A randomized controlled trial and cost-effectiveness analysis of early cannulation arteriovenous grafts versus tunneled central venous catheters in patients requiring urgent vascular access for hemodialysis

Emma Aitken, MBChB (Hons),[a,b] Peter Thomson, MD,[c] Leigh Bainbridge, BSc (Hons),[a] Ram Kasthuri, FRCR,[d] Belinda Mohr, PhD,[e] *and* David Kingsmore, MD,[a,b] *Glasgow, United Kingdom; and Flagstaff, Ariz*

ABSTRACT

Objective: Early cannulation arteriovenous grafts (ecAVGs) are proposed as an alternative to tunneled central venous catheters (TCVCs) in patients requiring immediate vascular access for hemodialysis (HD). We compared bacteremia rates in patients treated with ecAVG and TCVC.

Methods: The study randomized 121 adult patients requiring urgent vascular access for HD in a 1:1 fashion to receive an ecAVG with or without (+/−) an arteriovenous fistula (AVF; n = 60) or TCVC+/−AVF (n = 61). Patients were excluded if they had active systemic sepsis, no anatomically suitable vessels, or an anticipated life expectancy <3 months. The primary end point was the culture-proven bacteremia rate at 6 months, with the trial powered to detect a reduction in bacteremia from 24% to 5% ($\alpha = .05$, $\beta = .8$). Secondary end points included thrombosis, reintervention, and mortality. A cost-effectiveness analysis was also performed.

Results: Culture-proven bacteremia developed in 10 patients (16.4%) in the TCVC arm ≤6 months compared with two (3.3%) in the ecAVG+/−AVF arm (risk ratio, 0.2; 95% confidence interval, 0.12-0.56; $P = .02$). Mortality was also higher in the TCVC+/−AVF cohort (16% [n = 10] vs 5% [n = 3]; risk ratio, 0.3; 95% CI, 0.08-0.45; $P = .04$). The difference in treatment cost between the two arms was not significant (£11,393 vs £9692; $P = .24$).

Conclusions: Compared with TCVC+/−AVF, a strategy of ecAVG+/−AVF reduced the rate of culture-proven bacteremia and mortality in patients requiring urgent vascular access for HD. The strategy also proved to be cost-neutral. (J Vasc Surg 2017;65:766-74.)

Arteriovenous fistulas (AVFs) are the vascular access of choice for patients requiring hemodialysis (HD). Tunneled central venous catheters (TCVCs) are recommended only as an option of necessity.[1,2] In practice, AVF usage is limited by delays in operative planning, maturation time, and a failure to mature rate approaching 60% in some randomized trials.[3] If HD is required before the AVF is functionally mature, an alternative access (generally TCVC) is required.[1,2]

A recent study in Scotland of 2666 patients revealed a twofold to threefold increased risk in all-cause mortality and a sevenfold increase in death from septicemia with the use of TCVCs.[4] The complications of vascular access are responsible for >20% of hospitalizations in patients on HD and account for 33% of all in-patient renal bed usage.[5-7] It therefore follows that a strategy of TCVC avoidance is likely to have significant benefits for individual patients and health care providers.

Arteriovenous grafts (AVGs) provide an alternative means of vascular access. AVGs have traditionally been used only when all other native venous options have been exhausted. However, the recent development of early cannulation AVGs (ecAVGs) now allows grafts to be considered as an alternative to a TCVC in patients requiring vascular access imminently.[8,9] The benefits and limitations of an AVG lie somewhere between those of a TCVC and an AVF: they require significantly greater initial outlay in surgical expertise, time, and material cost[10] but have infection and complication rates lower than a TCVC.[11,12] Culture-proven bacteremia rates for TCVCs are 1.77/1000 catheter days compared with 0.6/1000 dialysis days for an AVG and 0.3/1000 dialysis days for an AVF.[11,12] Primary patency rates for AVGs range

From the Department of Renal Surgery, Queen Elizabeth University Hospital,[a] the College of Medical, Veterinary and Life Sciences, University of Glasgow,[b] and the Department of Nephrology[c] and Department of Interventional Radiology,[d] Queen Elizabeth University Hospital, Glasgow; and the W. L. Gore and Associates, Inc, Flagstaff.[e]

E.A.'s salary was funded by Darlinda's Charity for Renal Research.

The trial reported in this study was registered with the International Standard Randomised Controlled Trial Number (ISRCTN 80588541).

Author conflict of interest: D.K. received an Investigator Led Small Research Grant from W. L. Gore and Associates. B.M. is employed by W. L. Gore and Associates as a health economist.

Correspondence: Emma Aitken, MBChB (Hons), Department of Renal Surgery, Queen Elizabeth University Hospital, 1345 Govan Rd, Glasgow G51 4TF, Scotland (e-mail: emmaaitken@nhs.net).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2016.10.103

from 40% to 60% at 1 year.[13] However, with aggressive management of thrombosis, secondary patency rates as high as 90% at 1 year can be achieved.[14]

Between 30% and 35% of patients who need to start HD are referred for access creation <90 days before the date that they need to start HD, leaving insufficient time for planning, surgery, and maturation of an AVF.[15,16] In the United Kingdom, only 40% of patients commence HD through an AVF.[15] The ecAVG may have a role in these incident "crashlander" patients, in whom there has not been sufficient time to create and mature an AVF and avoid the need for TCVC.

In recent years, a number of case series, including one from our institution, have highlighted the potential role of an ecAVG as an alternative to a TCVC in patients requiring urgent vascular access for HD.[8,9] Results have been promising, albeit in small patient numbers. Observational data suggests that such a strategy could deliver a cost savings of nearly £1000 per patient after 6 months.[10]

We therefore designed a randomized controlled trial comparing ecAVGs vs TCVCs in patients requiring urgent vascular access for HD. We hypothesized that ecAVGs would result in a lower bacteremia rate than TCVCs and could potentially deliver cost savings.

