predominantly uses literature reports from the 1980's and early 1990's to support their standards. Hence, we analyzed AVF patency rates in 491 fistulae in 395 hemodialysis patients in **chapter 5.** We showed that AVF patency (from surgical creation date) and functional patency (from date of first cannulation) are markedly different. This difference appears to be caused by high primary failure rates. After adjustment for potential risk factors, primary functional patency was only decreased in diabetics. Secondary failure, defined as permanent failure of the AVF, after it had achieved adequacy for hemodialysis, varied from 0-38% among participating hospitals and was not related to patient characteristics or cardiovascular risk factors. Compared to eight hospitals with a low secondary failure rate combined, three hospitals had a significantly higher risk for secondary AVF failure, again emphasizing the role of local practice patterns.

In **chapter 6**, reduced baseline access blood flow (Qa) at approximately nine weeks after surgery was related to AVF failure during follow up. Interestingly, Qa values were different for forearm and upper arm AVFs, and there was no relation between baseline Qa and time to complication. In non-failed AVFs, Qa did not increase from approximately five months after creation. Forearm Qa was inversely associated with the presence of diabetes mellitus and decreasing BMI. No factors were significantly associated with decreased mean upper arm AVF Qa. These findings underscore the importance of adequate maturation for fistula function, and may have implications for preoperative vessel selection in different groups of patients.

The 6-month primary patency rate of the helical Swirlgrafts™ in **chapter 7** at 58% was similar to that of standard ePTFE AV-grafts, but the assisted primary (84%) and secondary patency (100%) rates are at the highest end of reported series. Angiographic examination in a limited number of grafts suggested that there was reduction of helical geometry at or after implantation, implying that they functioned like conventional ePTFE prostheses. However, together with the correct modifications of implantation techniques and Swirlgraft™ design, a randomized controlled trial with Swirlgraft™ is justified.

Preliminary data from the porcine arteriovenous graft pilot study are presented in **chapter 8.** Compared to conventional angioplasty alone, a single 20 seconds treatment with cryoplasty reduced the intima-media ratio at the venous anastomosis in 4 pigs by 51%, without obvious signs of adverse effects on graft flow or venous remodeling. These observations justify additional research on this subject with the porcine model.

Samenvatting in het Nederlands voor de niet-ingewijde lezer

Inleiding

De nieren hebben als belangrijke functie het volume en de samenstelling van lichaamsvloeistoffen nauwkeurig te reguleren. Door water en zouten uit te scheiden, blijven de bloeddruk, zoutbalans en zuur-base balans in evenwicht. Zo kunnen weefsels en cellen in een nagenoeg constant milieu hun functies uitvoeren. Verder scheiden de nieren afbraakproducten van de stofwisseling, geneesmiddelen en chemicaliën uit. Tot slot hebben ze nog een functie als producent van hormonen.

Als de nierfunctie gedurende een proces van maanden tot jaren afneemt, heet dit ‘chronische nierinsufficiëntie’. Belangrijke oorzaken van chronische nierinsufficiëntie zijn o.a. een te hoge bloeddruk (‘hypertensie’), chronische nierfilterontsteking en suikerziekte (‘diabetes mellitus’). Omdat de nieren een grote functionele reservecapaciteit hebben, krijgen patiënten vaak pas de eerste klachten als de functie gehalveerd is. Als er nog maar 5-10% restfunctie over is, zal de nierpatiënt moeten starten met niervervangende therapie omdat hij of zij anders zal overlijden aan de complicaties. Idealiter krijgen deze patiënten een niertransplantatie. Het aantal beschikbare transplantatienieren is echter niet toereikend waardoor de meeste patiënten moeten starten met peritoneaaldialyse of hemodialyse. Bij peritoneaaldialyse wordt een slang door de buikwand in de buikholte geplaatst. Via deze slang wordt een aantal keren per dag een speciale spoelvloeistof in de buikholte gebracht. Vocht, zouten en afvalstoffen worden dan via het buikvlies naar de spoelvloeistof getransporteerd en zo uit het lichaam verwijderd. De meeste patiënten kiezen voor hemodialyse. Bij deze behandelingsmethode wordt een bloedvat met 2 naalden aangeprikt waarna bloed via een slang uit het bloedvat naar een filter in een dialysemachine getransporteerd, en na zuivering weer teruggepompt. Voor een efficiënte behandeling moet er gedurende 3-4 uur 350-400 milliliter bloed per minuut naar de dialysemachine. Gemiddeld wordt een patiënt 3 keer per week behandeld. Een goede toegang tot de bloedvaten, een ‘vaattoegang’, is dus van levensbelang voor de hemodialysepatiënt.

