J Vasc Access 2014; 00 (00): 000-000
DOI: 10.5301/jva.5000213

ORIGINAL ARTICLE

Comparison of FLIXENE™ and standard PTFE arteriovenous graft for early haemodialysis

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ABSTRACT

Purpose: **The purpose is to compare the outcomes of FLIXENE™ arteriovenous graft (AVG) to standard polytetrafluoroethylene (PTFE) AVG for early haemodialysis.**

Methods: **This is a prospective observational study of all AVGs placed over a 40-month period between 2008 and 2011 at our vascular unit. Primary outcome was to examine early cannulation rates for FLIXENE™. Secondary outcomes included patency rates, usability of grafts, complications in particular infections, interventions and death in comparison to standard PTFE grafts.**

Results: **Forty-five FLIXENE™ and 19 standard PTFE AVGs were placed in the study period; 89% of FLIXENE™ grafts were used for dialysis, with 78% cannulated within 3 days. At 18 months, primary patency (FLIXENE™ 34% vs standard PTFE 24%), primary assisted patency (35% vs 36%) and secondary patency rate (51% vs 48%) were not statistically different; 20.2% of FLIXENE™ grafts were infected at 18 months requiring explantation compared with 40.3% of standard PTFE grafts (p=0.14).**

Conclusions: **FLIXENE™ can be cannulated for dialysis within 3 days. It has similar patency and complication rates as other prosthetic grafts in the market. In patients who have no access and require urgent dialysis, FLIXENE™ is a viable option.**

Key words: **Arteriovenous graft, AV graft patency, Early cannulation, Early dialysis, flixene, Graft infection, Renal access, Trilaminate PTFE graft, Vascular access**

Accepted: December 15, 2013

INTRODUCTION

The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Recommendations from the National Kidney Foundation is a landmark document to monitor standards in the management of renal patients and vascular accesses (1). Autologous arteriovenous fistulae (AVFs) are considered superior to arteriovenous grafts (AVGs) and central venous catheters (CVCs) in terms of patient outcome, access complications and hospital costs (2).

Formation of an AVF, however, requires a significant period of time to mature before use. Patients requiring urgent dialysis do not have this luxury, and CVCs are inserted during the interim period. Neither temporary nor tunnelled CVC are the ideal solution due to the risk of infection and central vein stenosis, potentially compromising haemodialysis and risking death. In the year 2011, Waikato Hospital inserted 269 CVCs and had 1.1 bloodstream infections per 1,000 CVC days in haemodialysis patients (unpublished data).

FLIXENE™ (Atrium™, Hudson, NH) is a trilaminate composite polytetrafluoroethylene (PTFE) graft. The unique structure and minimal weeping allow access targeted at less than 72 hours. These characteristics of FLIXENE™ make it an attractive alternative to CVC in those requiring urgent dialysis. The aim of this study was to determine if early cannulation of FLIXENE™ is safe without increased complications, in particular infection and patency.

MATERIALS AND METHODS

A comparative observational study was conducted at the Vascular Department of Waikato Hospital (New Zealand) evaluating the clinical outcome of renal patients requiring prosthetic AVG for haemodialysis. Consecutive patients undergoing surgery for formation of AVG for haemodialysis were included. The study period was over 40 months between Jan 2008 and May 2011. The grafts were inserted by four consultant surgeons in the department and the type of graft inserted depended on surgeon

preference and graft availability. All patients for planned vascular access underwent preoperative ultrasound mapping of the artery and vein. The indications for insertion of AVG included inadequate vein quality for AVF in patients who never had permanent renal access or previously failed AVG or AVF with no other options for AVF, and patients in urgent need for dialysis in progressive renal failure.

The surgical procedure for AVG formation was routine and standardised where the target artery and vein were exposed in the usual manner. Intravenous antibiotics were given prior to incision; 5,000 units of heparin were administered intravenously prior to arterial clamping. The grafts were tunnelled subcutaneously. End-to-side anastomoses of the graft to both target vessels at a suitable segment were performed with 6/0 Prolene or a similar synthetic, monofilament, non-absorbable polypropylene suture.