METHODS

Ethics

The study protocol was reviewed and approved by the West of Scotland Research Ethics Committee 4 (13/WS/0187). All trial procedures were in concordance with the Declaration of Helsinki, 1975 (revised 2000). All participants provided written informed consent. A Trial Steering Committee was convened before the start of the study and annually to evaluate data and safety. All serious adverse events, defined as death or life-threatening sepsis, were reported to the Research Ethics Committee.

Study design and participants

This prospective single-center randomized controlled trial was performed in the Department of Renal Surgery, Western Infirmary, Glasgow. The trial protocol has been previously published.[17] The study was inclusive. All patients aged ≥18 years with established renal failure who required urgent vascular access for HD (ie, needed for HD ≤48 hours for referral) were eligible to participate. Patients were excluded if they had a recent myocardial infarction (<4 weeks), active systemic sepsis, no anatomically suitable vessels for ecAVG based on preoperative imaging, anticipated life expectancy <3 months, an existing AVF thought likely to be useable ≤2 weeks, if they lacked capacity to provide informed consent, or declined to participate in the study.

Randomization

Patients were randomly assigned (1:1) by a computer-generated randomization sequence and sealed envelopes to receive a TCVC with or without (+/−) an AVF or an ecAVG+/−AVF. Masking the allocation of treatment to patient, surgeon, or study investigator was not possible because of the nature of the treatment and any subsequent interventions.

Procedures

Preoperative planning. All patients underwent duplex ultrasound imaging of both arms (and legs where no suitable upper limb option was determined). The venous and arterial trees were both assessed, and a preoperative plan was made to site both ecAVG and native AVF (if possible). A minimum arterial cross-sectional diameter of 2 mm was deemed necessary to sustain an AVF or ecAVG. Venous diameters of 2 mm at the wrist and 3 mm at the elbow were considered suitable for an AVF (or forearm loop graft). A patent basilic/axillary artery measuring at least 3 mm was deemed necessary to site the venous outflow of an ecAVG. Care was taken in the choice of anatomical site for the ecAVG to preserve all possible sites for future autologous access, with the site of native AVF favored distally in the nondominant arm. An ecAVG was placed to accommodate optimal AVF placement. For example, a native left radiocephalic fistula and right brachioaxillary graft was favored in a left-handed patient with good native vessels and no previous vascular access, whereas revision of an existing occluded left brachiocephalic fistula using an interposition ecAVG and contralateral elbow AVF would be considered in an elderly patient with poor vessels and occluded existing AVF.

TCVC+/−AVF strategy. The TCVC+/−AVF strategy reflected standard practice at our institution, with TCVC insertion performed by a radiologist or nurse specializing in TCVC insertion. One dose of intravenous vancomycin was administered before catheter replacement.

Tunneled Ash Split (Medcomp, Harleysville, PA) 14F double-lumen polyurethane HD catheters were inserted, with 280 mm (left) or 320 mm (right) catheters inserted by a Seldinger technique under image guidance. A standard protocol for catheter care was used throughout the study period. This demanded complete sterile precautions during insertion and manipulation with an assistant or a no-touch technique to manipulate the hub of the catheter. Full aseptic technique was used to commence and disconnect from dialysis. The catheter hubs were wrapped with 70% isopropyl alcohol wipes to maintain asepsis and permit no-touch initiation and discontinuation of dialysis. At the end of dialysis, the skin was cleaned with chlorhexidine before application of a new sterile dressing, and an interdialytic lock with TauroHep500 (TauroPharm GmbH, Waldbüttelbrunn, Germany) was used.

The first HD was performed by trained nursing staff within the InPatient Renal Unit. Subsequent dialysis

sessions occurred at regional outpatient dialysis units in the West of Scotland.

The ecAVG+/−AVF technique. Patients randomised to receive an ecAVG+/−AVF underwent anesthetic assessment and surgery ≤24 hours of randomization, wherever possible. Prophylactic vancomycin, 1 g intravenously (or teicoplanin if the patient was allergic to vancomycin), was given preoperatively. All ecAVG implantations were performed by a single operating surgeon under a supraclavicular block or general anesthetic.

Alcoholic Betadine (Purdue Pharma LP, Stamford, Conn) was used for cleaning the skin, and an Ioban skin covering (3M Healthcare, Bracknell, UK) was applied to maintain strict asepsis. The vessels were exposed and controlled in a standard fashion. Standard Kelly-Wick tunnelers were used to tunnel the Acuseal graft (W. L. Gore Associates, Flagstaff, Ariz) in the subcutaneous fat. A 4-cm longitudinal venotomy was performed, and the graft was spatulated at the venous end in an attempt to minimize venous stenosis. A 4-mm to 6-mm arteriotomy was made to accommodate the graft. Arterial and venous anastomoses were performed using continuous 5-0 Prolene (Ethicon, Somerville, NJ). Collatamp (Tribute Pharmaceuticals, Milton, ON, Canada) was inserted before wound closure to minimize the risk of infection. Drains were not routinely used.

First cannulation of the ecAVG was performed by trained dialysis nursing staff in the InPatient Renal Unit. The timing of cannulation was determined by clinical need, with no minimum period after surgery. Sharp needles (17 gauge), low flows (200 to 250 mL/min), and minimal heparin were used for the first cannulation. Full aseptic technique was used for cannulation, and direct pressure was applied at the needle sites for at least 10 minutes after the needles were removed. These same techniques were used for the first 2 weeks of cannulation. Thereafter, higher flow rates were permitted if necessary to achieve adequate dialysis clearance. Patients were discharged after at least two successful cannulations of the ecAVG. Maintenance dialysis was performed at Outpatient Dialysis Units in the West of Scotland.

