

# A novel electrospun nano-fabric graft allows early cannulation access and reduces exposure to central venous catheters

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## ABSTRACT

**Purpose:** The use of tunneled central venous catheters (CVC) as vascular access for hemodialysis treatment is increasing worldwide. We present a novel polycarbonate urethane nano-fabric graft, produced by electrospinning technology, which has self-sealing features that avoid seroma formation and allow puncturing within 48 hours. The aim of this study was to assess its advantages in a setting where late referral is common.

**Methods:** A retrospective single center study assessed 24 implanted grafts in 24 patients with maximal follow-up of 18 months; patency rates, time to first cannulation and post-operative complications were assessed.

**Results:** Successful access was achieved in all 24 patients within 48 hours. In 50% of the patients cannulation was performed within 24 hours without increasing the complication rate. Twelve month primary and secondary patencies were 50% and 70.8%, respectively. Excluding early failures (within 30 days) because of surgical problems, 12 month primary and secondary patencies were 75% and 81.2% respectively. Complication and infection rates were 10.94 and 0.49/1000 dialysis procedures, respectively. No pseudoaneurysms or seromas were documented at 18 months.

**Conclusions:** Early cannulation was successful in all patients with good 12-month primary and secondary patency rates, compared to data reported by others on polytetrafluoroethylene (PTFE) grafts. The infection rate was substantially lower than in tunneled CVCs. Therefore, the AVflo graft may improve the clinical status of dialysis patients by decreasing the exposure to CVCs.

**Key words:** Arterio-Venous-Access, Clinical study, Early access, Electrospinning, Hemodialysis graft, Nano-fabric, Polycarbonate urethane

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## INTRODUCTION

The prevalence of tunneled central venous catheters (CVC) as vascular access for hemodialysis (HD) treatment is increasing worldwide (1), with the exception of the USA, where the "Fistula First" programme has determined stable CVC usage and an increase in the use of arterio-venous fistulae (AVF) (1). A vascular graft is considered a better alternative than a CVC for patients whose AVF failed or could not be created for various reasons. However, in most countries other than the USA a decrease in the prevalence of AVFs has not been counterbalanced by an increase in the use of vascular grafts, but is associated with an increase in the use of CVCs. Thus, there are factors precluding more widespread use of vascular grafts despite an increase in the

use of catheters. One of them could be the need for grafts that can be punctured immediately after the implantation, that perform reliably and with additional advantages such as a short hemostasis time following HD needle removal.

The AVflo™ graft (NICAST, Lod, Israel) is made with a novel polycarbonate urethane nano-fabric, produced by electrospinning technology, and provides self-sealing features that avoid seroma formation and facilitate early HD puncturing (2). Clinical experience with this graft is still limited. In this article we report the results of 24 consecutive surgical interventions for placement of this novel graft, to determine its advantages in a setting where late referrals as well as catheter-related infection rates are common, and a rapid transition to permanent arterio-venous access is of the utmost importance.

## MATERIALS AND METHODS

This retrospective study was performed using available records of 24 consecutive patients who underwent implantation of a prosthetic graft for HD between July 2009 and April 2011. No ethics committee approval according to the Declaration of Helsinki was required for this retrospective study.

Patients were referred for construction of an arterio-venous access. The vascular department of the Hatay Antakya Devlet Hastanesi performs 400 vascular access procedures annually and provides vascular access services to five HD units in the province of Antakya. Most of the procedures are arterio-venous fistulae, but in selected cases grafts are implanted because of lack of alternative approaches, as in the case of the 24 patients included in this study, who underwent implantation of straight or looped AVflo™ vascular access grafts. Patients were selected for an early cannulation graft placement because they had commenced HD with a temporary central venous catheter (CVC) as late referrals. Rather than placing a tunneled catheter and creating an AV fistula, because of longer maturation times, we choose to directly implant an early cannulation graft, which can be used immediately after its implantation. In addition, in case of failure after at least two to three months, the graft can also be converted to an AV fistula with a secondary procedure (3). Another reason for placement of the graft in some of the cases was exhaustion of available vasculature, a classic indication for vascular graft implantation procedure.

