OPTIMISING VASCULAR ACCESS IN INCIDENT HAEMODIALYSIS PATIENTS

By

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ABSTRACT

Arteriovenous fistula (AVF) are widely considered to be the optimal form of vascular access for haemodialysis incurring fewer complications, superior patency, better dialysis quality and a lower mortality than tunnelled central venous catheters (TCVCs). The use of TCVCs is associated with a six-fold increase in the risk of systemic sepsis, long-term morbidity from central vein stenosis and a higher risk of cardiovascular and all-cause mortality compared to AVF.

Despite the relative success of strategies such as "Fistula First" and the best practice target in England and Wales (with simultaneous improvement in prevalent autologous access use) there has been no such associated improvement in incident vascular access rates.

The importance of "getting it right from the start" cannot be overemphasised. Patients who start dialysis via a line are more likely to remain with a line. Data from the UK Renal Registry indicate that 59.8% of patients starting on a TCVC remain dialysing via a TCVC at 3 months and >40% still have their TCVC after 1 year. The legacy of poor early vascular access decision-making remains with the patient throughout their life on dialysis.

This thesis sought to evaluate methods for improving vascular access within the incident patient cohort. A multifaceted approach was taken to address several key themes:

1. TCVC complications and central vein stenosis: avoiding problems for the future.
2. Predicting maturation in incident dialysis patients.
3. Promoting maturation: strategies to optimise maturation.
4. Right access, right patient, right time: individualised, patient-centred care.
5. 'Crashlanders': managing patients who present without prior warning.

The emphasis of this work was directed towards finding pragmatic, patient-focussed solutions to clinically relevant problems. The dogma of "Fistula First at all costs" is challenged.

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DECLARATION

The work presented in this thesis was undertaken during a dedicated period of research between 2012 and 2014 in the Department of Renal Surgery at the Western Infirmary, Glasgow. This work has been completed whilst working as a Specialist Registrar in General Surgery in the West of Scotland.

I declare that the work presented in this thesis was undertaken by me except where indicated below:

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PUBLICATIONS

The work presented in this thesis was awarded the Bakran Shield at the Vascular Access Society of Great Britain and Ireland in 2012 and 2014 and the Resident's Award at the Vascular Access Society of the Americas 2014 and 2016. It was also a finalist for the best abstract at the European Society of Vascular Surgery in 2013. It has resulted in the following peer-reviewed publications:

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ABBREVIATIONS AND DEFINITIONS

ANZDATA	Australia and New Zealand Dialysis and Transplantation (Registry)
AKI	acute kidney injury
APKD	adult polycystic kidney disease
ATG	anti-thymocyte globulin
AVF	arteriovenous fistula
AVG	arteriovenous graft
BA	brachial artery
BBF	brachiobasilic fistula
BCF	brachiocephalic fistula
BMI	body mass index
BP	blood pressure
BPAR	biopsy proven acute rejection
BPB	brachial plexus block
CAD	coronary artery disease
CARI	Caring for Australasians with Renal Impairment
CEPOD	Confidential Enquiry into Peri-Operative Deaths (i.e. emergency theatre)
CIT	cold ischaemic time
cRF	calculated reaction frequency
CVA	cerebrovascular accident
CVC	central venous catheter
CHF	congestive heart failure
CKD	chronic kidney disease
CRBSI	catheter related bloodstream infection
CVC	central venous catheter
CVS	central vein stenosis
DAC	Dialysis Access Consortium
DBD	donation after brain death
DCD	donation after circulatory death
DGF	delayed graft function
DHIS	distal hypoperfusion ischaemic syndrome
DOPPS	Dialysis Outcomes and Practice Patterns Study
DRIL	distal revascularisation and interval ligation
DSA	donor specific antibody
ecAVG	early cannulation arteriovenous graft
eGFR	estimated glomerular filtration rate
ePTFE	expanded polytetrafluoroethylene
ERA- EDTA	European Renal Association- European Dialysis and Transplant Association
ERF	established renal failure
ESRD	end stage renal disease
ESVA	end stage vascular access
FDA	United States Food and Drug Administration
FFBI	Fistula First Breakthrough Initiative
FTM	failure to mature
G	gauge
HD	haemodialysis
HLA	human leucocyte antigen
HeRO	Haemodialysis Reliable Outflow
HR	hazard ratio
HSP	Henoch Schonlein Purpura
IHD	ischaemic heart disease
IQR	interquartile range

ISD	Information Service Department
k	thousand
KAG	Kidney Advisory Group
Kt/V	a marker of dialysis adequacy determined by pre- and post-dialysis urea levels
LA	local anaesthesia
m	million
MDRD-4	Modifications of Diet in Renal Disease-4
MDT	Multidisciplinary Team
MI	myocardial infarction
MRSA	methicillin resistant *Staphylococcus aureus*
MSSA	methicillin sensitive *Staphylococcus aureus*
NHS	National Health Service
NHS-BT	National Health Service-Blood and Transplant
NICE	National Institute of Clinical Excellence
NKF-KDOQI	National Kidney Foundation- Kidney Disease Outcomes Quality Initiative
NR	not reported
NTCVC	non-tunnelled central venous catheter
o.d.	once daily
OR	odds ratio
PbR	payment by results
PD	peritoneal dialysis
pmp	per million population
PRD	primary renal disease
Pre-D	pre-dialysis
pt	patient
PTFE	polytetrafluoroethylene
PVD	peripheral vascular disease
Qa	vascular access blood flow
QALY	quality adjusted life year
QDS	four times per day
QI	Quality Improvement
QoL	quality of life
RCF	radiocephalic fistula
RCT	randomised controlled trial
RUDI	revision using distal inflow
rr	risk ratio
RR	relative risk
RRT	renal replacement therapy
SD	standard deviation
SERPR	Scottish Electronic Renal Patient Registry
SLE	systemic lupus erythematosus
SRR	Scottish Renal Registry
TCVC	tunnelled central venous catheter
tPA	tissue plasminogen activator
UK	United Kingdom
UK-RR	United Kingdom Renal Registry
URR	urea reduction ratio
US	United States
USRDS	United States Renal Data System
VSM	vascular smooth muscle
y.o.	years old

SUMMARY

Arteriovenous fistula (AVF) are considered the 'gold standard' vascular access for haemodialysis (HD) and are recommended as first line by both the Renal Association and Vascular Access Society. AVF have superior patency rates and provide better quality HD than alternative access modalities. The use of TCVCs is associated with a six-fold increase in the risk of systemic sepsis, long-term morbidity from central vein stenosis and a higher risk of cardiovascular and all-cause mortality compared to AVF. For these reasons there has been significant drive to improve rates of autologous vascular access, both through the "Fistula First" Campaign in the USA and best practice (PbR) targets in England and Wales. Quality improvement drives have resulted in significant increase in autologous vascular access rates among prevalent HD patients; however, to date, there has been no associated improvement in the number of functional AVF in incident patients.

The importance "getting it right from the start" cannot be overemphasised. Patients who start dialysis via a line are more likely to remain with a line. Data from the UK Renal Registry indicate that 59.8% of patients starting on a TCVC remain dialysing via a TCVC at 3 months and >40% still have there TCVC after 1 year. Successful AVF maturation is poorer in patients who have already commenced dialysis. The legacy of poor early vascular access decision-making remains with the patient throughout their life on dialysis.

This thesis seeks to evaluate methods for improving vascular access within the incident patient cohort. A multifaceted approach was taken to address several key themes:

1. TCVC complications and central vein stenosis: avoiding problems for the future.
2. Predicting maturation in incident dialysis patients
3. Promoting maturation: strategies to optimise maturation.
4. Right access, right patient, right time: individualised, patient-centred care.
5. 'Crashlanders': managing patients who present without prior warning.

The emphasis of the work was directed towards finding pragmatic, patient-focussed solutions to clinically relevant problems. The dogma of "Fistula First at all costs" is challenged.