All patients completed 1 week of intravenous vancomycin postoperatively. Heparin, warfarin, and antiplatelet agents were administered at the discretion of the operating surgeon. All patients who re-presented with thrombotic complications were anticoagulated with warfarin unless contraindicated. All ecAVGs underwent surveillance ultrasound imaging and angiography at 3 months and at 3-month intervals thereafter. Any stenosis (on either imaging modality) in the context of access dysfunction was considered clinically significant, prompting angioplasty with or without stenting (for recurrent lesions). In the event of thrombosis, aggressive attempts at declotting were made by a combined surgical and radiologic approach.

Autologous AVF creation. Patients in both treatment arms also underwent creation of an autologous AVF (if this was anatomically possible). In the ecAVG cohort, this was performed at the same time as the ecAVG, if possible; otherwise, every effort was made to provide the patient with the opportunity of AVF creation on the next available operating theater list (≤1 to 2 weeks). The ecAVG/TCVC was used for HD until the AVF was mature enough to cannulate. The decision to perform the first cannulation of the AVF was taken by the clinical team (normally ~6 weeks after creation) after clinical assessment by the Vascular Access Co-ordinator.

Once established on dialysis via an AVF, the fate of a redundant ecAVG was decided after discussion between the patient and surgical team. The ecAVG was left in situ in most patients, but on occasion was removed or ligated if required or wished. The surgical team removed TCVCs after six successful AVF cannulations, as is standard practice.

Follow-up

Patients were reviewed at 1 day, 7 days, and at 3 and 6 months. In addition, data on access-related complications were recorded prospectively at each dialysis session. In addition to demographics and operative details, data were collected on perioperative complications, date of first access use, treatment delays, requirement for antibiotics or urokinase infusions, or both, access complications (bacteremia, local infection, thrombosis, stenosis, poor flows), and reinterventions (new access creation or insertion, thrombectomy, angioplasty). Quality of life (QoL) data were collected at entry to the study and at 6 months of follow-up.

Outcomes

The primary outcome measure was culture-proven bacteremia at 6 months, defined according to the Centers for Disease Control and Prevention as laboratory-confirmed positive peripheral blood cultures in association with clinical symptoms of access infection or failure to identify infection at a secondary site.[18]

Secondary outcomes were local infection, thrombosis, stenosis, reinterventions (including thrombectomy, antibiotics, and urokinase locks), additional vascular accesses, QoL, whether the access provided a "personal vascular access solution,"[9] length of inpatient hospital stay, and death at 6 months. Local infection was also defined according to Centers for Disease Control and Prevention definitions as proven (laboratory-confirmed positive cultures from local swabs) or suspected (clinical signs and symptoms but no positive culture).[18] Thrombosis was defined clinically as the absence of thrill or bruit from a graft and inability to dialyze via it, or the inability to dialyze via flush, or to aspirate from a TCVC. Health-related QoL (HR-QoL) was evaluated using the EuroQoL-5D (EQ-5D) questionnaire.[19]

Sample size calculation

We postulated a reduced incidence of systemic bacteremia in the ecAVG+/−AVF group. Using previously