Primary outcome was to examine early cannulation rates for FLIXENE™. Secondary outcomes included patency rates, usability of grafts, complications in particular infections, interventions and death in comparison to standard PTFE grafts (Taperflow™, Vascutek™).

Data were prospectively gathered during the perioperative period. Information on study outcome following this period was collected from follow-up outpatient clinic appointments, patient records and clinical notes. Patients were regularly seen by the Renal Medicine Service and quality of AVG was assessed by venous measurements and adequacy of dialysis by biochemistry and body weight. The Vascular Surgical Service was involved if there were graft-threatening problems. All patients were followed up to the end of the study unless they died or moved outside the district.

The outcomes in terms of primary, assisted primary and secondary patency rates, as well as graft infection and death rates, were assessed using Kaplan-Meier Survival analysis with Log-Rank test to test 5% significance. Appropriate statistical methods with $p<0.05$ were used for evaluation of other secondary outcomes: Chi-square/Fisher's exact tests for discrete variables and student's *t*-test (two-tailed) for continuous variables.

There was no conflict of interest in conducting the study. Ethical approval was obtained from Northern Y Ethics Committee, NZ (NTY/08/08/081).

RESULTS

A total of 64 patients underwent surgery for formation of AVG during the study period. Forty-five FLIXENE™ and 19 standard PTFE grafts were placed. During the latter phase of the study, FLIXENE™ grafts were preferred due its early cannulation benefits. The mean age of our population was 49 years with a range of 17 to 75 years. Patients in the FLIXENE™ group were statistically significantly older (52 years) compared with those in the standard PTFE group (42 years) with a p-value of 0.003. Median age showed a similar difference (53 vs 41 years); 30 patients (47%) were male, 37 (58%) were of indigenous Maori descent. More patients received FLIXENE™ as their first AVG for haemodialysis when compared with those that received standard PTFE grafts as their first AVG (62% vs. 32%, p=0.03). Table I provides additional comparisons between the two patient groups.

Forty of the 45 (89%) FLIXENE™ AVG placed were cannulated for haemodialysis. This rate was similar to the standard PTFE graft, where 16 of the 19 (84%) grafts were successfully used (p=0.60). The median number of days postoperatively to cannulate FLIXENE™ grafts was 2.5; 78% of the FLIXENE™ grafts were accessed within 72 hours as designed. As expected, none of the standard PTFE grafts were needled before at least 3 weeks.

Thirty-one FLIXENE™ (69%) and 7 (37%) standard PTFE grafts were still in use at the end of the 40-month study period (p=0.02). However, the mean follow-up period for the standard PTFE grafts appeared to be longer and this may be a confounding factor.

TABLE I - CHARACTERISTICS OF PATIENTS

Characteristics	FLIXENE™ (n=45)	Standard PTFE (n=19)	p-Value
Mean age, yrs	52	42	0.003
Male, n (%)	23 (51)	7 (37)	0.30
Maori, n (%)	26 (58)	11 (58)	0.99
Diabetes, n (%)	27 (60)	9 (47)	0.35
Smoking history, n	19	6	0.43
Heart disease, n	14	8	0.40
Hypertension, n	35	13	0.43
Hypercholesterolaemia, n	24	7	0.22
First access, n (%)	28 (62)	6 (32)	0.03
Failed native fistula, n	6	6	0.08
Failed PTFE AVG, n	11	7	0.31
Brachio-basilic, n (%)	21 (47)	5 (26)	0.13
Brachio-cephalic, n (%)	9 (20)	8 (42)	0.07
Brachio-cubital, n	7	2	0.60
Brachio-brachial, n	6	1	0.24
General anaesthetics, n (%)	27 (60)	15 (79)	0.14
Mean length of stay, days	2	6	0.02
Mean follow-up period, days	280	477	0.08

AVG, arteriovenous graft; PTFE, polytetrafluoroethylene.