Chapter 2 describes the extent of the problem of TCVC usage locally in the West of Scotland and the impact of a Quality Improvement project to reduce prevalent TCVC usage. Aggressive strategies to create autologous access resulted in one-fifth of patients with prevalent TCVCs successfully having an AVF created, but this was offset against the

morbidity of a high fistula failure rate in patients already dialysing via TCVC and no overall reduction in prevalent TCVC usage rates. The complexities of autologous access creation in a long-standing prevalent population are highlighted, demonstrating the importance of targetting incident autologous access creation.

Chapter 3 focusses on central vein stenosis as a consequence of long-term TCVC use. The significant personal and economic costs are highlighted: multiple and frequent interventions to relieve symptoms, loss of vascular access, and poor outcomes for all access modalities in patients with bilateral central venous occlusion and "end stage" vascular access. A novel strategy of expedited renal transplantation with extended criteria organs from donation after circulatory death (DCD) donors for patients with "end stage" vascular access is described.

Chapter 4 evaluates some factors predictive of autologous AVF maturation. It is the first clinical study to evaluate the relationship between renal function and AVF outcome. No association was found between eGFR at the time of access creation and either short or long-term patency. However increasing serum urea was associated with worse clinical patency at 6 weeks and poorer long-term outcomes from RCF, highlighting that in incident patients timing of AVF creation (to avoid the significant uraemia late in the pre-dialysis period) may actually influence AVF outcome.

Chapters 5 and 6 report randomised controlled trials (RCTs) of operative and peri-operative techniques aimed to improve autologous AVF early patency rates. An interrupted suturing technique yielded higher immediate (92.9% vs. 66.6%; $p<0.001$) and 6 week (71.4% vs. 47.2%; $p=0.01$) primary patency rates for RCF than a continuous suturing technique. It is hypothesised that the interrupted suturing technique improves anastomotic compliance and reduces the narrowing and puckering that can occur upon suture tightening in small calibre vessels. Similarly, Chapter 6 details a RCT comparing regional anaesthesia (brachial plexus block) and local anaesthesia for primary AVF creation. Primary patency at 3 months was higher in the brachial plexus block cohort (84.1% (73.0%, 91.3%) vs. 61.9% (49.5%, 72.3%); P=0.005; OR 2.1).

Finally, Chapters 7-9 evaulate the role of early cannulation arteriovenous grafts (ecAVGs) as novel devices to provide vascular access for patients in imminent need of haemodialysis. Chapter 7 presents observational data of the early local experience with ecAVGs. A relatively high complication rate (thrombosis and local infection) was observed. A description of the subsequent experiential learning and interventions to

improve graft outcomes is provided. Chapter 8 proposes the novel concept of ecAVG as an alternative to TCVC in “crashlanders”. Prospective observational data and a cost-consequence analysis demonstrate that ecAVG are a practical, acceptable and cost-effective alternative to TCVC in this patient cohort. Chapter 9 confirms similar findings in a randomised controlled trial. A reduction in both systemic bacteraemia (16.4% vs. 3.3%; rr 0·2 95% CI 0·12, 0.56; P=0·02) and mortality (16·4% vs. 5.0%; rr 0·3 95% CI 0·08, 0·45; P=0·04) at 6 months in patients requiring “urgent vascular access for haemodialysis” treated with ecAVG compared to TCVC was shown.

In conclusion, the work presented in this thesis has highlighted the importance of optimising vascular access provision in incident haemodialysis patients and the importance of timely autologous access creation whenever possible. Several strategies to target the traditionally poor AVF maturation rates, which limit autologous access use, have been outlined (interrupted suturing techniques and regional anaesthesia). However, it is recognised that autologous vascular access is not always the best option for every patient. In incident patients presenting without vascular access, ecAVG have been shown to be a viable and cost-effective alternative to TCVC. A planning strategy that targets vascular access to the individual in order to find a “personal vascular access solution” is essential.

INTRODUCTION

1.1. END STAGE RENAL DISEASE

1.1.1. Definition

Chronic kidney disease (CKD) is defined as an estimated glomerular filtration rate (eGFR) <90mL/min/1.73m^2 (The Renal Association, 2013; KDOQI, 2000) . It is a common and progressive condition that affects >15% of the population in the United States (Archer et al. 2013; USRDS, 2014). A smaller proportion of patients (0.5%) will progress to end stage renal disease (ESRD) (Archer et al. 2013). The terms end stage renal disease, chronic kidney disease stage V and established renal failure (ERF) are used, largely interchangeably, to describe patients with eGFR <15mL/min/1.73m^2 or a requirement for haemodialysis (The Renal Association, 2013; KDOQI, 2000).

1.1.2. The Burden of End Stage Renal Disease

The incidence of ESRD has increased exponentially over the past 30 years (Scottish Renal Registry, 2015). United States Renal Data System (USRDS) figures indicate a 43% increase in the number of incident haemodialysis (HD) patients in 2006 compared to 1991 (USRDS, 2006). The prevalence of patients with ESRD is doubling every 10 years in the United States (US) and it is projected that there will exceed half a million patients on dialysis in America by 2020 (Finn 2008; Collins et al. 2009). In the United Kingdom (UK), the incident rate of patients starting renal replacement therapy (RRT) increased from 109 per million population (pmp) in 2014 to 115ppm in 2015 (UK Renal Registry, 2016). Similarly, there was a 4% absolute increase in the number of prevalent RRT patients between December 2015 and the same time the previous year (UK Renal Registry, 2016). United Kingdom Renal Registry (UK-RR) figures (December 2014) indicate that there are 58,968 adult patients on RRT on the UK, 4,900 of whom are in Scotland (Scottish Renal Registry, 2015). Even acknowledging inaccuracies in international data collection, there are approximately 2 million people worldwide currently receiving RRT (Daugirdas, 2012; Kimmel & Rosenberg, 2014).

ESRD has a significant negative impact on both longevity and quality of life (Kimmel & Rosenberg, 2014). Survival from ESRD is worse than that of most cancers (USRDS, 2014;

Cancer Research UK, 2014). The 5-year survival with ESRD in Scotland is 36%, compared to 59% in patients with bowel cancer, 87% for breast cancer and 85% in prostate cancer (Cancer Research UK, 2014; Scottish Renal Registry, 2015). In the US, only half of patients survive for 3 years after commencing dialysis (USRDS, 2014). Adjusted all cause mortality rates are 6.5-7.9 times greater in dialysis patients than for individuals in the general population (USRDS, 2014). A 25-year old diabetic commencing dialysis in Scotland has only 50% chance of living beyond 5 years (Scottish Renal Registry, 2015). Similarly, a female dialysis patient in her 30s is likely to survive just a quarter as long as a counterpart without ESRD (median life expectancy: 12.1 vs. 47.1 years) (USRDS, 2014).

A high incidence of both cardiovascular disease (Go et al. 2004; USRDS, 2014) and infection (Henrich, 2012; USRDS, 2014) in the ESRD population leads to frequent hospitalisation and poor quality of life (Valderabano et al. 2001; Iliescu, 2003; Terada & Hyde, 2012; USRDS, 2014). Mean health-related quality of life (QoL) scores for patients recently commenced on HD corresponded to the lowest 10-15% of scores within the general population across all domains of function, whilst elderly HD patients demonstrate a physical function QoL score almost half of that observed amongst an age-matched cohort of non-ESRD patients (Rebello et al. 1998; Parkerson & Gutman, 1997).

Notwithstanding the personal burden of ESRD, the disease also places considerable demand on healthcare resources. Patients with ESRD have an average of 1.84 hospital admissions annually and 11.7 bed days are utilised per year for patients on HD (USRDS, 2014). Frequent hospitalisation, coupled with the cost of RRT (out-patient haemodialysis costs between £30 000 and £35 000/ patient/ year) means that 3% of the NHS budget intended for a population of 65 million is utilised on kidney failure services for just 50,000 patients (NKF-KDOQI, 2013; NICE, 2011). Similarly within the US, in 2009 the overall Medicare expenditure for people with ESRD totaled $33.8 billion (6% of the total Medicare budget on less than 1% of the population) (American Kidney Fund, 2013). As a result of these financial and societal costs, CKD and ESRD are a significant public health concern (Henrich, 2012).