In de normale anatomische situatie is een vaattoegang met de vereiste eigenschappen niet beschikbaar. Daarom moet deze chirurgisch gecreëerd worden. Er zijn ruwweg 3 variaties te onderscheiden. Bij de eerste variant wordt ter plaatse van de pols of de elleboog een ader ('vene') aan een slagader ('arterie') gehecht, een zgn. 'arterioveneuze fistel (AVF)'. Door het grote bloeddrukverschil stroomt er direct na de operatie al tien keer zoveel bloed door de aanvoerende slagader. Tijdens de weken erna neemt de bloedstroom nog verder toe tot 500-1500 ml/min. Het gevolg is dat de ader zich aanzienlijk gaat verwijden en goed aanprikbaar wordt voor dialyse. Deze ontwikkelingsperiode duurt ongeveer 4-8 weken en heet 'rijping'. Echter, als gevolg van de afgenomen nierfunctie zelf, maar ook door het steeds vaker voorkomen van diabetes mellitus en ouderdom (≥ 65 jaar), treedt slagaderverkalking ('atherosclerose') vaker op en is de bloedvatkwaliteit van dialysepatiënten aanzienlijk verslechterd. Het gevolg kan zijn dat het rijpingsproces inadequaat verloopt of dat stolselvorming ('trombose') optreedt. Als een AVF eenmaal gerijpt is, treden er nauwelijks complicaties op en zijn ze lang bruikbaar voor dialysedoeleinden. Daarom zijn arterioveneuze fistels volgens de huidige richtlijnen de eerste keus vaattoegang.

Als tweede variant kan een kunststof vaatprothese onderhuids ingehecht worden tussen slagader en ader. Deze optie wordt veelal gebruikt wanneer bloedvaten vernauwingen of een te kleine diameter hebben. Een prothese wordt 'arterioveneuze graft (AVG)' genoemd en is meestal gemaakt van teflon®. Het voordeel is dat grafts al binnen twee weken te gebruiken zijn voor dialyse. Bovendien hebben ze een hoge bloedstroom (oplopend tot wel 2 liter per minuut) wat efficiënte hemodialyse mogelijk maakt. Het nadeel is dat ze snel vernauwingen ('stenose') ontwikkelen ter plaatse van de aanhechtingsplaats met de ader ('veneuze anastomose'). Een stenose leidt tot afname van de bloedstroom waardoor uiteindelijk trombose optreedt. Verder is de kans op een infectie ongeveer 10 keer groter dan bij AVFs.

Als derde mogelijkheid kan een katheter in de halsader geplaatst worden. Hierbij ligt het ene uiteinde in de rechter hartboezem en het andere deel wordt buiten het lichaam in de hals aan de slangen van de dialysemachine gekoppeld. Katheters hebben doorgaans een beperkte verblijfsduur met de aanzienlijke complicatierisico's en worden daarom afgeraden als permanente vaattoegang.