### Graft description and structure

The AVflo™ (Nicast Ltd, Israel) is a multi-layered self-sealing vascular access graft made of electrospun polycarbonate urethane nanofibers (2).

It features a self-bonded, four-layer design (Fig. 1). The self-sealing middle layer is highly flexible and imparts elastic properties that mimic those of the natural blood vessel. This layer eliminates bleeding from the suture line. It also decreases blood loss and hemostasis time after dialysis needle removal (2). In addition, it may decrease the rate of AV graft pseudoaneurysm formation, which is mainly attributed to needling in a restricted area of PTFE arteriovenous grafts (AVGs). A third filmy layer serves as a barrier that prevents the diffusion of serum and molecules (“non-weeping” layer) and thus prevents seroma formation. This layer also provides strength and elasticity to the graft’s structure and anchors the coil (Fig. 1) in the coiled configurations. The nanofiber fourth rough outer layer is specially designed for tissue integration that eliminates the dead space between the graft and the perigraft tissue and thus it should

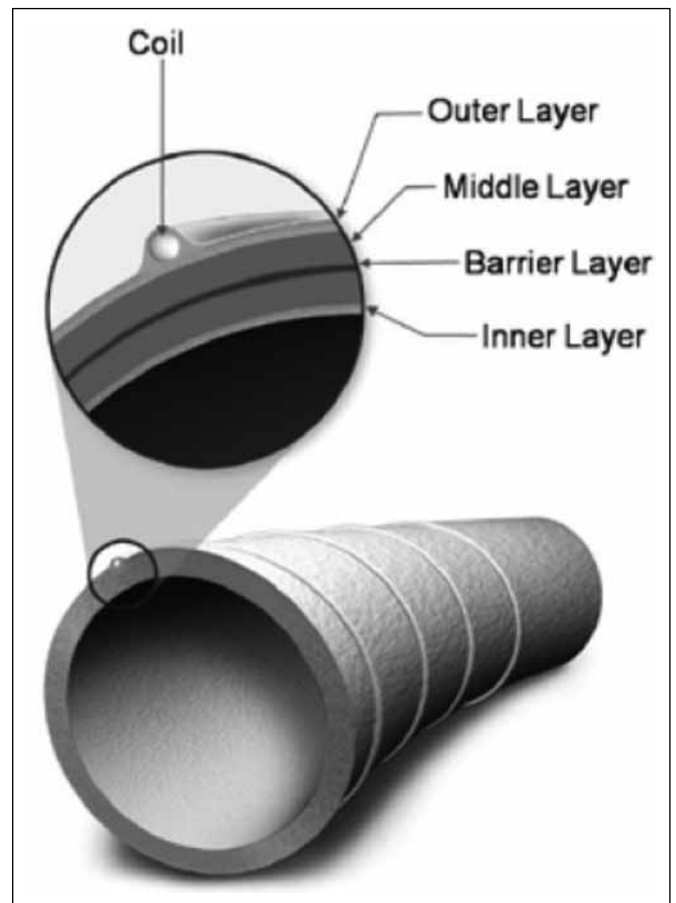


Fig. 1 - The four layer design of the AVflo™ graft (reprinted with permission from Wijeyaratne SM JVA 2011;12:28-35).

decrease infection rates and prevent perigraft hematomas and seromas.

### Surgical procedure

Surgical implantation was performed according to current surgical practice by a single implanting physician (CK). Straight or centered-coil configurations with an internal diameter of 6 mm were implanted in the forearm or upper arm. The grafts were placed subcutaneously by employing a Kelly-Wick sheathed tunneler (Bahadir, Samsun, Turkey) in accordance with manufacturer’s instructions.

A single intravenous bolus of 5000 U unfractionated heparin was administered during implantation. Post-operatively, hand exercises were encouraged and graft flow was monitored clinically by palpating the thrill and by auscultation. Post-operative follow-up information was obtained for all patients through review of their logs at the vascular outpatient clinic and the affiliated HD units. Interventions included thrombectomies for intraluminal thrombosis or graft removal. No other surgical

or endovascular interventions were employed. All patients were followed up to 18 months or until the graft was removed.