1.1.3. Changing demographics of the RRT population

In recent years, more inclusive acceptance policies for RRT have resulted in changing demographics of the ESRD population (Thomson, 2009; Vacharanjani et al. 2014). Increasingly elderly and co-morbid patients are now sustained on RRT (UK Renal

Registry, 2016; Scottish Renal Registry, 2015). The median age for starting RRT in Scotland was 64 years in 2012, compared to 61 years in 1995 and just 32 years old in 1978 (Scottish Renal Registry, 2013). Similarly, the elderly (64-75 year-old) now represent the fastest growing group of prevalent RRT patients, with the median age of prevalent HD patients in the UK 66 years old (UK Renal Registry, 2016). The number of extreme elderly (>85 year old) patients accepted onto RRT in the UK has doubled between 2006 and 2011, whilst the percentage of patients aged >70 years has increased from 19.2% in 2000 to 24.9% in 2012 (UK Renal Registry, 2014). Figure 1.1 highlights a similar, though less extreme, trend in Scotland (Scottish Renal Registry, 2013).

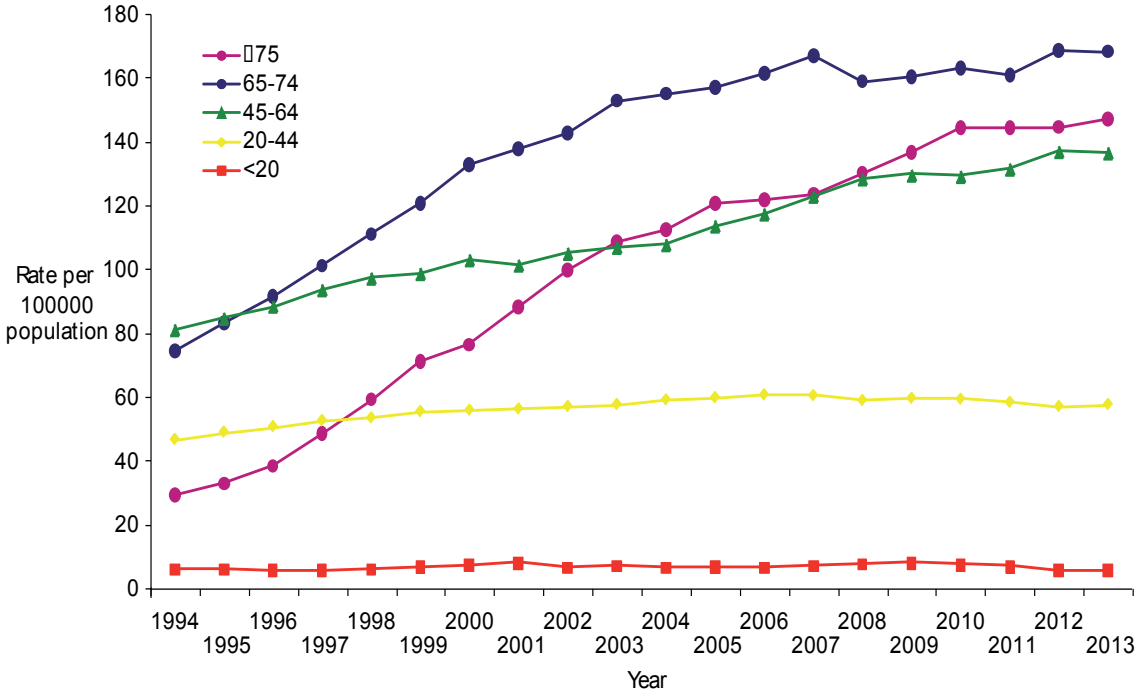


Figure 1.1: Age specific prevalence of RRT patients in Scotland by year. Reproduced with permission from Information Service Department (ISD), Scotland (Scottish Renal Registry, 2013)

With advancing age comes additional co-morbidity. The most recent UK Renal Registry Report (2016) highlights that 49.8% of patients with ESRD had one or more co-morbidities (13% had more than 3 co-morbidities). In the ≥65 year-old age group, this proportion increases to 63% of patients with one or more co-morbidity.

Due to a shared pathogenesis and clustering of risk factors, ESRD, IHD, diabetes, hypertension and peripheral vascular disease (PVD) commonly co-exist (Go et al. 2004; Sahay 2012; USRDS, 2014). Reduced kidney function is associated with increased levels

of inflammatory mediators, abnormal apoliporotein levels, elevated plasma homocystine, enhanced coagulability, anaemia, left ventricular hypertrophy, increased arterial calcification and endothelial dysfunction, all of which are risk factors for cardiovascular disease (Go et al. 2004). 19% of patients in the UK with ESRD also have IHD (defined as angina, myocardial infarction or prior coronary artery bypass grafts). Like other co-morbidities, the prevalence of ischaemic heart disease (IHD) in patients with ESRD also increases exponentially with advancing age (UK Renal Registry, 2016.).

Prior to 1980, it was practically unheard of for diabetic patients with ESRD to receive RRT. Now nearly a quarter of patients commencing RRT in Scotland have diabetes as their primary renal disease (PRD) (Figure 1.2) (Scottish Renal Registry, 2016). In 2012, 35% of patients in the UK with ESRD had diabetes either as their PRD or additional co-morbidity and in the US diabetes is now the leading cause of ESRD (USRDS, 2014; American Kidney Fund, 2013; UK Renal Registry, 2016). The well publicised "diabetes explosion" is likely to see 4 million people in the UK with diabetes by 2025, 40% of whom will develop CKD, making diabetes the leading cause of ESRD in the UK within the next 10 years (Gray, 2011; British Broadcasting Corporation, 2009; Diabetes UK, 2014; Diabetes Leadership Initiative, 2012).

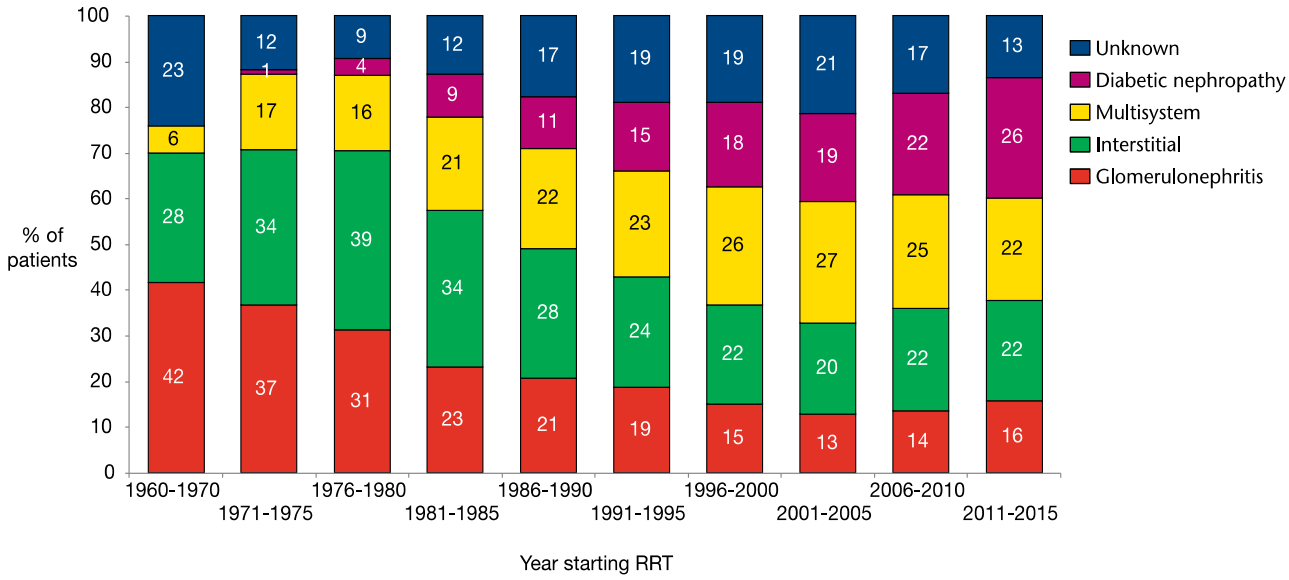


Figure 1.2: Percentage of patients in each diagnosis group starting RRT by year in Scotland. Reproduced with permission from Information Service Department (ISD), Scotland (Scottish Renal Registry, 2015)