Het proefschrift

Naast diverse aspecten van zowel AVF gebruik als functie, zijn in **hoofdstuk 1** van dit proefschrift de veranderingen beschreven van de populatie dialysepatiënten. Niet alleen neemt het aantal dialysepatiënten elk jaar toe, ook ziet de hemodialysepopulatie van nu er heel anders uit dan 30 jaar geleden. Ten eerste is de hedendaagse dialysepatiënt gemiddeld 10 jaar ouder dan in 1980. Verder is diabetes mellitus als oorzaak van nierfalen fors toegenomen. In de Verenigde Staten is het zelfs al oorzaak nummer één. Dit hangt samen met een ongezonde levensstijl die leidt tot zwaarlijvigheid. Als laatste komen hart- en vaatziekten tegenwoordig vaker voor. Omdat atherosclerose een aandoening is die door het hele lichaam aanwezig is, kan het ook in armen voorkomen en zo vaattoegangchirurgie bemoeilijken.

Verder wordt het belang beschreven van het driedimensionale verloop van arteriën. Drie dimensionaliteit veroorzaakt een ‘wokkelvormige’ voorgeleiding van bloed door de slagaders. Het voordeel hiervan is dat zuurstof en voedingsstoffen goed gemixt worden. Bovendien leidt deze gunstige bloeddynamica tot minder tangentiële krachten van bloed op de vaatwand en voorkomt het stagnatie of instabiliteit van de bloedstroom. Echter, een studie heeft laten zien dat arteriële kunststof bypasses in het been een meer tweedimensionale geometrie hebben met ongunstige bloeddynamica als gevolg. Dezelfde theorie zou ook mogelijk kunnen zijn voor de arm en arterioveneuze grafts.

Als laatste is in hoofdstuk 1 beschreven dat het ‘dotteren’ van een stenose in arterioveneuze grafts, d.w.z. oprekken van een vernauwing in het bloedvat door het opblazen van een ballon, nogal teleurstellende uitkomsten heeft. Door een sterke littekenreactie na behandeling heeft gemiddeld de helft van de grafts binnen zes maanden alweer opnieuw behandeling nodig om doorgankelijk te blijven. Een belangrijk onderdeel van de littekenreactie is het groeien van zgn. gladde spiercellen uit de vaatwand in het lumen. Deze reactie heet ‘intima hyperplasie’.

In 2002 is een grote studie gepubliceerd waarin het vaattoegang gebruik van de dialysepatiënten in 145 Amerikaanse dialysefaciliteiten en 101 faciliteiten in Duitsland, Frankrijk, Italië, Spanje en het Verenigd Koninkrijk was geanalyseerd. Deze *Dialysis Outcomes and Practice Pattern Study (DOPPS)* liet zien dat gemiddeld 24% van de Amerikaanse en 80% van de

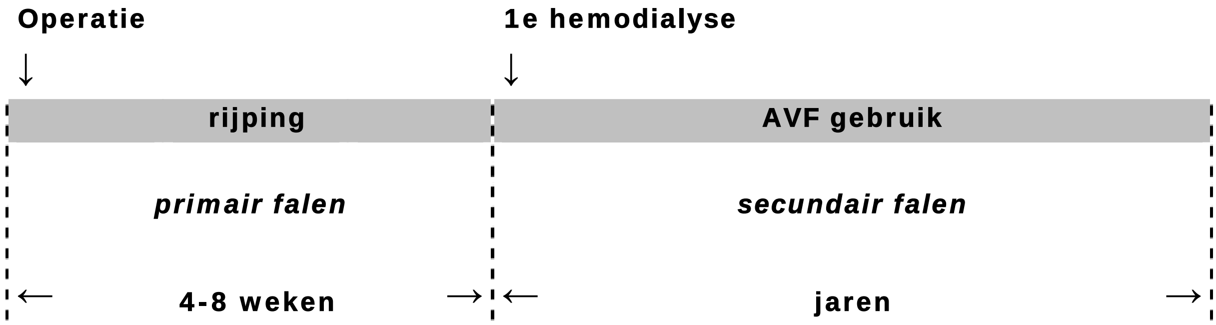
Europese hemodialysepatiënten gebruik maakten van een AVF. Nog veel opvallender was de enorme spreiding in AVF gebruik. In de V.S. varieerde het AVF gebruik in dialysecentra van 0-87%, en in Europa van 39-100% (zie ook figuur 1 van hoofdstuk 2). Deze grote verschillen bleken niet verklaard te kunnen worden door demografische factoren zoals leeftijd en geslacht of door verschillen in de aanwezigheid van hart- en vaatziekten. Uit een landelijke enquête bleek de spreiding wat betreft AVF gebruik ook groot te zijn in Nederland: 31-91% (gemiddeld 60%).