*Analysis end points*

The primary endpoint of the study was to assess patency rates, which are defined as follows (4).

*Primary patency rate*, or intervention-free access survival, was defined as the time interval from access surgery to any intervention designed to maintain or re-establish patency, or to access thrombosis, or the time of assessment of patency.

*Secondary patency rate*, or access survival until abandonment, was defined as the time interval from access surgery to access abandonment or the time of assessment of patency, regardless of interventions designed to maintain or re-establish patency. *Surgery censored patency rate* was defined according to NKF-KDOQI Guidelines, (5) which state that primary access failure of AVGs is considered failure of patency within the first 30 days after placement, caused by technical problems or selection of inappropriate vessels (artery or vein). In this type of access survival analysis we excluded the primary access failure cases since they are not considered to be device related, although peri-surgical kinking of the graft, which can ultimately cause thrombosis, may in part be related to the physical properties of the polyurethane fibers.

*Secondary endpoints*

Time to first dialysis access (early access): time in hours between completion of the implantation surgery and time of the first dialysis cannulation.

Complication rates: immediate complications and complications recorded during follow-up, particularly thrombosis and infections. The complication and infection rates were calculated in two ways, in order to compare them to published data:

- (1) Number of complications/1000 dialysis procedures:  
[Number of complications divided by number of observed dialysis procedures] × 1000
- (2) Number of complications/1000 device days:  
[Number of complications divided by cumulative follow-up days.] × 1000

*Statistical analysis*

Standard descriptive statistics were used to assess baseline demographic and clinical characteristics of patients at the time of surgery. Data were analyzed with Statistic Analysis Software (SAS version 9; SAS, Inc, Cary, NC, US). Survival analyses were performed using the Kaplan-Meier product limit estimator.

**RESULTS**

Twenty-four consecutive patients were included in the study: 10 (42%) women, 14 (58%) men, with a mean ± SD age of 56.2±17.5 (range 18-80) years. Mean time on dialysis was 3.95±2.1 years. Twenty-one (87.5%) patients had a central venous catheter and 19 (79.2%) had undergone previous access surgery at least once prior to current implantation (Tab. I).

Mean post-surgery follow-up was 195±126 days (range 2-556), with a total cumulative follow-up of 4691 days, representing 2010 HD sessions. A straight configuration graft was used in 18 (75%) patients, while for the remaining six patients the center-coiled configuration was chosen. No significant statistical differences were noted between the different configurations in respect to complication rates (P=0.0755).

As expected, time to first cannulation was very short, in all cases less than 48 hours (Tab. II). In 50% of the cases time to first access was less than 24 hours. There were no differences in thrombosis or infection rates between these patients and those punctured between 24 and 48 hours after surgery (P=0.34).

**TABLE I - PATIENT CHARACTERISTICS**

		Patients (n=24)
Sex (n, %)	Female	10 (41.7%)
	Male	14 (58.3%)
Age (y)	Mean ± SD	56.22±17.48
	Median [range]	62 [17-80]
Time under dialysis treatment (y)	Mean ± SD	4.38±2.45
	Median [range]	3.5 [1-9]
Patients with previous AVF operations (n, %)		19 (79.2%)
Number of previous AVF operations	Mean ± SD	2,45±1.07
	Median [range]	2 [1-5]
Prior use of catheters in the past six months (n, %)		21 (87.5%)

AVF, arterio-venous fistula; SD, standard deviation; y, years.