The implications of an aging, increasingly co-morbid population are significant. Data from the Scottish Renal Registry supports an association between age, co-morbidity and adverse

clinical outcome (Metcalfe et al. 2000; Metcalfe et al. 2003). Median survival of a patient <20 years old on RRT is 27.5 years, but only 1.3 years if the patient is >75 years old (Scottish Renal Registry, 2013). Likewise, the 5-year survival after starting RRT for a 45 year old patient with diabetic nephropathy is only 31%, compared to 67% in a similar patient whose PRD is glomerulonephritis (Scottish Renal Registry, 2016).

Despite the changing population of patients with ESRD, the overall mortality for incident patients remains static and prevalent mortality is declining (USRDS, 2014; Scottish Renal Registry, 2015; UK Renal Registry, 2016). This is testament to improvements in RRT and the quality of care provided for patients with ESRD (Alwall et al. 1949; Fernandez-Martin et al. 2015; Iseki, 2015). Nevertheless, an ever increasing number of patients with ESRD coupled with growing numbers of aged, co-morbid patients (with their additional challenges and complexities) exemplifies that the burden of ESRD and the impact of the disease on healthcare resources is likely to continue to escalate for the foreseeable future.

1.2. RENAL REPLACEMENT THERAPY

1.2.1. Methods of renal replacement therapy

Renal replacement therapy (RRT) serves as a substitute for many of the functions of a native kidney and prolongs survival in patients with ESRD. It may be delivered in the form of renal transplantation, haemodialysis (either within the hospital or at home) or peritoneal dialysis (PD). Of the 4,561 patients currently on RRT in Scotland, 1,920 (39%) are on HD, 226 (4%) are on PD and 2,773 (56%) have a functioning renal transplant (Scottish Renal Registry, 2015). (Figure 1.3) A similar distribution in the provision of RRT is seen elsewhere within the UK, with a small but steady growth of the HD population in England and Wales (2.6% pmp annually) (UK Renal Registry, 2014).

Renal transplantation is the optimal form of RRT with better survival rates and improved QoL than dialysis (Wolfe et al. 1999; Port et al. 1993; Ojo et al. 2000; Laupacis et al. 1996). It is also the most cost-effective form of RRT costing just £17 000 in the first year and £5 000 for each subsequent year following transplantation compared to the average £30 800 per patient/ year for dialysis (de Wit et al. 1998; NKF-KDOQI, 2013; Organ Donation Taskforce, 2008). Unfortunately however, transplantation is not an option for every patient. Advancing age and multiple co-morbidities are relative contraindications which preclude transplantation in many cases (Knoll, 2013; Schold, 2014; Schold et al.

2009). In Glasgow, only 226 (32.6%) of the 694 patients on RRT are currently active on the renal transplant waiting list, with 152 patients transplanted in 2015 (M. Clancy, personal communication). Due to an imbalance between supply and demand of organs, there are currently 7,000 people on the cadaveric renal transplant waiting list in the UK and median wait time for a cadaveric kidney is 3.6 years (Hudson & Curnow, 2013). As a result, dialysis is the reality for most patients with ESRD (at least in the short-term).

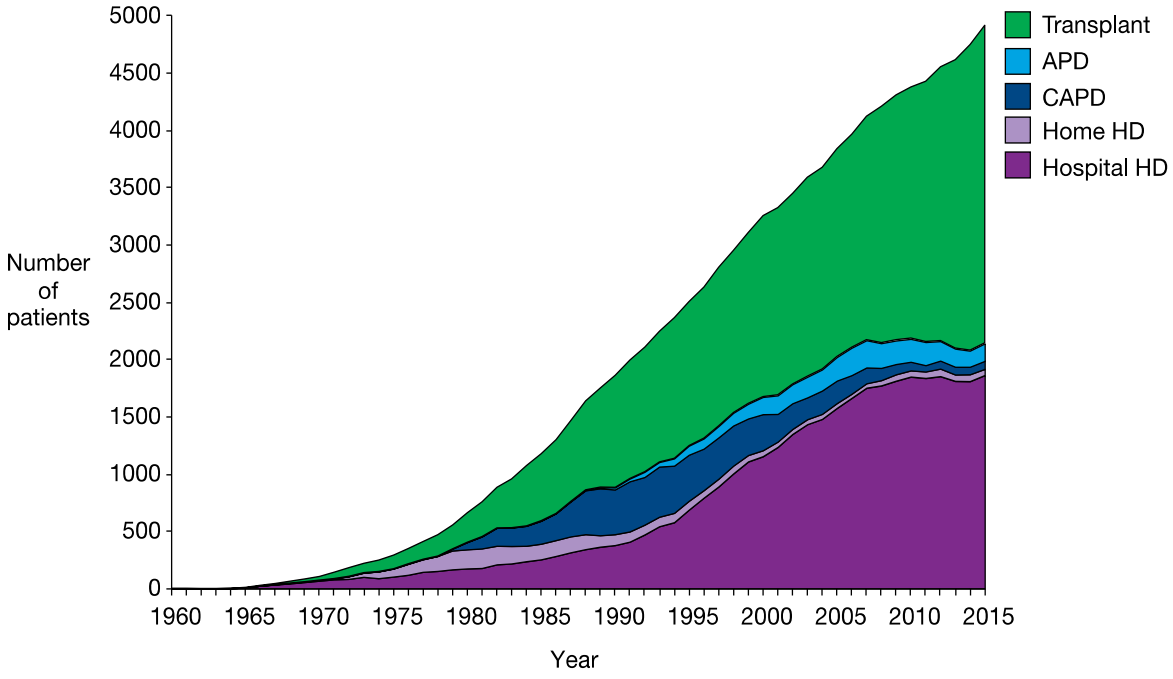


Figure 1.3: Growth in number of patients by treatment modality 1960-2015. Reproduced with permission from Information Service Department (ISD), Scotland (Scottish Renal Registry, 2015)**.**

1.2.2. Haemodialysis

Although not a true replacement for native renal function, haemodialysis serves to remove waste solutes and body water and restore biochemical and acid-base balance akin to a normally functioning kidney (Thomson, 2009). In the longer term it may also assist in the control of blood pressure (BP) and the prevention of uraemic complications (Kirk & Tattersall, 2015). It is a life prolonging treatment for patients with ESRD (Thomson, 2009).

To permit haemodialysis blood must be removed from the intravascular component of the patient's circulation, passed through an extracorporeal circuit into the "dialyser" where waste solutes and excess water are removed, and then returned to the patient's venous

circulation (Figure 1.4) (Kirk & Tattersall, 2015; Hamilton, 1999). There are many different dialysis treatment regimens, however most patients in the UK will receive hospital haemodialysis for 4 or 5 hours three times per week (NHS Choices, 2013).