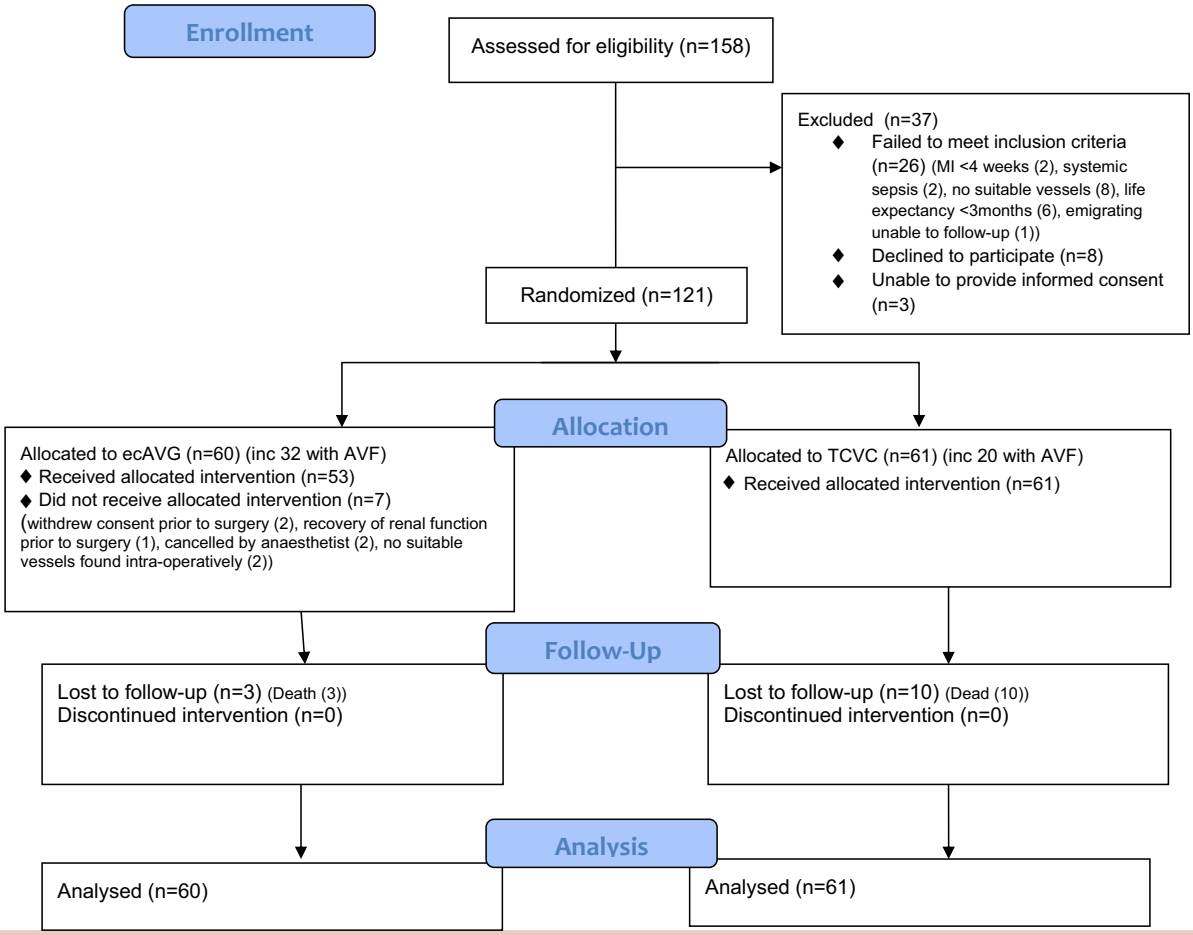

Fig. Trial profile. *AVF,* Arteriovenous fistula; *ecAVG,* early cannulation arteriovenous graft; *MI,* myocardial infarction; *TCVC,* tunneled central venous catheter.

published bacteremia rates for TCVCs and ecAVG in our own institution,[9,10] we calculated that 53 patients would be needed in each group to provide 80% power to detect a reduction in the incidence of systemic bacteremia from 24% to 5% at 6 months of follow-up with an $\alpha = .05$. To account for attrition/loss to follow-up of 10%, we aimed to recruit 118 patients (n = 59 per arm).

Statistical analysis

All analysis was performed on an intention-to treat basis. Any patient randomized but who withdrew from the study before the procedure was replaced by another patient but continued to be monitored on an intention-to-treat basis. Normal distribution of data was confirmed by limited skewness and kurtosis. Results for continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range [IQR]). Access-related bacteremia rates are presented as a proportion of the total population (and risk ratio) and as a rate per 1000 access days. Having confirmed normal distribution, treatment groups were compared using *t*-tests for continuous variables and χ^2 tests for categoric variables.

In additionally, a cost-effectiveness analysis was performed (B.M.) to compare the average total treatment costs within each arm. Average costs per patient were derived from direct resource utilization data along with the unit costs for each procedure. Unit costs were obtained from National Health Service Reference Costs (2013-2014), Scottish Health Service Costs (2014-2015), and Personal Social Services Research Unit: Unit Costs of Health and Social Care (2015).[20,21] All costs (eg, bed days, material costs of ecAVG/TCVC, or antibiotics) were derived directly from those observed in the study. An intention-to-treat analysis was conducted with the perspective of the provider. Results summarize the average cumulative total costs per patient from trial initiation to 6 months of patient follow-up.

RESULTS

Between December 5, 2013, and February 5, 2015, 121 patients were randomly assigned to the ecAVG+/−AVF group (n = 60) or the TCVC+/−AVF group (n = 61). Thirteen patients (11%) died during the follow-up period. No other patient was lost to follow-up (Fig). Table I reports baseline characteristics of randomized patients. Thirty-one percent of patients (n = 38) commenced dialysis for the first time, of whom 39% (n = 15) were

Table I. Baseline characteristics

Variable[a]	Overall patient population (n = 121)	AVG (n = 60)	TCVC (n = 61)	*P* value
Age, years	57.8 ± 15.6	54.5 ± 15.3	60.9 ± 15.5	.02
Male sex	66 (54)	32 (53)	34 (57)	.77
Primary renal disease				
Diabetes	30 (24)	19 (31)	11 (18)	
Multisystem	17 (14)	4 (7)	13 (22)	
Interstitial	28 (23)	15 (25)	13 (22)	
Glomerulonephritis	26 (21)	12 (20)	14 (23)	
Unknown	20 (16)	20 (18)	9 (15)	.09
Comorbidities				
Diabetes	39 (32)	22 (37)	17 (28)	.3
Ischemic heart disease	25 (21)	13 (22)	12 (20)	.56
Cerebrovascular accident	20 (16)	10 (17)	10 (16)	.81
Hypertension	43 (35)	20 (33)	23 (38)	.27
Obesity	19 (16)	10 (17)	9 (15)	.68
Access modality at randomization				
Failing transplant	5 (4)	3 (5)	2 (3)	
HD	67 (55)	38 (63)	29 (48)	
Peritoneal dialysis	7 (6)	3 (5)	4 (7)	
Predialysis	42 (35)	16 (27)	26 (43)	.1
Time on dialysis, median (IQR), years	3.4 (2.5-5.2)	3.4 (3.2-6.8)	3.2 (1.8-6.2)	.85
Previous vascular access, median (range), absolute no. of previous vascular accesses				
AVF	2 (0-6)	2 (0-6)	1 (0-6)	.12
TCVC	1 (0-43)	2 (0-43)	0 (0-25)	.03
Access modality at randomization				
AVF	29 (24)	18 (30)	11 (18)	
AVG	8 (7)	7 (12)	1 (2)	
Peritoneal dialysis	6 (5)	3 (5)	3 (5)	
Predialysis/failing transplant	47 (39)	19 (31)	28 (46)	
TCVC	30 (25)	13 (22)	17 (28)	<.001

AVF, Arteriovenous fistula; *AVG*, arteriovenous graft; *HD*, hemodialysis; *IQR*, interquartile range; *TCVC*, tunneled central venous catheter.
[a]Continous data are presented mean ± standard deviation, or as indicated, and categoric as number (%).

crashlanders (ie, known to a nephrologist <90 days before starting dialysis). The rest of the patients had previously been on renal replacement therapy via another modality or vascular access that had failed (Table II). AVF was the ultimate intended vascular access in 62% of patients (n = 75), with the intention of long-term AVG in 33% (n = 40). A total of 52 AVFs in 34 patients were also made during the follow-up period.