**TABLE II - TIME TO FIRST CANNULATION (N. 24)**

	Frequency (n)	Percent	Cumulative Percent
Up to 12 hours	1	4.2	4.2
12-24 hours	11	45.8	50.0
24-48 hours	12	50.0	100.0

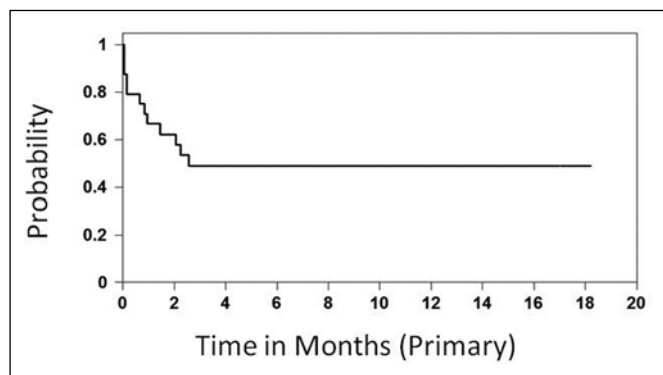


Fig. 2 - Primary patency: Kaplan-Meier analysis for time until first complication or end of follow-up. All Cases.

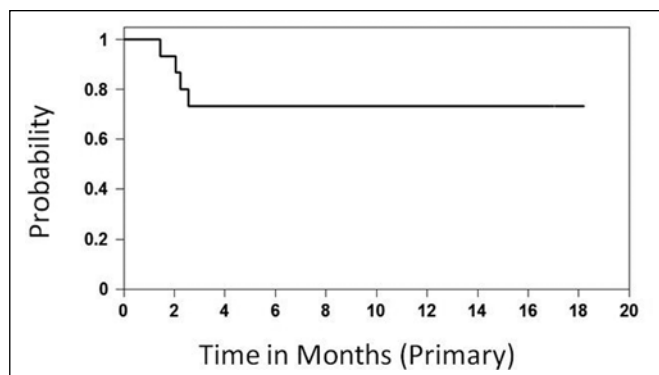


Fig. 4 - Primary patency: Kaplan-Meier analysis for time until first complication or end of follow up, excluding complications within 30 days of surgery.

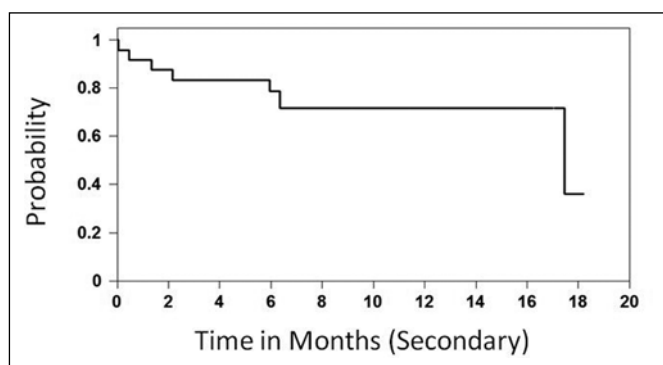


Fig. 3 - Secondary patency: Kaplan-Meier analysis for time until graft loss or end of follow-up. All Cases.

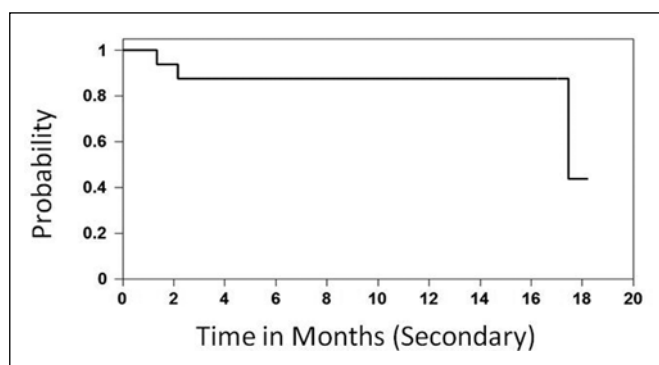


Fig. 5 - Secondary patency: Kaplan-Meier analysis for time until graft loss or end of follow up, excluding complications within 30 days of surgery.

Patencies

Primary and secondary patencies were recorded. Two sets of analyses were performed. A standard approach included all cases (primary patency, Fig. 2; secondary patency, Fig. 3). Primary and secondary patencies at six months were 50% and 75%; at one year 50% and 70.8%, respectively. In addition, we analyzed surgery censored primary (Fig. 4) and secondary (Fig. 5) patencies, excluding cases of primary access failure, as defined by the NKF-KDOQI Guidelines. Surgery censored primary and secondary patency, identical at six and 12 months, were 75% and 81.2%, respectively.