The secondary patency rate of FLIXENE™ at 12 months was 63% which was similar to standard PTFE AVG (55%). Table II describes in detail the patency rates of FLIXENE™ and standard PTFE grafts. Kaplan-Meier survival analysis and log-rank test did not reveal statistical differences between the two groups in terms of primary, assisted primary and secondary patency rates. Survival plots are shown in Figures 1, 2 and 3.

TABLE II - PATENCY RATES COMPARING FLIXENE TO STANDARD PTFE GRAFTS

Patency rate	FLIXENE™	Standard PTFE	p-Value
Primary			0.95
1 month	70%	84%	
6 months	55%	51%	
12 months	44%	31%	
18 months	34%	24%	
Assisted primary			0.59
1 month	73%	84%	
6 months	55%	56%	
12 months	45%	50%	
18 months	35%	36%	
Secondary			0.77
1 month	89%	90%	
6 months	71%	73%	
12 months	63%	55%	
18 months	51%	48%	

PTFE, polytetrafluoroethylene.

Eleven graft infections requiring excisions were observed during the study period comprising five FLIXENE™ grafts (11.1%) and six standard PTFE grafts (31.6%). Log-rank analysis did not reveal a difference at 18 months (20.2% FLIXENE™ vs. 40.3% standard PTFE, p=0.14). Kaplan-Meier analyses are shown in Table III and Figure 4.

During the study period, 22 (48%) FLIXENE™ grafts became occluded and failed to be used for dialysis, compared with 10 (53%) standard PTFE grafts, with no statistically significant difference (p=0.78).

A total of 19 of the 45 FLIXENE™ (42%) and 4 of the 19 standard PTFE (21%) grafts were used for dialysis without complications (p=0.07). Graft interventions during the study period to prolong patency for graft failure or impending failure included endovascular or open surgical approaches as described in Table IV. Decisions on the appropriate intervention were based on clinical and investigation findings, patient comorbidities and surgeons' discretion. Some grafts had multiple interventions.

Eight patients with FLIXENE™ grafts and six patients with standard PTFE grafts died during the study period. There were no deaths related to graft complications. There was no statistical difference in survival between the two