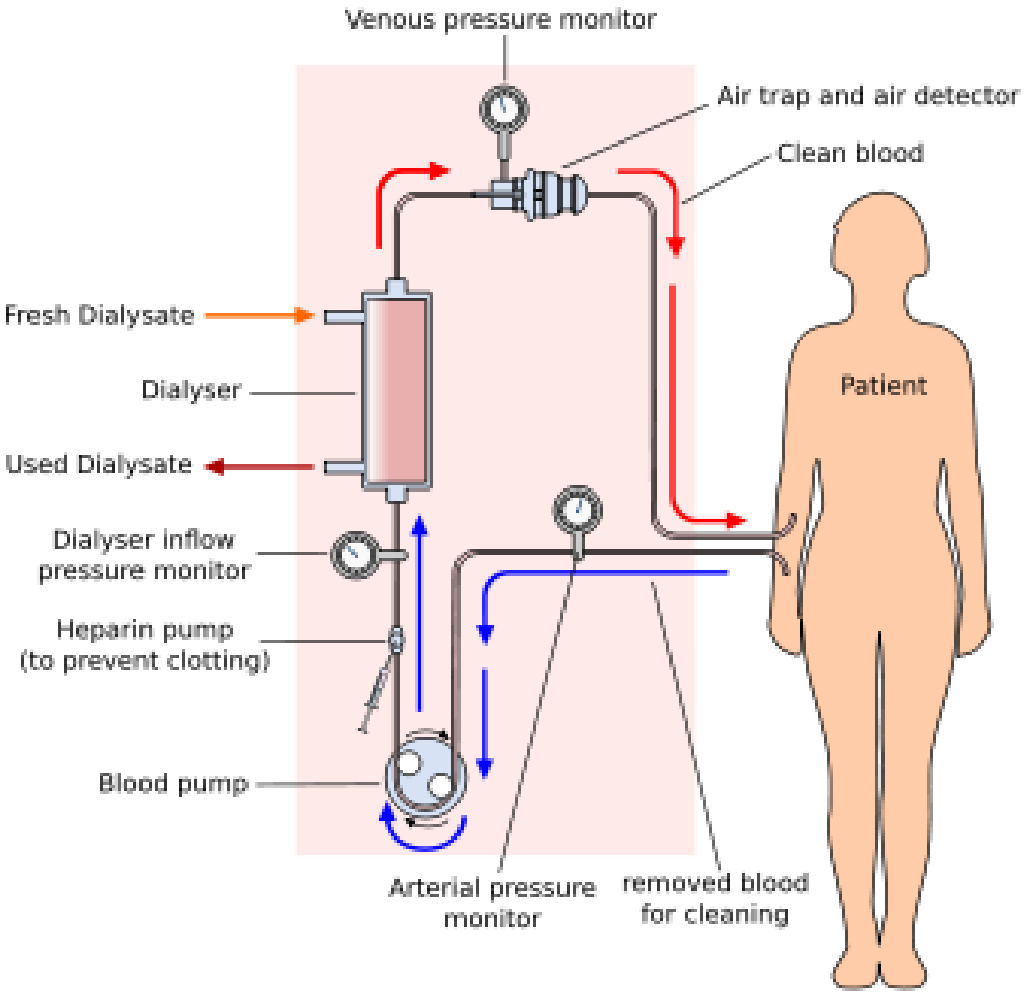


Figure 1.4: Haemodialysis circuit demonstrating extra-corporeal circuit and "dialyser". Reproduced with permission from Adam Kirk.

Dialysis works on the principles of diffusion (of solutes) and ultrafiltration (of fluid) across a semi-permeable membrane. Diffusion is the process whereby substances dissolved in water will move from an area of high to low concentration across a semi-permeable membrane, while ultrafiltration is the movement of fluid across the membrane created by a transmembrane pressure gradient (Hamilton, 1999; Freemesm, 2013). By altering the hydrostatic pressure within the dialysate compartment, water and some dissolved solutes can be encouraged to cross the membrane. These processes are analogous to those occurring within the glomerulus of the native kidney. The characteristics of the semi-

permeable membrane e.g. membrane permeability (pore size) and surface area will determine exactly what substances can cross the membrane (Hamilton, 1999). A larger pore size (high-flux membrane) will allow larger molecules to be removed by dialysis (Ambalavanan et al. 1999). Like the nephron of a native kidney, haemodialysis utilise a countercurrent mechanism whereby the dialysate is flowing in one direction and the blood within the extracorporeal circuit flowing in the opposite direction to maximise the concentration gradient and increase the efficiency of dialysis (Hamilton, 1999). All these functions occur within the "dialyser" of the circuit.

Adequacy of dialysis i.e. how well the waste is being removed is influenced by a number of factors including rate of blood flow, membrane resistance and recirculation (Ambalavanan et al. 1999; Kapoian et al. n.d.). In most cases a rapid blood flow (>250mL/min) will be required to achieve adequate dialysis (Kapoian et al. n.d.). Dialysis adequacy can be assessed by monitoring the patient's urea reduction ratio (URR) and Kt/V (Kapoian et al. n.d.; Mactier et al. 2013).

1.3. VASCULAR ACCESS

1.3.1. What is vascular access?

An entry point into the patient's circulatory system must be provided to permit the removal and return of blood from the extracorporeal dialysis circuit. This entry point to the bloodstream is the "vascular access". Successful haemodialysis is entirely reliant on the provision of safe, efficient and durable vascular access (Fluck & Kumwenda, 2011). The vascular access serves as the patient's 'lifeline to the dialysis machine' (Riella et al, 2013, pp.348).

Vascular access provision is the 'cornerstone to providing adequate haemodialysis' (Hammes, 2014, pp.105) and a 'fundamental aspect of the treatment of haemodialysis patients' (Fluck & Kumwenda, 2011, pp.3). Good quality vascular access saves more lives in patients with ESRD than the targetted treatment of anaemia and phosphate metabolism combined (DOPPS Collaborators, 2012). However the provision of good quality vascular access can prove challenging to achieve, both for the individual patient and for the overall delivery of renal services (Thomson, 2009). Several authors acknowledge these difficulties, describing vascular access as the 'Achilles' heel' of haemodialysis (Konner, 1999, pp.2094).

20% of all hospital admissions and one-third of all in-patient bed days utilised by patients on HD are the result of problematic vascular access (Akoh & Hakim, 2001; Hirth, 1996; DOPPS Collaborators, 2012; Pisoni et al. 2009; Rayner et al. 2004). Half of all hospital admissions in the first year of dialysis are access-related (Vassalotti et al. 2012). In the last decade, prevalent hospitalisation rates for infection in patients with ESRD have almost doubled (Lok, 2007; USRDS, 2014; Collins et al. 2009). Infection is now the leading cause of hospitalisation and the second commonest cause of death (after cardiac events) for patients on HD (USRDS, 2014). Access-related bacteraemia is responsible for nearly 30% of all infections in the HD population and is the leading cause of preventable hospital admission (Collins et al. 2009).

Frequent hospitalisation can have a significant negative impact on QoL and the patient's perception of the "burden of dialysis" (Afsar et al. 2012; Wasse et al. 2007). Furthermore, access-related complications are associated with significant financial costs to the healthcare system. The average cost for treatment for a single episode of line sepsis is £20 000, whilst the morbidity associated with vascular access complications costs Medicare approximately $1 billion annually in the US (Feldman et al. 1993; Taylor et al. 2002; Allon et al. 2011; Ramanathan et al. 2007; Allon & Robbin, 2002).

1.3.2. Which vascular access to choose?

The National Kidney Care Vascular Access Report (2012, pp.10) states that:

> 'The ideal form of vascular access should be safe and efficient. It should be easy to use. It should provide effective therapy. It should minimise the risk of complications related to its use and presence.'

However, there is no single "ideal" vascular access that is long-lasting and permits safe and reliable haemodialysis for every patient. As a result, a range of access modalities exist.