The culture-proven bacteremia rate was significantly higher in the TCVC+/−AVF cohort (0.97/1000 catheter days) than in the ecAVG+/−AVF cohort (0.19/1000 access days), with culture-proven bacteremia developing in 16% of patients (n = 10) during the first 6 months in the TCVC+/−AVF arm compared with 3% (n = 2) in the ecAVG+/−AVF arm (risk ratio, 0.2 95% confidence interval, 0.12-0.56; *P* = .02). Mortality was also higher in the TCVC+/−AVF cohort, at 16% (n = 10) vs 5% (n = 3; risk ratio, 0.3 95% confidence interval, 0.08-0.45; *P* = .04). No patient died as a result of access-related complications (including access-related sepsis). One patient in the ecAVG+/−AVF arm died of a perioperative myocardial infarction.

Median waiting time was 6 days (range, 1-21 days) for TCVC insertion and 14 hours (range, 1-168 hours) for ecAVG insertion (*P* < .001). Twice as many patients in the TCVC+/−AVF cohort required a bridging temporary catheter than in the ecAVG+/−AVF cohort (49% [n = 30] vs 25% [n = 15]; *P* = .006). Median hospital length of stay for vascular access (including associated delays) was 4 (IQR, 2-7) days in the ecAVG+/−AVF cohort and 7 (IQR, 3-13) days in the TCVC+/−AVF cohort (*P* < .0001). Four patients in the ecAVG arm had perioperative complications: myocardial infarction (n = 2), venous hypertension and limb swelling (n = 1), and pseudoaneurysm (n = 1). Attempts at TCVC insertion failed in four patients, and initial attempts at insertion were abandoned in 1 one patient because of flash

Table II. Indications for requiring urgent vascular access

Indication for needing access	No. (%)
Acute-on-chronic renal failure	
Late presentation	14 (12)
Problems with AVF maturation	5 (4)
Rapid progression to end-stage	4 (3)
Failed transplant	6 (5)
Problematic AVF/AVG	
Aneurysm/rupture	17 (14)
Thrombosis	28 (23)
Infection	1 (1)
Problematic TCVC	
Thrombosis	13 (11)
Infection	12 (10)
Failed peritoneal dialysis	6 (5)
Crashlander[a]	15 (12)

AVF, Arteriovenous fistula; *AVG,* arteriovenous graft; *TCVC,* tunneled central venous catheter.
[a]Describes a patient presenting with established renal failure who has not been known to a nephrologist for >90 days.

pulmonary edema. Sites of ecAVG were upper arm (brachioaxillary) in 33, forearm (brachial artery to basilic vein forearm loop) in 2, lower limb (superficial femoral artery to subsartorial femoral vein) in 10, and interposition (inserted into previous fistula at site of aneurysm excision etc) in 8. Median time to first graft cannulation was 22 hours (range, 30 minutes-130 hours).

Access complications and their implications are outlined in Table III. Thirty-four episodes of graft thrombosis were observed in 16 patients (27%). Patients in the TCVC+/−AVF arm spent an average of 4.7 days/patient in the hospital for access-related complications compared to 2.7 days/patient in the ecAVG+/−AVF arm ($P < .001$). The total number of hospital days were reduced in the ecAVG+/−AVF cohort in the 6 months after graft insertion compared with the 6 months before ecAVG insertion (4 [IQR, 3-7] days vs 8 [IQR 4, 12] days; $P = .02$). A similar trend was not seen in the TCVC+/−AVF cohort (10 [IQR, 8-14] days vs 8 [IQR, 4-10] days). Initial HR-QoL scores were comparable at entry to the study (total EQ-5D: 67 ± 12 vs 67 ± 14; $P = .89$). However at the 6-month follow-up, patients in the ecAVG+/−AVF cohort had better HR-QoL scores (74 ± 18 vs 63 ± 16; $P = .001$).

At the 6-month follow-up, only 23% (n = 14) of patients in the ecAVG+/−AVF arm and 16% (n = 10) of patients in the TCVC+/−AVF arm were dialyzing via an autologous AVF. At the end of the 6-month follow-up, 34 patients were still awaiting further attempts at achieving autologous access. In the ecAVG+/−AVF cohort 50% (n = 30) were still using their ecAVG. In the TCVC+/−AVF arm, 52% (n = 32) of patients were still dialyzing via a TCVC. The ecAVG was deemed to be a "personal vascular access solution" (ie, it was still being used for access,

Table III. Other vascular access complications and the implications of these including interventions and need for alternate vascular access