Complications

The total complication rate was 10.94 events/1000 dialysis procedures. No intra-operative complications were reported. Mean time to the first complication was 29±28 days (range 2-79). The main complication was access thrombosis. Nineteen episodes were recorded in 10 (41.7%) patients (Tab. III). Fourteen of the 19 (73.7%) thrombotic events occurred in five patients; while five patients (20.8%) had a single thrombotic event and 14

TABLE III - THROMBOTIC EVENTS

Thrombotic events per patient (n)	Affected patients - n (%)	Cumulative thrombotic events - n (%)
0	14 (58.3%)	0
1	5 (20.8%)	5 (26.3%)
2	2 (8.3%)	4 (21.05%)
3	2 (8.3%)	6 (31.6%)
4	1 (4.2%)	4 (21.05%)
Total	24 (100%)	19 (100%)

(58.3%) were thrombosis free. In relation to the follow-up time, thrombotic complications were 4.05 events/1000 graft-days and 9.45 events/1000 dialysis procedures. Thrombotic events were managed surgically when feasible, because of the unavailability of endovascular salvage procedures. Only one episode of hematoma and one episode of infection (0.213 events/1000 graft-days and 0.49 infection events/1000 dialysis procedures) were recorded. Twelve (50%) patients had no complications during the

follow-up period. In seven (29%) patients, the graft was finally removed because the thrombosis could not be resolved. No pseudoaneurysms or seroma formation – typical graft complications – were observed.

## DISCUSSION

A patent vascular access is the lifeline of a renal patient on HD. The arteriovenous fistula, first introduced in 1966 (6), is still the access of choice, owing to low incidences of stenosis, thrombosis and infection (7). However, vascular access failure is common and is a major source of complications (8). The availability of vascular grafts allows continuing dialysis with an arterio-venous access when native vessels are not adequate or exhausted, although graft patency can be problematic. Interestingly, the overall adjusted relative risk of dialysis access failure may be affected by as yet poorly defined factors. For example, access failure was found to be significantly lower in Europe than in the U.S. for both grafts (RR=0.69) and AV fistulae (RR=0.62) (9).

The placement of a central venous catheter (CVC) is simple and does not require the availability of an operating room. Moreover, once the CVC is placed, dialysis can be performed immediately. For those practical reasons, CVC implantation has gained popularity among physicians. This is reflected by the Dialysis Outcomes and Practice Patterns Study (DOPPS) (1), which shows that at least 23% of current HD patients in the years 2005-2007 in the UK, Belgium, Sweden, Canada and the USA used a catheter. Increased dependence upon catheters is not limited to elderly patients with extensive comorbidities. In non-diabetic HD patients aged 18-70, catheter use doubled in the USA and more than tripled in France, Germany, Italy and Spain, between DOPPS I (1996-2000) and DOPPS III (2005-2007) (1). However, the risks of dialyzing via a catheter have been well delineated, in terms of anatomic, thrombotic, infectious and dialysis adequacy issues, as well as in terms of mortality (10-13). Wasse et al (14) have shown that 44% of patients at 90 days after commencing dialysis were still using a catheter. Of those who started with a catheter, only 15% transitioned to a fistula. A graft was eventually used in 25% of patients who started with a catheter. In this respect, AV grafts are generally considered more readily cannulated than fistulae and can be used for HD sooner after surgery. However, most of them still need at least a two-week resting period, usually because of the presence of edema and the need for correct tissue integration. In order to further reduce the resting period and ideally to use the graft promptly, thereby avoiding the use of central venous catheters, several early cannulation AV grafts were recently introduced, including the AVflo™ graft (2) used in this study.

Our data demonstrate that early cannulation of the AVflo™ vascular access may avoid or reduce the exposure to central venous catheters, and also show the satisfactory long-term secondary patency of the AVflo™ despite the unavailability of endovascular salvage procedures.