Early attempts at providing vascular access, developed in parallel with haemodialysis because vascular access provision was integral to the success of maintenance HD. Initially, vascular access methods relied on repeated peripheral cannulation to deliver arterial blood to the dialysis machine and return it via an accompanying vein (Thomson, 2009). This method led to the rapid exhaustion of the peripheral vasculature and did not prove

sustainable outwith an acute setting. In 1949, Alwall made the first attempt to directly connect an artery and vein using glass cannulae and rubber tubing. This device was intended to allow blood to be diverted into an extracorporeal circuit for dialysis as required. His attempt was unsuccessful, however it provided the template for the 'Scribner shunt' developed by Quinton, Dillard and Scribner in 1960 (Quinton et al. 1962). Their device consisted of two Teflon cannulae inserted at the wrist, one into the radial artery and one into the cephalic vein. The external ends of the cannulae could then be connected to the extracorporeal circuit by flexible tubing. Whilst the Scribner shunt has subsequently been subjected to multiple refinements and ultimately superseded by other forms of vascular access, its development was instrumental in permitting the provision of maintenance haemodialysis to the chronic ERSD population.

In 1966, Brescia and colleagues published their experience of arteriovenous fistulae (AVF) for vascular access in the *New England Journal of Medicine* (Brescia et al. 1966). By using native vessels in an entirely subcutaneous configuration, the thrombotic, infectious and dislodgement complications of the Scribner shunt were significantly reduced. An AVF is an artificial connection between artery and vein. The vein is divided and anastomosed onto the artery. This vein can then be directly cannulated with needles to permit HD (Figure 1.5). Although troubled with a high primary failure rate (Wong et al. 2011; Dember et al. 2008), matured AVF have excellent long-term patency with a low rate of infectious complications (Akoh & Hakim, 2001; Hoen et al. 1995; Huijbregts et al. 2008; Kinnaert et al. 1977).

Like AVF, arteriovenous grafts (AVG) also provide a man-made subcutaneous connection between artery and vein. However in AVG the cannulatable segment is not formed by native vessel, rather a foreign implant to bridge the gap between artery and vein (Figure 1.5). This non-native segment may be biological (autologous vein from an alternative site, allogeneic vein, umbilical cord vein or bovine carotid artery) or, more commonly, synthetic (Dacron® or polyterafluroethylene (PTFE)) (May et al. 1969; Kester, 1978; Moshe Haimov, 1974; Windus, 1993; Morgan & Lazarus, 1975). AVGs have the advantage that they obviate the need for maturation and the risk of early failure associated with AVF use (Windus, 1993). However, like all prosthetics, they are associated with higher rates of infection (Bell & Rosental, 1988).

Tunnelled central venous catheters (TCVC) were first used for HD in 1969 following the successful use of silastic catheters for chemotherapy and parenteral nutrition (Erben et al.

1969). A double-lumen catheter (or previously two single lumen catheters) is inserted into a central vein (subclavian, internal jugular or femoral) and venous blood removed into the extracorporeal dialysis circuit via one lumen and returned via the other (Figure 1.5). TCVCs are simple and easy to insert and can be used immediately and conveniently for dialysis (Akoh & Hakim, 2001). Their use has revolutionised the practice of acute HD. However again, infection rates are considerably higher that those observed in autologous access (Kessler et al. 1993; Hoen et al. 1998).

Arteriovenous fistulae are widely considered to be 'the best form of vascular access for HD' (Lok et al, 2007, pp.1043) incurring fewer complications, superior patency, better dialysis quality and a lower mortality than TCVCs (Lok, 2007; Thomson et al. 2007; Fluck & Kumwenda, 2011). The use of TCVCs is associated with a significantly increased risk of systemic sepsis, long-term morbidity from central vein stenosis and a higher risk of cardiovascular and all-cause mortality compared to AVF (Bray et al. 2012; Thomson et al. 2007; Agarwal et al. 2007; Lok, 2007).

The enduring patency of AVF is superior to other access modalities, with long-term access survival of approximately 90% for AVF compared to 60% for AVG (Fluck & Kumwenda, 2011; Crowther et al. 2002; Rayner et al. 2003). AVF also require fewer remedial actions to maintain patency. Approximately 0.2 interventions are required annually to maintain the patency of an AVF, compared to 1.0 interventions per patient per year in AVG (Ifudu et al. 1998). CVCs demonstrate similar patency rates to AVG with a median thrombosis-related malfunction rate of 0.3 events/ patient/ year (Donati et al. 2012).

The risk of sepsis attributable death in a HD patient is 100 times that of the general population and TCVC use is the greatest risk factor for infection-related mortality (Lok et al. 2014). The systemic bacteraemia rate in patients dialysing via an AVF is approximately 0.03 per 1,000 dialysis days, compared to 0.06 per 1,000 dialysis days for an AVG and 1.4 per 1,000 catheter days for TCVC (Taylor et al. 2002). Local data from the West of Scotland demonstrates TCVC use to be associated with a hazard ratio (HR) for bacteraemia of 5.4 compared to AVF (Thomson et al. 2007). The time to first episode of bacteraemia was also significantly longer in patients with AVF compared to AVG or central venous catheter (CVC) (Figure 1.6) (Thomson et al. 2007). Given that each episode of bacteraemia confers a 2.8 times relative risk (RR) of death in a dialysis patient (Bloembergen et al. 1996), infections in this patient cohort cannot be considered trivial events.