Hoewel de richtlijnen al jaren aangeven dat de arterioveneuze fistel de eerste keus vaattoegang is, bleken ze dus niet overal toegepast te zijn. In **hoofdstuk 2** is daarom een overzicht gemaakt van de aspecten van vaattoegangzorg die wél veranderd kunnen worden en potentieel leiden tot meer AVF gebruik en verbetering van vaattoegang functie. De rode draad door deze acties is de motivatie van het héle team van nierspecialisten, vaatchirurgen, interventieradiologen en dialyseverpleegkundigen om gezamenlijk de huidige standaarden te halen in combinatie met de bereidheid behandelwijzen aan te passen indien nodig.

Omdat het AVF gebruik in Nederland achterliep met West Europa (±60% vs. 80%) is in **hoofdstuk 3** een richtlijnen implementatieprogramma geïntroduceerd onder de naam 'CIMINO'. CIMINO staat voor: *Care Improvement by Multidisciplinary approach for Increase of Native vascular access Obtainment*. Dit acroniem is vernoemd naar dr. Cimino die samen met enkele collega's voor de eerste keer over AVFs publiceerde in 1966. De hoofddoelstelling van CIMINO was een versnelde toename van AVF gebruik in 11 deelnemende dialysecentra ten opzichte van een controle groep. Voorafgaand aan het programma zijn alle vaattoegangteams bezocht en geïnformeerd over de laatste richtlijnen. Per ziekenhuis was een verpleegkundige aangesteld die de patiëntgegevens, risicofactoren, operatiegegevens en follow-upgegevens van alle nieuwe permanente vaattoegangen registreerde in een nieuwe database.

In januari 2006 was het AVF gebruik in de CIMINO groep versneld toegenomen in vergelijking met 22 controle dialysecentra (zie figuur 1 in hoofdstuk 3). Wel was in beide groepen de spreiding in AVF gebruik afgenomen en werden er minder katheters gebruikt. Dit geeft aan dat de controlegroep eenzelfde soort proces onderging maar dat het proces langzamer verliep dan in de studiegroep. Omdat de patiënten in beide groepen nagenoeg hetzelfde waren, hebben we geconcludeerd dat het CIMINO project, of ten minste een aantal aspecten van het project, geresulteerd hebben in een versnelde toename van AVF gebruik. Bovendien suggereren deze resultaten dat centrumspecifieke factoren in belangrijke mate bijdragen aan de huidige (inter)nationale verschillen in vaattoegang gebruik.

Rijpingsproblematiek en vroege trombose komen voor bij 20% tot wel 50% van de AVFs. Deze grote verschillen kunnen slechts gedeeltelijk verklaard worden doordat er geen afgesproken definitie bestaat voor dit primaire AVF falen. Wanneer gebruik gemaakt wordt van te kleine bloedvaten (diameter <2,0 mm) neemt de kans op primair falen aanzienlijk toe. In **hoofdstuk 4** hebben we bij 395 patiënten onderzocht welke andere aspecten een risico vormen voor primair AVF falen. Van de niet-veranderbare factoren waren het vrouwelijke geslacht, diabetes mellitus en de duur van niervervangende therapie gerelateerd aan primair AVF falen. In vergelijking met elleboog-AVFs, hadden pols-AVFs een grotere kans om vroeg te falen. Het percentage primair falen varieerde van 8 tot 50% tussen de 11 deelnemende centra. In vergelijking met de 2 centra met het laagste percentage primair falen, bleek het risico voor primair falen ruim 1,5 tot bijna 9,5 keer verhoogd in de andere 9 centra, zelfs na correctie voor potentiële risicofactoren. Zowel in de pols-AVF groep als de elleboog-AVF groep was de interne diameter van de aders was niet voorspellend. Deze resultaten bewijzen dat er dialysecentrum specifieke factoren ten grondslag liggen aan de enorme verschillen. Omdat de vaatchirurg de bloedvaten selecteert voor AVF aanleg, en natuurlijk de ingreep uitvoert, lijkt het voor de hand te liggen dat deze specialist een grote invloed heeft op de vroege AVF functie. Verdere analyse van locale protocollen en behandelwijzen kunnen dus mogelijk leiden tot een afname van primair falen en daardoor resulteren in minder ingrepen voor de patiënt en kostenbesparing voor het ziekenhuis.