The optimal waiting time before first use of vascular access, as a potential predictor of vascular access failure, is debated. This issue has been addressed within the DOPPS, with data from 2730 grafts and 2154 AV fistulae (9). For grafts, first cannulation occurred in US, Europe and Japan within two weeks in 16%, 17% and 42% of facilities respectively, and within 4 weeks in 78%, 78% and 84% of facilities. The study concluded that earlier cannulation of a newly placed vascular access was not associated with increased risk of vascular access failure, although the potential for confounding because of selection bias could not be excluded, implying the importance of clinical judgment in determining time to first use of vascular access. These data indicate that there is a need for earlier cannulation grafts, because most of the currently available regular grafts need at least two weeks before being punctured.

Early cannulation grafts can be particularly useful when there is a need for urgent access, if one wants to avoid catheters, such as in cases of late referral for dialysis, failed planning of vascular access, unexpected access thrombosis that cannot be salvaged or requiring extensive surgery, thus precluding maintenance of a puncture site of the access. Early cannulation grafts can be punctured within 24 hours after implantation, because they are not associated with “weeping” following surgical implantation with the consequent edema. In addition to the polycarbonate urethane nano-fabric AVflo™ graft considered here, several different grafts are already available on the market, in which the main material is expanded polytetrafluoroethylene (ePTFE) (Flixene™ - Atrium Medical Corporation, Hudson, NH, USA; Acuseal™ - W.L. Gore & Associates, Flagstaff, AZ, USA; Rapidax® - Vascutek Ltd., Renfrewshire, UK) or a silicone modified polyether urethane (Vectra® Vascular Access Graft, CR Bard, Murray Hill, NJ, USA). The AVflo™ manufacturer advises that cannulation of the graft is possible within 24-48 hours after implantation, provided there are no contraindications. In our study, 50% of the cases were cannulated within 24 hours, with no increase in complication rates.

The most common complication recorded in this study was thrombosis, while the infection rate was very low, strikingly different from those reported in dialysis using central venous catheters. Data on primary and secondary survival are available in the literature for standard dialysis grafts (15) and for some of the early cannulation grafts. In a DAC (Dialysis Access Consortium) study, a U.S. multicenter randomized controlled trial of extended-release dipyridamole and aspirin versus placebo in patients with grafts composed of PTFE, the incidences of primary

unassisted patency at one year were 23% in the placebo group and 28% in the dipyridamole-aspirin group, and conversely the incidences of cumulative (secondary) graft failure were 53% and 50%, respectively (16). These figures can be compared to those recorded in this study: one year primary and secondary patencies were 50% and 71%, while one year primary and secondary surgery censored patencies were 75% and 81% respectively, indicating a better outcome with the AVflo™ graft. Other data regarding graft survival are from two European randomized controlled studies comparing AV fistulae and grafts (17,18). The first study (17) enrolled 182 patients whose pre-operative vascular mapping revealed marginal forearm vessels at the wrist. Those patients were randomized to receive either a forearm fistula or a graft. The one year primary patencies of fistulae and grafts were 33% and 44%, respectively, with cumulative survivals of 52% and 79%, respectively. The second study (18) enrolled 105 patients with a failed radiocephalic and/or brachiocephalic fistula, or those with vessels unsuitable for either fistula type. Those patients were randomized to receive either a transposed brachio-basilic fistula or a forearm loop graft. That study reported a poor performance of the forearm graft. Specifically, the one year primary patency of grafts was 22%, but a good surveillance system allowed a cumulative graft one year survival of 85%.

It should be noted, however, that in the current study the average patient age ( $56.2 \pm 17.5$ ) is considerably lower than in the average European or American HD patient, as reported in the DOPPS I + III (1). The current results should therefore be validated in the elderly by performing more clinical studies.