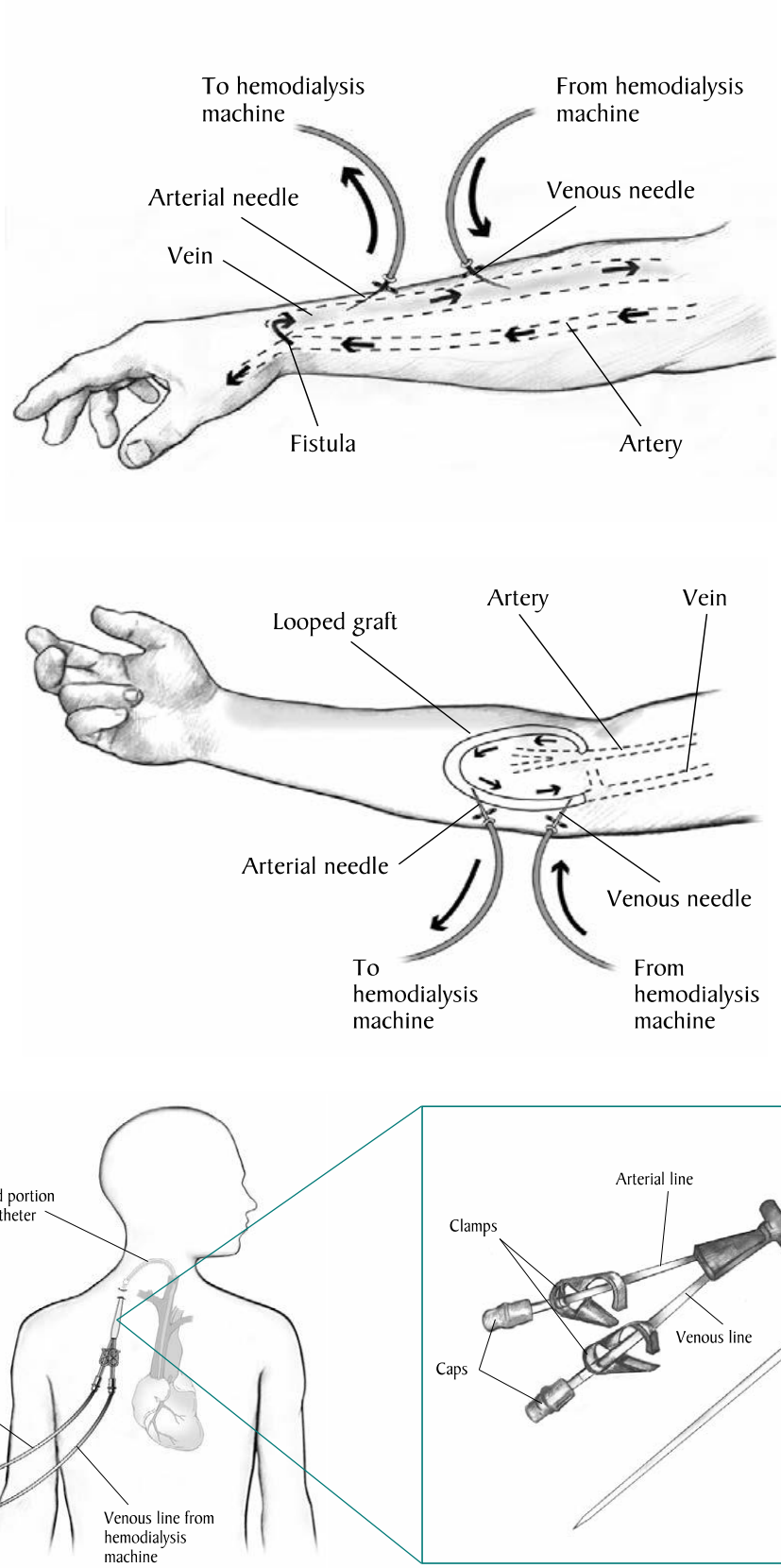


Figure 1.5: Forearm arteriovenous fistula (top), arteriovenous graft (middle) and tunnelled central venous catheter (bottom). Adapted from National Institute of Diabetes, Digestive and Kidney Diseases, 2014.

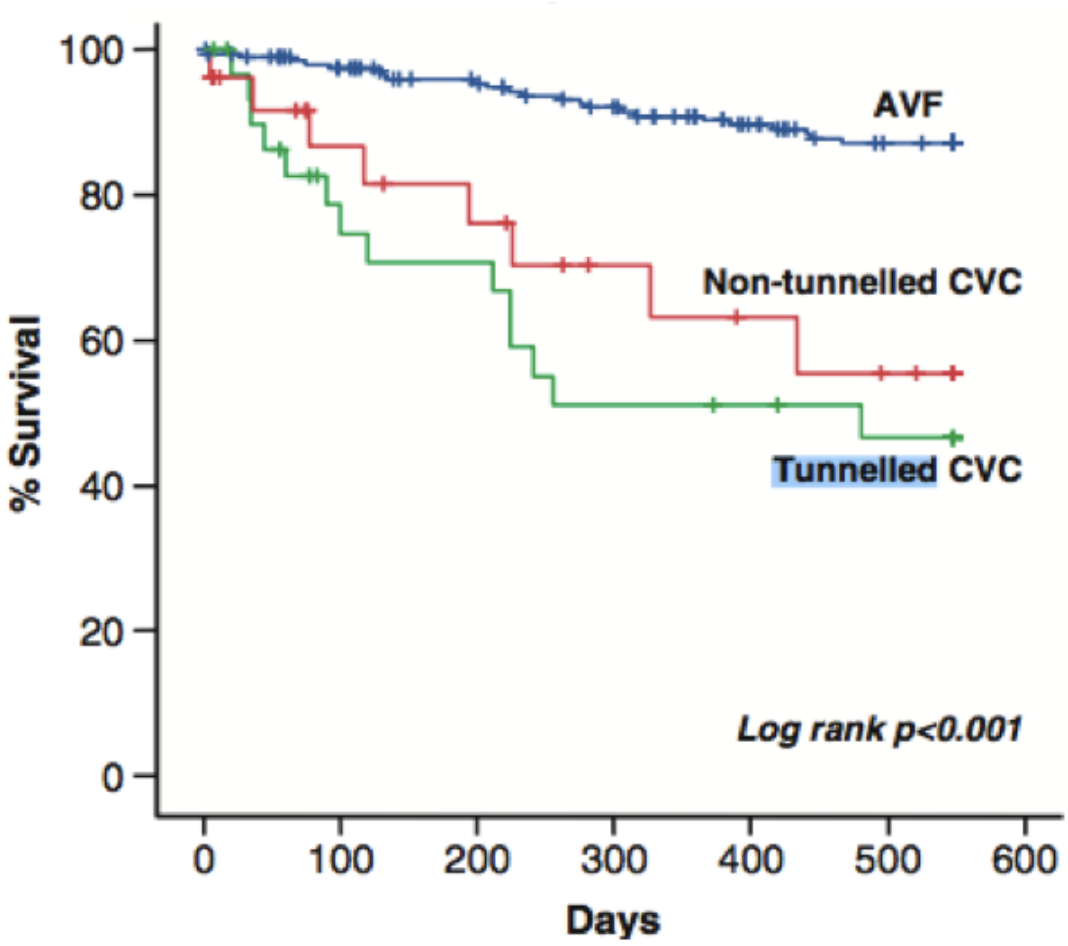


Figure 1.6: Kaplan Meier survival plot of the time to bacteraemia by vascular access type (CVC= central venous catheter, AVF=arteriovenous fistula, AVG= arteriovenous graft). Reproduced with permission from Dr. Peter Thomson. (Thomson et al. 2007)**.**

Several large studies have shown reduced survival in patients dialysing via a TCVC (Bradbury et al. 2007; Bray et al. 2012; Astor et al. 2005). Ravani and colleagues (2013b) recently conducted a systematic review of over half a million patients. They found a higher rate of all-cause (risk ratio (rr) =1.53, 95% confidence interval (CI)=1.41–1.67), infectious (2.12, 1.79–2.52), and cardiovascular (1.38, 1.24–1.54) mortality in patients dialysing via TCVC compared to AVF. Similarly, compared with AVGs, patients with TCVCs had a higher risk of mortality (1.38, 1.25–1.52), fatal infections (1.49, 1.15–1.93) and cardiovascular events (1.26, 1.11–1.43). AVGs conferred a higher risk of all-cause mortality (1.18, 1.09-1.27) and fatal infection (1.36, 1.17-1.58) than AVF but no difference in cardiovascular death was observed (Ravani et al. 2013a). Similarly, Bradbury and colleagues (2007) observed a higher mortality rate at both 120 and 365 days in patients commencing dialysis via a catheter. A recent national Scottish study of 2,666 patients revealed a 2-3 fold increased risk of both all-cause and cardiovascular mortality and 7- fold increase in death from septicaemia in patients receiving HD via a TCVC (Bray et al. 2012). These findings mirror those observed in our unit where TCVC usage conferred nearly three

times the risk of all-cause mortality than dialysis via an AVF (HR 2.75) (Thomson et al. 2007).