Figuur. Tijdschema van arterioveneuze fistel functie. Na chirurgische aanleg moet een AVF 4-8 weken rijpen voordat ze gebruikt kan worden voor hemodialysebehandelingen. Als de bloedstroom onvoldoende toeneemt tijdens deze periode (inadequate rijping), of als er vroege trombose optreedt, heet dit primair falen. Complicaties die leiden tot functieverlies ná ingebruikname heten secundair falen. Als een AVF eenmaal gerijpt is, functioneert ze doorgaans enkele jaren.

De duurzaamheid van vaattoegangen wordt uitgedrukt als *patency*. *Patency* start op de dag dat de vaattoegang is aangelegd en wordt uitgedrukt in dagen. Omdat een vaattoegang eigenlijk pas functioneel is bij gebruik voor dialyse, wordt de rijpingsperiode in de literatuur soms achterwege gelaten bij *patency* berekeningen. Deze vorm heet 'functionele *patency'.* Omdat een aanzienlijk deel van de AVFs primair faalt, kan dit dus leiden tot misleidende vergelijkingen. Daarom hebben we in **hoofdstuk 5** een nauwkeurige uitwerking van zowel *patency* als functionele *patency* beschreven van 491 AVFs. Bovendien worden risicofactoren voor 'secundair' AVF falen beschreven. Bij secundair falen verliest de AVF functionaliteit na aanvang met dialyse. Alleen diabetes mellitus werd geïdentificeerd als risicofactor voor het krijgen van een complicatie na ingebruikname. Er waren echter geen risicofactoren die geassocieerd waren met een verminderde duurzaamheid. Opvallend was dat drie van de 11 deelnemende dialysecentra een hoger risico hadden op secundair AVF falen dan de andere acht. Ook op langere termijn blijkt AVF functie dus beïnvloed te worden door centrumspecifieke factoren. In dit geval is 't het meest voor de hand liggend dat de nierspecialist en de dialyseverpleegkundigen hierop de meeste invloed hebben. Immers, zij controleren de functie van de vaattoegang en verwijzen de patiënt naar een radioloog of chirurg als er complicaties dreigen op te treden.

De tussentijdse conclusie is dus dat centrumspecifieke factoren in belangrijke mate bijdragen aan het soort vaattoegang dat wordt aangelegd, en het risico wat een hemodialysepatiënt loopt om primair of secundair AVF falen te krijgen.

Een belangrijke maatstaf om de functionele eigenschappen van AVFs te controleren, zijn zgn. bloedflow metingen. Zoals in de inleiding is beschreven, vindt de belangrijkste bloedflow toename plaats tijdens de eerste weken na de operatie. Hoe de bloedflow zich ontwikkelt vanaf 3 maanden na de operatie, is niet goed bekend. Echter, als de bloedflow daalt tot 500-700 ml/min, betekent dit dat er waarschijnlijk ergens een stenose ontstaat die uiteindelijk tot trombose kan leiden. Om meer inzicht te krijgen in de voorspellende waarde van bloedflow zijn de uitgangswaarde en het natuurlijke beloop geanalyseerd.