Complication	Episodes per patient in 6 months	No.
TCVC arm		
Infection		
Systemic proven	0.16	10
Systemic suspected	0.07	4
Access removed	0.26	15
Additional hospital days	2.49	152
Days with antibiotic treatment	3.16	193
Thrombosis/inadequate flow[a]	0.15	9
Urokinase	0.27	17
Line displaced[a]	0.07	4
Additional vascular access		
AVF	0.38	23
Tenckhoff catheter	0.03	2
AVG	0.08	5
Temporary catheter	0.16	10
TCVC	0.32	32
AVG arm		
Infection		
Systemic proven	0.03	2
Local proven	0.1	6
Local suspected	0.03	2
Access removed	0.05	3
Additional hospital days	0.7	42
Days with antibiotic treatment	3.37	160
Thrombosis/stenosis[b]		
Thrombosis	0.57	34
Stenosis	0.6	36
Surgical thrombectomy	0.52	31
Surgical revision	0.12	7
Angioplasty	0.5	30
Stent	0.12	7
Revision with additional graft (including HeRO)	0.03	2
Graft erosion[a]	0.03	2
Steal syndrome[a,c]	0.08	5[d]
Wound dehiscence	0.02	1
Pseudoaneurysm (re-exploration)	0.02	1
Additional vascular access		
AVF	0.48	29
Tenckhoff catheter	0.02	1
AVG	0.03	2
Temporary catheter	0.12	7
TCVC	0.27	16

AVF, Arteriovenous fistula; *AVG,* arteriovenous graft; *HeRO,* hemodialysis reliable outflow device; *TCVC,* tunneled central venous catheter.
[a]All of these complications resulted in access loss, unless otherwise stated.
[b]Of the 36 episodes of stenosis requiring intervention, 26 were venous, 7 were arterial, 1 was cephalic arch, and 2 were central veins.
[c]One patient required urgent graft ligation for steal syndrome. The other cases were clinically relatively mild and did not require urgent intervention. Three further grafts were ligated, but this was after alternative AVF access had been established.
[d]Four grafts were ligated.

Table IV. Average costs per patient at 6 months of follow-up by treatment group[a]

Costs	AVG (n = 60) (£)	TCVC (n = 61) (£)	Difference (AVG − TCVC)	*P* value
AVG procedure	2400	210	2200	<.001
AVF procedure	420	460	−40	.7
TCVC	390	1800	−1400	<.001
Temporary catheter	60	120	−60	.003
Index TCVC bed days	240	4200	−4000	<.001
Infection	450	2000	−1600	.02
AVG or AVF intervention	1000	80	960	<.001
Bed day	3800	2000	1800	.004
Other[b]	860	490	370	.52
Average total costs per patient at 180 days	9700	1100	−1700	.24

AVF, Arteriovenous fistula; *AVG,* arteriovenous graft; *TCVC,* tunneled central venous catheter.
[a]All costs are calculated in 2014-2015 pounds sterling.
[b]Refers to peritoneal dialysis catheter insertions and transplants.

had served as a bridge to AVF maturation or transplantation, or was the vascular access at time of death) in 73% (n = 44) of patients. In the TCVC+/−AVF arm, 69% (n = 42) could consider the initial TCVC to be their personal solution.

At the start of the study, 32 patients (52%) in the ecAVG+/−AVF arm had an AVF planned as their definitive vascular access, of which 8 AVFs (25%) thrombosed immediately, 6 were deemed unsuitable to ever provide dialysis, and 4 required an additional procedure to try to achieve functional patency. Nine of the 14 patients with failed AVF underwent a second attempt at AVF creation during the study follow-up. Only 14 patients (23%) were using their AVF at 6 months. With regards to relative placement of ecAVG and AVF in the 32 patients in whom both were created, 15 were deemed to have a radiocephalic fistula option, 14 a brachiocephalic option, and 3 only had a midforearm or lower limb autologous option at the time of graft placement. A contralateral brachioaxillary graft was placed in 21 patients, an interposition graft (into an otherwise defunct fistula) was placed in 8, forearm loops in 2, and a leg graft in 1. In both the patients with forearm loops, the ecAVG was used to mature an outflow cephalic or basilic vein, which was subsequently used to create an autologous fistula, suitable for immediate cannulation. No autologous access option was lost as a result of the ecAVG, even in the 10 patients whose grafts thrombosed.

There was no significant difference in overall costs per patient at 6 months in the ecAVG+/−AVF compared with the TCVC+/−AVF arm (£11,393 vs £9692; $P = .24$). Infection-related costs made up the largest proportion of costs in the TCVC+/−AVF arm and were significantly higher than infection costs incurred in the ecAVG+/−AVF arm (£2011 vs £453; $P = .02$). Reinterventions made up the largest proportion of costs in the ecAVG+/−AVF arm (average £1042 reintervention costs per patient; Table IV).

DISCUSSION

The incidence of culture-proven bacteremia in patients requiring urgent vascular access for HD was higher in those dialyzing via a TCVC than in those using an ecAVG. A higher mortality rate was also observed in the TCVC+/−AVF cohort. The cost analysis found ecAVGs were cost neutral, with the initial outlays and costs of reintervention offset against lower costs conferred from the treatment of sepsis and treatment delays. This is the first randomized controlled trial of TCVCs compared with AVGs; however, there is a significant quantity of observational data supporting the findings of this study.

The higher mortality rate in patients dialyzing via TCVCs is well described.[4,12,22] The survival difference between the access modalities emerges early in the life of the vascular access and is only partly attributable to infectious deaths.[4,6] Recent United States Renal Data System data indicate that cardiovascular and all-cause mortality is higher in patients dialyzing via TCVC.[22] Although no patient in our study died as a result of access-related bacteremia, a clear difference in mortality rates was observed as early as 6 months after insertion of the vascular access.