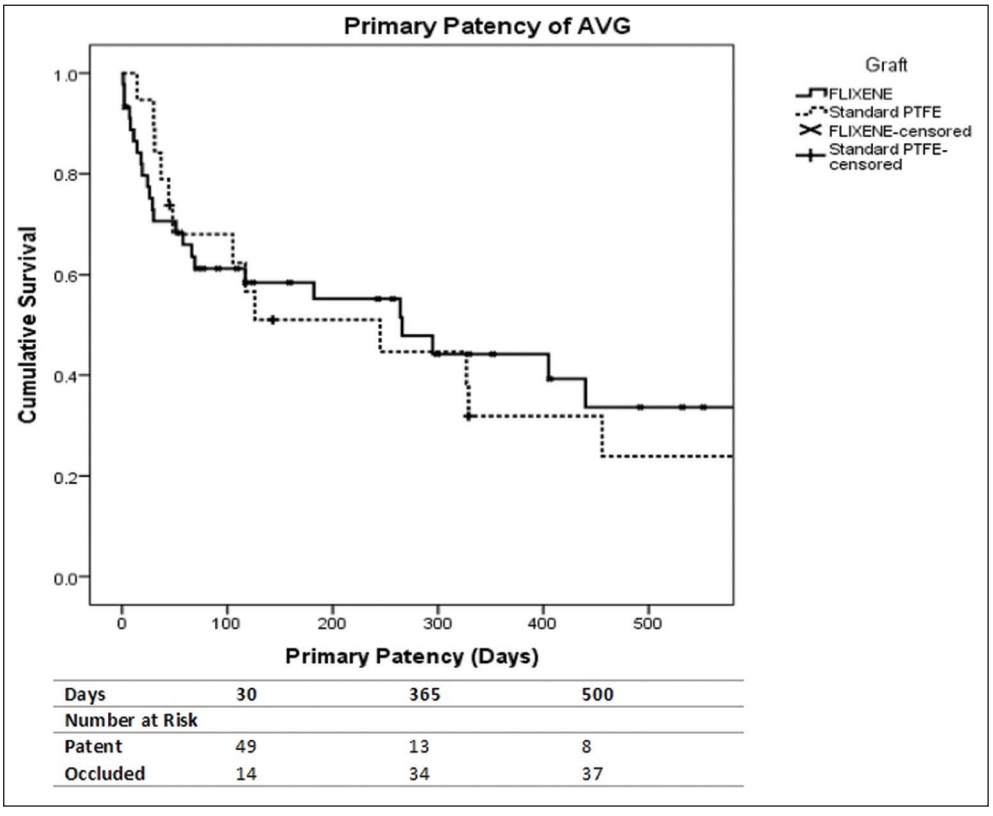
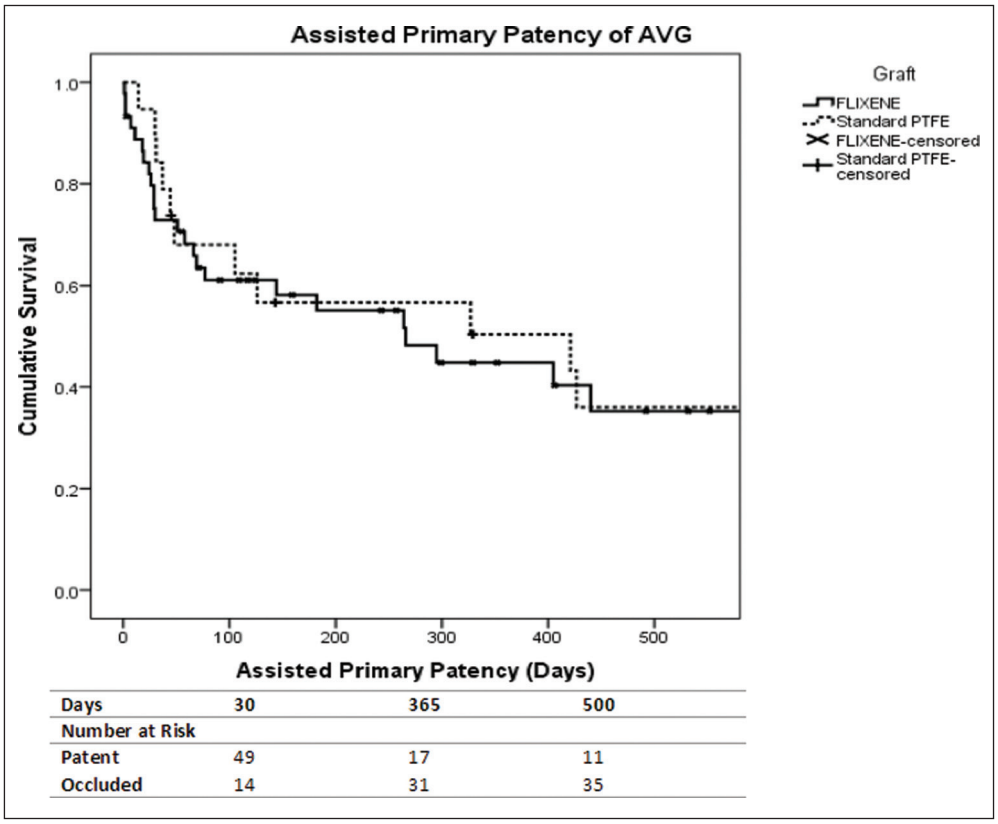