In **hoofdstuk 6** wordt beschreven dat AVFs die uiteindelijk gaan falen al tijdens de eerste meting een lagere bloedflow hebben dan AVFs die niet behandeld hoeven te worden in de toekomst. Omdat de primair gefaalde fistels niet meegerekend waren en dus alle fistels geschikt waren bij aanvang van de eerste dialysebehandeling, is er geen goede verklaring voor deze bevinding. Mogelijkerwijs is de bloeddynamica bij een lagere bloedflow ongunstiger met als gevolg het ontstaan van stenoses. Ook chirurgische technieken kunnen een rol spelen maar dat moet verder onderzocht worden.

Verder bleek dat bloedflow zowel in pols- als elleboog-AVFs niet meer verandert vanaf 4-5 maanden na de operatie. Dialysepatiënten met diabetes mellitus of een lage gewicht-lengte verhouding (magere mensen) hebben vaker een lage bloedflow. Het klinische belang van deze bevindingen is dat de eerste weken na de operatie cruciaal zijn voor een functionele AVF. Een gestoord begin wordt later niet meer goedgemaakt. Bovendien lijkt het nuttig om een preoperatief risicoprofiel the maken voor een aantal patiënt subgroepen zoals diabeten en magere mensen.

In **hoofdstuk 7** worden de resultaten beschreven van de eerste toepassing van een wokkelvormige vaatprothese, de ‘Swirlgraft™’, bij 20 dialysepatiënten. Deze innovatieve geometrie moet ervoor zorgen dat bloed op een meer natuurlijke manier door de prothese stroomt en zodoende stenosevorming ter plaatse van de graft-ader overgang ('veneuze anastomose') voorkomt. Zes maanden na aanleg waren de resultaten van deze studie echter niet beter in vergelijking met de literatuur. Een oorzaak kan zijn dat de wokkelvormige geometrie tijdens, of nét na de operatie verloren is gegaan doordat de graft is uitgerekt. Daardoor krijgt de Swirlgraft™ namelijk weer dezelfde geometrie als een gewone graft. Met aanpassingen in chirurgische technieken en een versteviging van de wokkelvorm kan deze prothese opnieuw getest worden.

In **hoofdstuk 8** zijn de resultaten van een experiment met 5 varkens beschreven. In dit model wordt aan beide kanten een graft ingehecht tussen de halsslagader en de halsader. Binnen vier weken ontstaat dan intima hyperplasie (uitgroei van cellen uit de aderwand) op de veneuze anastomose. Door enkelzijdig een veneuze anastomose te behandelen met een dotterballon waarvan de temperatuur gedurende 20 seconden naar -10ºC werd gebracht ('cryoplasty'), kon het ontstaan van intimahyperplasie met de helft worden verminderd. De controlekant was behandeld met een standaard dotterballon. Deze resultaten rechtvaardigen een uitbreiding van het experiment. Hopelijk kan cryoplasty in de toekomst bijdragen aan een vermindering of vertraging van stenosevorming na een dotterbehandeling.

In **hoofdstuk 9** zijn alle bevindingen en conclusies die beschreven zijn in dit proefschrift nog eens op een rijtje gezet. Bovendien zijn de resultaten uit hoofdstuk 3 en 4 gecombineerd beschouwd. Het klinkt logisch dat ziekenhuizen met een flinke toename in het AVF gebruik ook meer primaire falers hebben omdat er meer patiënten met moeilijke vaten geopereerd moesten worden. Dit bleek niet zo te zijn. Het percentage primaire AVF falers lijkt voornamelijk afhankelijk te zijn van het AVF gebruik aan de start van het CIMINO project. Met andere woorden, de vaatchirurgische ervaring is één van de belangrijkste factoren is die betrokken is bij het risico op primair AVF falen. Bij een programma als CIMINO wordt een hoog percentage AVF gebruik vooraf gegaan door een leerproces dat zich kenmerkt door afnemende percentages primair falen.