Large observational studies report threefold higher rates of bacteremia for TCVC than for AVG.[11,12] Data from these population-based studies are inherently vulnerable to selection bias, with frailer, sicker patients more likely to dialyze through a catheter.[6] The magnitude of difference observed in the cohort studies is, however, similar to that observed in our series, adding validity to our results. We acknowledge that most of the reported bacteremia rates for AVGs relate to traditional polytetrafluoroethylene grafts and not ecAVGs. Previously published small case-series of ecAVGs report slightly lower culture-proven bacteremia rates of 0.2 to 0.3 per 1000 access days.[9,23,24] The rate of culture-proven bacteremia observed in this study was also lower than previously published in both the ecAVG+/−AVF and

TCVC+/−AVF cohorts. We attribute this to good practice, with strict infection control measures used at the time of access insertion and for graft cannulation/catheter care.

Most importantly, this study reflects real-world practice with an inclusive recruitment strategy. We have demonstrated the role that ecAVGs can play in an unselected cohort of patients requiring urgent vascular access for HD, making the findings clinically applicable and generalizable to a wide variety of patients. Conversely, however, the population is very heterogenous. It may be that specific subgroups of patients are more likely to benefit from ecAVG/TCVC. One such subgroup of interest is the crashlanders. We anticipated that this would be a study principally of crashlanders; however, less than one-third of patients were actually new starts onto dialysis. De novo dialysis patients pose unique challenges. The National Kidney Foundation Vascular Access report[15] found that 60% of crashlanders still had their TCVC 6 months after commencing dialysis and that AVF maturation rates are poorer in patients already on HD via a TCVC,[25,26] supporting the adage "start with a line, stay on a line." Optimizing the initial vascular access is essential, because a legacy of bad access decision making may have lifelong implications for patients. For these reasons we hypothesize that the beneficial effects of the ecAVG may be even more marked in the cohort of crashlanders, but this study was not powered to demonstrate this.

We observed a high rate of autologous fistula failure, with 2.2 attempts at AVF creation for every successfully matured AVF. This high failure rate is not significantly different from that observed in other randomized trials. Dember et al[3] found that 60% of AVFs remained unsuitable for use 5 months after creation and reflects the difficulties of creating autologous access in a contemporaneous dialysis patient cohort. These patients run the risk of surgical fatigue, with second and subsequent AVFs having lower success rates, long-term catheter use leading to central vein stenosis, and ultimate patient refusal of further perceived futile attempts at vascular access.[16,27] Although the high thrombosis rate of AVGs is well recognized,[13,14] there are good observational data to suggest that the cumulative patency rates of AVGs are at least comparable to AVFs up to 2 years, accounting for the high early primary failure of AVFs.[28,29] Although we do not advocate choosing an AVG over a native AVF, such factors need to be considered in choosing the correct access for the correct patient, particularly if the patient's life expectancy is short.

Before embarking on the study, we had concerns that the ecAVG would risk compromising future sites for upper limb autologous access, particularly given the whole premise of the work was to view vascular access planning as a lifetime journey, which was initially inspired by trying to minimize autologous options lost as a result of central vein stenosis from inappropriate TCVC use. We did not find this to be the case, however. Of the 32 patients in whom an ecAVG and AVF were both made, one had a lower limb ecAVG and eight had interposition grafts into an already defunct AVF, so no potential autologous option was compromised. In two patients, a forearm loop ecAVG was actually used to mature the outflow vein for subsequent successful AVF creation.

More than a study of ecAVGs vs TCVCs, we consider this to be a study comparing strategies and approaches to vascular access provision. We have evaluated a change in practice, with a move away from the TCVC as the default to one that considers alternatives to permit catheter avoidance. Such a change in practice requires a concerted, team-based approach to minimize inertia in the system, as evidenced by the fact that, with effort, an ecAVG could be inserted within 14 hours of referral compared with a 6-day waiting time for a TCVC (acknowledging that this may lead to bias with fewer temporary lines inserted in the ecAVG+/−AVF cohort). We adopted an ethos of native primary (with preservation of the best autologous option) and future access planning.

No access was placed in a patient without considering what the exit strategy from that access was (ie, a long-term plan). Such a change in approach to vascular access requires a greater integration in care. We observed a shift in service demands away from interventional radiology, which traditionally placed TCVCs in all of these patients, toward surgery, with a greater ownership of complications by the surgical service for patients within the ecAVG+/−AVF cohort. A policy of ecAVG insertion requires flexibility in operative planning and commitment to provide a 24/7 graft thrombectomy service to achieve a catheter-minimization culture. Significant education of nephrology and nursing colleagues is also required to ensure correct cannulation techniques and to minimize graft complications.

CONCLUSIONS

We have demonstrated that a strategy of ecAVG+/−AVF for patients requiring urgent vascular access for HD reduces the culture-proven bacteremia rate and mortality at 6 months compared with TCVC+/−AVF. The implementation of these findings into clinical practice will necessitate a paradigm shift in thinking towards vascular access, and supports a culture of "Fistula First" rather than "Line Last." Successful vascular access provision requires a team-based approach that incorporates close integration between the prescription of care by nephrologists and the provision of care by surgeons and interventional radiologists. The successful delivery of this philosophy can help patients receive a more optimally tailored and personalized vascular access solution.