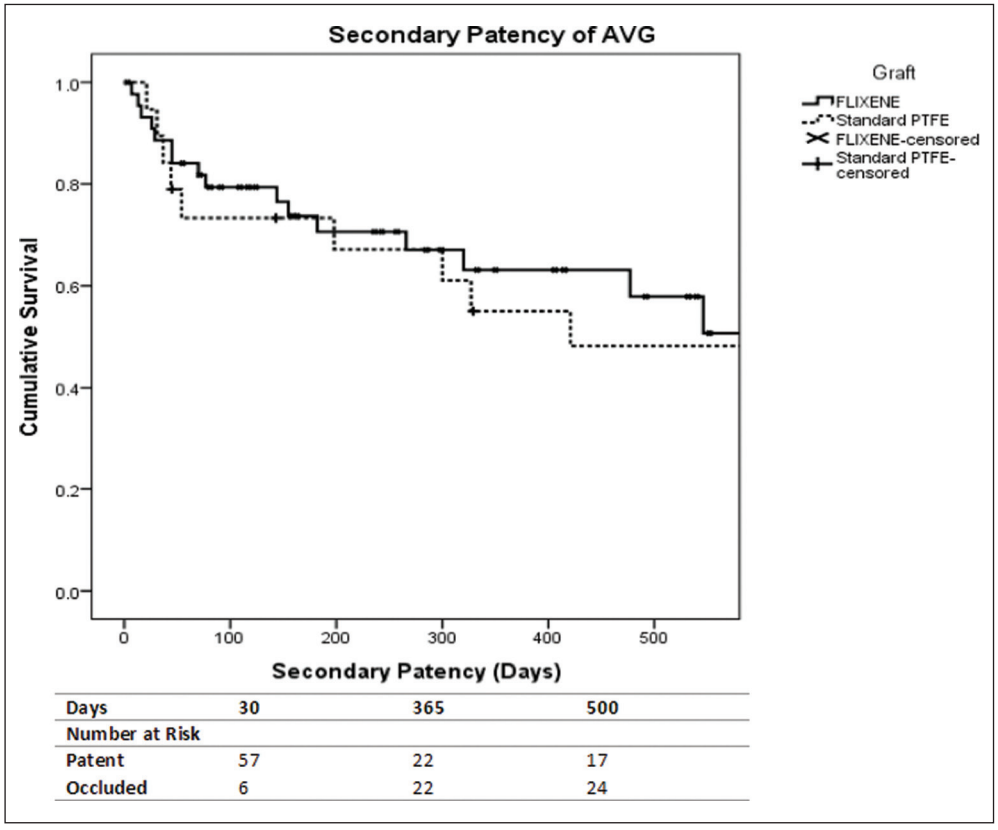