Among early cannulation grafts, the silicone-modified polyetherurethane-based Vectra® was studied by Kakkos et al (19), who found in a sample of 239 grafts a one year primary patency of 50% and three year primary patency of 15%. Secondary patencies were 80% at one year and a satisfactory three year patency of 69%, although some questions were raised by pseudo-aneurysm formation, usually at the needle-stick site, in 17% of grafts over three years of follow-up. In the same study, the straight graft configuration demonstrated a better graft survival, with secondary patency at one year of over 80%. The same group previously published an article (20) comparing the Vectra® vascular access graft and basilic vein transposition in 76 patients, showing a primary graft patency of 50%. However, as a result of strict graft surveillance and frequent endovascular interventions, the graft secondary patency rate at 12 months was 87%. Chemla et al (21) compared Flixene™ (10 grafts) and Rapidax® (six grafts). Overall, the primary patency rate was 65.7% and the secondary patency rate was 83.5% at one year, with no statistically significant difference in patency rates between grafts. Schild (22) showed that in 33 patients where fistulas had failed, the Flixene™ graft could be cannulated

within 24-72 hours (29 patients within 24 hours), while maintaining an overall primary patency at six months of 49%, whereas the primary-assisted patency at six months was 80%. Since in the current study there were no endovascular interventions, the cumulative patency rate in all cases was somewhat lower than those reported by Schild and Kakkos, while the primary patency was comparable. The Flixene™ graft was also studied in Europe by Lioupis et al (23), who reported in 48 patients with a brachioaxillary graft configuration a one year primary patency rate of 30% and a secondary patency rate of 73%.

In a previous study with the AVflo™ graft, Wijeyaratne and Kannangara (2) showed primary and secondary patency rates at six months of 72.7% and 81.8%, and at 12 months 54.5% and 72.7%, respectively which are comparable with the current study.

Median cumulative survival for fistulas and grafts is markedly different when short-term primary failures are excluded, but similar when primary failures are included in the survival analysis (24). We analyzed the AVflo™ primary and secondary patency rates in two ways: (a) including all the grafts, and (b) excluding primary access failures that occurred in the first 30 days after surgery. Using this analysis, as illustrated in Figures 4 and 5, the primary and secondary patency of the AVflo™ graft was 75% and 81.2% at one year, respectively. In this respect, the surgeon's experience and learning curve in placing the AVflo™ graft could be a factor affecting the complication rate.

In addition, the dispersion of patients in several different dialysis centers and the lack of specific cannulation training could also be factors negatively affecting graft survival. The graft infection rate was 0.45 events/1000 dialysis procedures, which is less than previously reported for AV grafts (0.6 episodes per 1000 dialysis procedures). The infection rate is much lower than those reported in tunneled CVCs (3.1 per 1000 dialysis procedures) and non-tunneled CVCs (5.2 per 1000 dialysis procedures), and approximately twice that for AV fistulae (0.2 episodes per 1000 dialysis procedures) (25). The AVflo™ infection rate in this study can also be expressed as 0.213 events/1000 graft-days, which compares to 0.77 to 0.94 events/1000 catheter days reported in a recent Canadian study (26).

The low graft infection rate may be attributed to the improved graft external tissue integration layer (Fig. 1), which is specially designed for tissue integration and the prevention of perigraft seromas and hematomas.

#### *Limitations of the study*

Primary assisted patency was not assessed, since in the specific organization of our vascular access center it was not possible to perform endovascular procedures to prevent loss of the graft. Patients were mostly dialyzed in distant dialysis centers and could not be referred prior to complete thrombosis of the graft.

The results of this study must be interpreted with caution considering the small sample (n=24) and the relatively young age of the patients. However, the encouraging data showing good performance and low complication rates in a setting where late referral is very common should be kept in mind, while awaiting the results of larger studies currently underway.

## CONCLUSIONS

The European Best Practice Guidelines, the K/DOQI VA 2006 guidelines and the Fistula first breakthrough initiatives (FFBI) recommend refraining from prolonged ( $\geq 90$  days) catheter dependence, since this is associated with frequent episodes of catheter-related bacteremia,

central vein stenosis and early patient mortality. Our study using the AVflo™ graft conforms to this “Fistula First, Lines Last” approach. The results of this study demonstrate that this graft is at least comparable to, if not better than, other prosthetic grafts with respect to patency, time to first dialysis, and low complication rate. Further studies on larger numbers of patients are mandatory in order to further strengthen our conclusions.

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