De centrumspecifieke risicofactoren zoals beschreven in dit proefschrift suggereren in sterke mate dat de verschillen tussen de deelnemende centra verklaard worden door mensenwerk. Omdat iedere arts z'n best doet voor zijn of haar patiënten kan juist de registratie van operaties en complicaties leiden tot meer inzicht over de werkelijke prestaties ten opzichte van collega's in andere ziekenhuizen. Uiteindelijk moet een project als CIMINO een basis vormen voor zorgverbetering voor de patiënt.

Dankwoord

Veel mensen hebben direct of indirect bijgedragen aan de totstandkoming van dit proefschrift. Zonder iemand te kort te doen, zijn er een aantal mensen wie ik persoonlijk wil bedanken.

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Curriculum vitae

De auteur van dit proefschrift werd op 11 mei 1976 geboren in Capelle aan den IJssel. Na een onbezorgde jeugd in het gemoedelijke Brabantse land, werd in 1994 het V.W.O. diploma behaald aan het Hertog Jancollege te Valkenswaard. Na één jaar Civiele Techniek aan de Hogeschool Midden Brabant te Tilburg werd in 1995 begonnen met de studie Geneeskunde aan de Universiteit Utrecht. Tijdens zijn studie was hij student-assistent bij de afdeling Anatomie en deed hij onderzoek naar de dynamica van HIV-DNA tijdens *Highly Active Antiretroviral Therapy* bij het Eijkman-Winkler Instituut voor Microbiologie, Infectieziekten en Ontsteking (Prof. dr. J. Verhoef).

Na het behalen van het Artsexamen in maart 2003 begon hij aan de afdelingen Vaatchirurgie (Prof. dr. F.L. Moll) en Nefrologie (Dr. P.J. Blankestijn) van het Universitair Medisch Centrum Utrecht met het onderzoek dat heeft geleid tot dit proefschrift. Vanaf juli 2007 zal hij werkzaam zijn als arts-assistent Orthopedie in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider: Dr. W.J. Willems). Per 1 januari 2008 zal hij starten met de opleiding tot Orthopedisch Chirurg bij de Regionale Opleidingsgroep Orthopedie Midden-West (opleider: Prof. dr. R.M. Castelein).

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Submitted

Huijbregts HJTAM, Bots ML, Wittens CHA, Schrama YC, Moll FL, Blankestijn PJ. Access blood flow in mature arteriovenous fistulas is related to the risk of secondary failure
Submitted

Appendix

Order of acknowledged hospitals in the appendix does not correspond with numerical order of hospitals in the text.

- St. Franciscus Gasthuis, Rotterdam: Dr. YC Schrama; Dr. CH Wittens; H. Aerts, RN; T. van Westen, RN
- Isala Clinics, Zwolle: Dr. JR Beukhof; A. de Groot, RN; S. Temmink, RN
- University Medical Center Utrecht, Utrecht: E. van Wijk, RN
- Jeroen Bosch Hospital, 's-Hertogenbosch: Dr. AA Hollander; Dr. JG Olsman; T. Kokx, RN; C. Boeren, RN
- Dianet & Diakonessenhuis, Utrecht: Dr. BC van Jaarsveld; Dr. SK Nagesser; M. Baars, RN
- Rijnstate Hospital, Arnhem: Dr. KJ Parlevliet; A. van de Kaaden, RN
- Medical Center Alkmaar, Alkmaar: Prof. dr. MJ Nube; J. Wijnker, RN
- Erasmus Medical Center, Rotterdam: Dr. MG Betjes; L. Chardon, RN; M. Konings, RN
- Deventer Hospital, Deventer: Dr. CJ Doorenbos; Dr. CG Vermeij; M. Voskamp, RN
- Medical Center Rijnmond Zuid, Rotterdam: Dr. MA van den Dorpel; Dr. AA de Smet; L. Steegman, RN
- Canisius Wilhelmina Hospital, Nijmegen: Dr. MA ten Dam; Dr. WB Barendregt; Dr. PH Haarbrink; F. Dastnaei, RN; A. Jilisen, RN.