Fig. 1 - *Kaplan-Meier curve on primary patency rate.*



Days	30	365	500
Number at Risk			
Patent	49	17	11
Occluded	14	31	35

Fig. 2 - *Kaplan-Meier curve on primary assisted patency rate.*



Days	30	365	500
Number at Risk			
Patent	57	22	17
Occluded	6	22	24

Fig. 3 - *Kaplan-Meier curve on secondary patency rate.*

TABLE III - INTERVENTIONS ON FLIXENE AND STANDARD PTFE GRAFTS

Intervention	FLIXENE™ (n)	Standard PTFE (n)
Angioplasty	6	7
Patchplasty	0	2
Thrombolysis	18	11
Thrombectomy and/or patchplasty	23	7
Revision	10	5

PTFE, polytetrafluoroethylene.

TABLE IV - GRAFT COMPLICATIONS COMPARING FLIXENE TO STANDARD PTFE GRAFTS

	FLIXENE™ (n=45)	Standard PTFE (n=19)
Complications per graft	1.6	2.3
Angioplasty	4	5
Patchplasty	0	2
Thrombolysis	12	8
Thrombectomy	14	4
Revision	10	4
Complication free	19	4

PTFE, polytetrafluoroethylene.

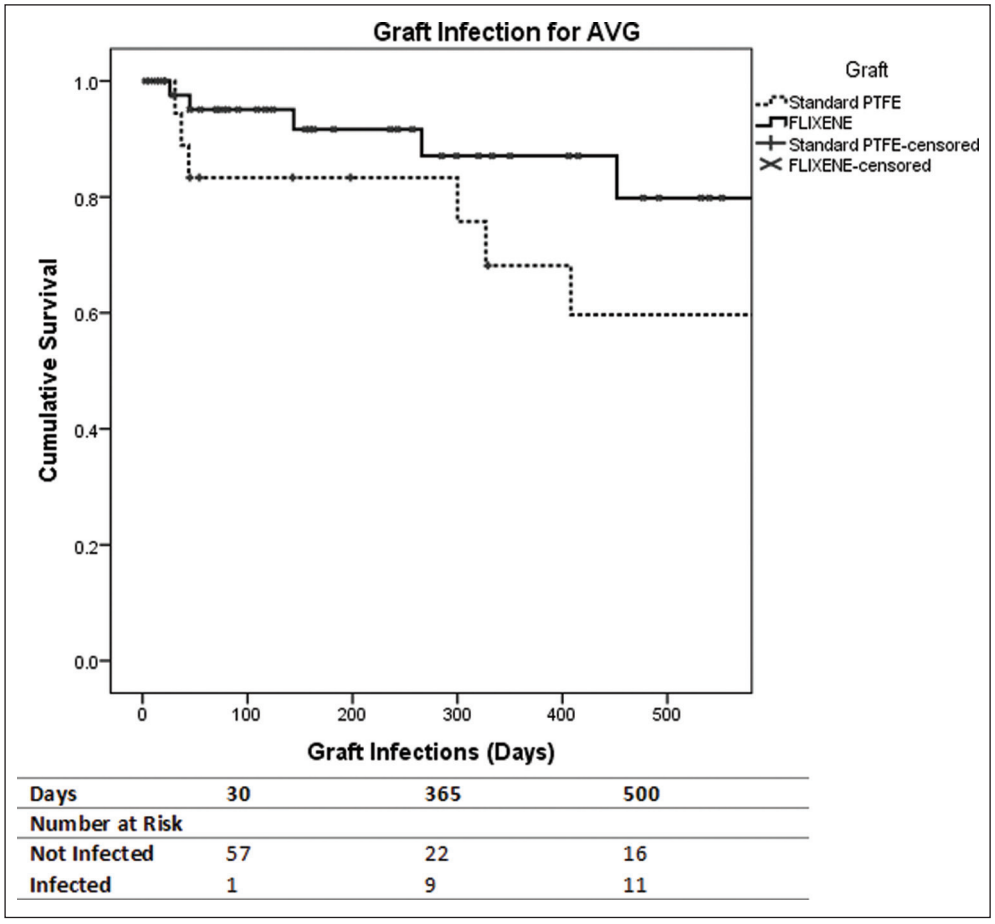


Fig. 4 - *Kaplan-Meier curve on graft infection for AVG*

groups at 12 months using Kaplan-Meier survival analysis [79.5% FLIXENE™ vs. 67.8% standard PTFE (p=0.67)].

DISCUSSION

This study demonstrated that the majority of FLIXENE™ grafts were successfully cannulated for early dialysis within 72 hours. The results also suggested that the rate of complications and patency rates were not affected by early cannulation. Reassuringly, the infection rate was similar to standard PTFE in spite of early cannulation.

Schild et al published a similar study in 2011 interrogating the efficacy of FLIXENE™ with a follow-up of 6 months (3). Primary patency rate of the 33 grafts was 49% and primary assisted rate was 80%. Secondary patency rate was not documented.

Lioupis et al compared the outcome of 48 FLIXENE™ AVG to transposed autogenous brachio-brachial and

brachio-basilic fistulae (4). Primary patency for FLIXENE™ at 18 months was 21%, primary assisted patency 38% and secondary patency 57%. Three FLIXENE™ grafts (6%) became infected that resulted in operative exploration or removal of the graft.

KDOQI recommended that primary failure rate (failure within 30 days or before use of dialysis) should not be more than 5% for upper arm grafts (1). Our rate of 13% was higher and might be related to the demographics of our patients and their associated comorbidities. As described in Table I, nearly 60% of our patients were of Maori origin. According to the latest national health survey, Maoris have a higher prevalence of diabetes, obesity and atherosclerotic diseases, and are more likely than other groups to experience unmet need for health care (5). Anecdotally from observations within our unit, the quality of artery and vein in the Maori population appeared to be relatively suboptimal at the time of requiring renal access when compared with Europeans. The arteries were usually calcified and vein diameters even at the upper arm appeared to be smaller. This might also account for the slightly lower patency rates from our centre. Previous studies reported 1 and 2 year cumulative patency rates of 59%-90% and 47-85%, respectively, for standard PTFE grafts (6).