AUTHOR CONTRIBUTIONS

Conception and design: EA, PT, DK
Analysis and interpretation: EA, PT, RK, BM

Data collection: EA, LB, RK, DK
Writing the article: EA
Critical revision of the article: EA, PT, LB, RK, BM, DK
Final approval of the article: EA, PT, LB, RK, BM, DK
Statistical analysis: EA, BM
Obtained funding: DK
Overall responsibility: DK

REFERENCES

1. Fluck R, Mitra S, Reid C. Clinical practice guidelines vascular access for haemodialysis. 6th ed. Bristol, UK: UK Renal Association; 2015. Available at: http://www.renal.org/guidelines/modules/vascular-access-for-haemodialysis#sthash.n3dx1tzq.4JItfm6Z.dpbs. Accessed October 31, 2015.
2. National Kidney Foundation. NKF KDOQI Guidelines. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification 2000. Available at: http://www2.kidney.org/professionals/KDOQI/guidelines_ckd/p4_class_g1.htm. Accessed October 30, 2015.
3. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for haemodialysis: a randomised controlled trial. JAMA 2008;299:2164-71.
4. Bray BD, Boyd J, Daly C, Donaldson K, Doyle A, Fox JG, et al. Vascular access type and risk of mortality in a national prospective cohort of haemodialysis patients. QJM 2012;105:1097-102.
5. Rayner HC, Pisoni RL, Gillespie BW, Goodkin DA, Akiba T, Akizawa T, et al. Creation, cannulation and survival of arteriovenous fistulae: data from the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2003;63:323-30.
6. Thomson PC, Stirling C, Traynor J, Morris S, Mactier R. A prospective study of catheter-related bacteraemia and thrombosis in a haemodialysis cohort: univariate and multivariate analyses of risk association. Nephrol Dial Transplant 2010;25:1595-604.
7. Feldman HI, Kobrin S, Wasserstein A. Haemodialysis vascular access morbidity. J Am Soc Nephrol 1996;7:523-35.
8. Tozzi M, Franchin M, Ietto G, Soldini G, Carcano G, Castelli P, et al. Initial experience with the Gore® Acuseal graft for prosthetic vascular access. J Vasc Access 2014;15:385-90.
9. Aitken EL, Jackson AJ, Kingsmore DB. Early cannulation prosthetic graft (Acuseal) for arteriovenous access: a useful option to provide a personal vascular access solution. J Vasc Access 2014;15:481-5.
10. Aitken EL, Thomson P, Kingsmore DB. Early cannulation arteriovenous grafts: a viable alternative to tunneled central venous catheters? An observational "virtual study" and health economic analysis. J Vasc Access 2015;16:e48.
11. Taylor G, Gravel D, Johnston L, Embil J, Holton D, Paton S. Prospective surveillance for primary bloodstream infections occurring in Canadian hemodialysis units. Infect Control Hosp Epidemiol 2002;23:716-20.
12. Thomson PC, Stirling CM, Geddes CC, Morris ST, Mactier RA. Vascular access in haemodialysis patients: a modifiable risk factor for bacteraemia and death. QJM 2007;100:415-22.
13. Schild AF. Maintaining vascular access: the management of haemodialysis arteriovenous grafts. J Vasc Access 2010;11:92-9.
14. Akoh JA. Prosthetic arteriovenous grafts for haemodialysis. J Vasc Access 2009;10:137-47.
15. National Kidney Care Vascular Access Report 2011. Available at: http://www.renal.org/docs/default-source/patient-safety-docs/haemodialysis/vascular-access-audit-report-rr-nhs-kidney-care-2012.pdf?sfvrsn=2. Accessed October 31, 2015.
16. Aitken EL, Stevenson KS, Gingell-Littlejohn M, Aitken M, Clancy M, Kingsmore DB. The use of tunneled central venous catheters: inevitable or system failure. J Vasc Access 2014;15:344-50.
17. Aitken E, Geddes C, Thomson P, Kasthuri R, Chandramohan M, Berry C, et al. Immediate access arteriovenous grafts versus tunneled central venous catheters: study protocol for a randomised controlled trial. Trials 2015;16:42.
18. Centers for Disease Control and Prevention. Bloodstream infection event (central line- associated bloodstream infection and non-central line-associated bloodstream infection. Available at: https://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf. Accessed October 31, 2015.
19. Szende A, Oppe M, Devlin N. EQ-5D Value Sets. Dordrecht: Springer Netherlands; 2007.
20. Curtis L. Unit costs of health and social care 2015. Canterbury, Kent, UK: Personal Social Services Research Unit, University of Kent; 2015. Available at: http://kar.kent.ac.uk/32408/1/full-with-covers.pdf. Accessed May 20, 2016.
21. UK Department of Health. NHS reference costs: financial year 2013-2014. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014. Accessed May 20, 2016.
22. Malas MB, Canner JK, Hicks CW, Arhuidese IJ, Zarkowsky DS, Qazi U, et al. Trends in incident hemodialysis access and mortality. JAMA Surg 2015;150:441-6.
23. Glickman MH, Burgess J, Cull D, Roy-Chaudhury P, Schanzer H. Prospective multicenter study with a 1-year analysis of a new vascular graft used for early cannulation in patients undergoing hemodialysis. J Vasc Surg 2015;62:434-41.
24. Chiang N, Hulme KR, Haggart PC, Vasudevan T. Comparison of Flixene™ and standard PTFE arteriovenous graft for early haemodialysis. J Vasc Access 2014;15:116-22.
25. Weber CL, Djurdjev O, Levin A, Kiaii M. Outcomes of vascular access creation prior to dialysis: building the case for early referral. ASAIO J 2009;55:355-60.
26. Brunori G, Ravani P, Mandolfo S, Imbasciati E, Malberti F, Cancarini G. Fistula maturation: doesn't time matter at all? Nephrol Dial Transplant 2005;55:355-60.
27. Nica A, Lok CE, Harris J, Lee TC, Morkrzycki MH, Maya ID, et al. Understanding surgical preferences and practice in hemodialysis vascular access creation. Semin Dial 2015;26:520-6.
28. Lok CE. Fistula First Initiative: advantages and pitfalls. Clin J Am Soc Nephrol 2007;2:1043-53.
29. Allon M, Lok CE. Dialysis fistula or graft: the role for randomised clinical trials. Clin J Am Soc Nephrol 2010;5:2348-54.

Submitted May 25, 2016; accepted Oct 19, 2016.