One of the reasons AVG is considered inferior to AVF is the increased graft infections requiring explantation. Published figures on AVG infection ranged from 3.5% to 19.7% (7-9). Our data demonstrated that FLIXENE™ grafts did not have a higher infection rate than standard PTFE grafts but still higher than native AVFs.

Schild et al also published a large retrospective review in 2008 of 1,700 consecutive vascular accesses between 1997 and 2005 comparing AVF and AVG (10). Expectedly, AVGs were associated with higher incidences of infections (9.5% vs. 0.9%) and occlusions (24.7% vs. 9%). Interestingly, this large series concluded there was no difference between AVG and AVF in terms of patency irrespective of the location of the access.

The KDOQI recommend that a standard AVG should be placed at least 3-6 weeks before the anticipated start of haemodialysis, and AVF at least 6 months prior, allowing time to "mature" and potentially for revisions (1). Unfortunately, for many patients, the need to access haemodialysis is more imminent. Locally, nearly 50% of our patients present late and do not have the luxury of time for AVFs to mature. Traditionally, immediate access could be achieved with a temporary or permanent CVC. According to the literature, 63% of renal patients in the United States commenced haemodialysis with a CVC (11). The benefit of immediate access could be weighed against the high rate of CVC complications, in particular, line infections and central vein stenosis and thrombosis. In a national cohort study of haemodialysis patients in Scotland in 2012, patients with CVC had higher risk of all-cause mortality [adjusted hazard ratio (HR) of 1.83-2.08], infection-related deaths (adjusted HR 3.10-3.63) and more alarmingly 6.9-fold increased risk of death from septicaemia compared with AVFs or AVGs (12). In a review publication by Yevzlin in 2008 which described central vein stenosis in CVC, the incidence of central vein thrombosis from internal jugular CVC ranged 10-40%, of which a higher proportion had previous line infection or inflammation. Furthermore, AVG or AVF had better long-term patency in patients without history of CVC insertions (13).

For these reasons, the KDOQI recommended that less than 10% of chronic haemodialysis patients should be maintained on CVC (1). A FLIXENE™ graft provides an alternative option to CVC for patients who require urgent haemodialysis by allowing early cannulation within 72 hours. As mentioned previously, Waikato Hospital had 1.1 bloodstream infections per 1,000 catheter days as a result of CVC. This was in stark contrast to our data which showed 0.4 infections per 1,000 FLIXENE™ AVG days (5 infections/12,531 graft days). FLIXENE™ insertion would benefit these patients by also avoiding central venous problems.

In addition, a functioning forearm FLIXENE™ has the potential benefit of continuing to "mature" the outflow venous vessel. Therefore, should the patient become suitable for an AVF, the transition can be made without having to wait as long for the fistula to mature.

There was a mean age difference between those patients who had FLIXENE™ and those with standard PTFE. A probable explanation for this observation could be the liberal policy in introducing haemodialysis in renal patients in recent years where there was increased trend in dialysing the older population. Despite this patency, the FLIXENE™ group was no worse than standard PTFE.

Mean hospital stay was longer in the standard PTFE group and related to comorbidities and not directly related to the surgery. Of the nine patients with standard PTFE who stayed longer than 3 days, only one was a result of surgery where the patient was monitored for a postoperative wound haematoma with a history of thrombocytopaenia and chronic liver disease.

In conclusion, we have demonstrated that FLIXENE™ has the advantage of safe early access compared with standard PTFE. FLIXENE™ may also be a potentially superior option to CVC in patients requiring urgent haemodialysis.

Financial support: No competing interests or financial support declared.

Conflict of interest: None.

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