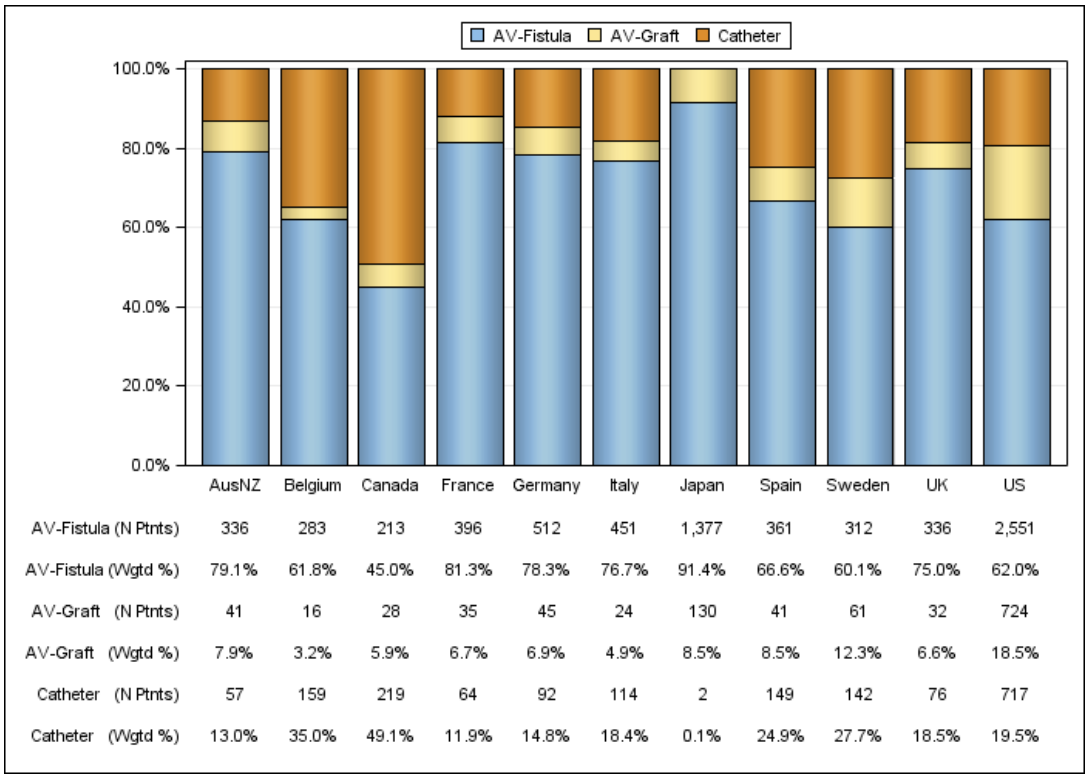
It is for these reasons that AVF are widely regarded as the 'gold standard' vascular access for HD (Smith et al, 2012, pp.84). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Vascular Access (NKF-KDOQI, 2006) in the USA, European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Best Practice Guidelines (Tordoir et al. 2007), Caring for Australasians with Renal Impairment (CARI) (KHA-CARI, 2012) and Renal Association (UK) Vascular Access Guidelines (Fluck & Kumwenda, 2011) all advocate that AVF should be the access modality of choice wherever possible (Table 1.1).

Table 1.1; Recommendations regarding choice of access modality from renal advisory groups around the world (ERA-EDTA= European Renal Association- European Dialysis and Transplant Association; CARI= Caring for Australasians with Renal Impairment; KDOQI= Kidney Disease Outcomes Quality Initiative) (Oxford CEBM, 2009).

Advisory group	Recommendation	Level of Evidence
The Renal Association (UK)(Fluck & Kumwenda, 2011)	'We recommend that any individual who commences haemodialysis should do so with an arteriovenous fistula as the first choice, arteriovenous graft as second choice, a tunnelled central venous catheter as third choice and a non-tunnelled central venous catheter as an option of necessity' (pp.63)	1B
ERA-EDTA (Tordoir et al. 2007)	'Every chronic renal failure patient who have opted for haemodialysis should start dialysis via a functioning vascular access' (p.88)	III
	'Autogenous AVF should be preferred over AV grafts and AV grafts should be preferred over catheters' (pp.92)	III
	'No recommendation possible based on level I and II evidence' (pp.1)	
CARI (KHA-CARI, 2012)	'Wherever possible it is suggested that a native arteriovenous fistula is superior to an arteriovenous graft and to central venous catheter' (pp.1)	III
	'When a native arteriovenous fistula is not possible, an artificial arteriovenous graft should be used in preference to a central venous catheter' (pp.1)	III
KDOQI (National Kidney Foundation, 2006)	'The access should be placed distally and in the upper extremities whenever possible. Options for fistula placement should be considered first, followed by prosthetic grafts if fistula placement is not possible. Catheters should be avoided for HD and used only when other options listed are not available' (pp.8)	IV
	'The order of preference for placement of fistulae in patients with kidney failure who choose HD as their initial mode of KRT should be (in descending order of preference): • Preferred: Fistulae • Acceptable: AVG of synthetic or biological material • Avoid if possible: Long-term catheters' (pp.8)	1B

Despite this, of the 478 patients who commenced on dialysis in Scotland during 2015, only 42.1% started HD via an AVF, the rest via a CVC. 71.8% of prevalent patients currently receive HD via an AVF or AVG and 28.2% via a CVC (Scottish Renal Registry, 2015). Nationally in the UK, during a similar time period, 80% of prevalent patients received HD via an AVF, 4% via an AVG and only 16% via a TCVC (UK Renal Registry, 2016).

Globally, there is considerable variation in practice. The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a large-scale study of dialysis practice, which began in 1996 and now collects data from over 20 countries worldwide. Most recent DOPSS data indicates that 92% of prevalent patients in Russia and 91% in Japan are dialysing via AVF, compared to only 68% in the US (Figure 1.7) (DOPPS Collaborators, 2012; Pisoni et al. 2015). In the 1990s this difference was even more marked with fewer than 20% of prevalent patients in the US dialysing via an AVF compared to almost 80% in Europe (DOPPS Collaborators, 2012.; Allon & Lok, 2010). These international variations in practice likely reflect disparities in both the provision of pre-dialysis and vascular access services, as well as differences between the dialysis populations, with the patients in the US being significantly more co-morbid than those in Japan or Europe (Pisoni et al. 2015; Ethier et al. 2008).



	AusNZ	Belgium	Canada	France	Germany	Italy	Japan	Spain	Sweden	UK	US
AV-Fistula (N Ptnts)	336	283	213	396	512	451	1,377	361	312	336	2,551
AV-Fistula (Wgtd %)	79.1%	61.8%	45.0%	81.3%	78.3%	76.7%	91.4%	66.6%	60.1%	75.0%	62.0%
AV-Graft (N Ptnts)	41	16	28	35	45	24	130	41	61	32	724
AV-Graft (Wgtd %)	7.9%	3.2%	5.9%	6.7%	6.9%	4.9%	8.5%	8.5%	12.3%	6.6%	18.5%
Catheter (N Ptnts)	57	159	219	64	92	114	2	149	142	76	717
Catheter (Wgtd %)	13.0%	35.0%	49.1%	11.9%	14.8%	18.4%	0.1%	24.9%	27.7%	18.5%	19.5%

Figure 1.7: Prevalent vascular access in DOPPS 4 countries in 2012. Reproduced with permission from the Arbor Research Collaborative for Health (DOPPS, 2012).

1.4. ARTERIOVENOUS FISTULAE

1.4.1. What is an arteriovenous fistula?

As previously described, arteriovenous venous fistulae (AVF) are regarded as the 'gold standard' vascular access (Smith et al, 2012, pp.84). They have the lowest infection rate and best long-term patency of any form of vascular access (National Kidney Care Vascular Access Report, 2012), making them the vascular access of choice according to British, European and American Renal Advisory Groups (NKF-KDOQI, 2013; Fluck & Kumwenda, 2011; Tordoir et al. 2007). Patients dialysing via an AVF are three times less likely to be admitted to hospital (for any reason) than their counterparts with TCVCs (National Kidney Care Vascular Access Report, 2012). The recent Dialysis Outcomes Practice and Patterns Study (DOPPS) reported a relative risk of death of 1.19 for TCVC and 1.08 for AVG compared to AVF (Pisoni et al. 2015). AVF are able to deliver a higher dialysis dose and are believed to provide better quality dialysis than TCVCs (a fact which may, in part, explain the lower cardiovascular mortality rate observed in patients dialysing via AVF) (KDOQI, 2012; Bray et al. 2012).

AVF are created by anastomosing an artery and vein together during a minor surgical procedure. Almost universally they are created in the upper limb under either local or regional anaesthesia. They may be created at a variety of sites, but a distal site in the non-dominant arm is preferred (Fluck & Kumwenda, 2011). Wherever possible, a wrist (radiocephalic (RCF)) fistula should be created between the radial artery and cephalic vein. Second choice would be an elbow brachiocephalic fistula (BCF), followed by the more complex brachiobasilic fistula (BBF) (Figure 1.8) (Allon & Robbin, 2002). In actual fact, a fistula can be created at any site where the artery and vein are in close proximity. In most cases an end-to-side anastomosis of the cut end of the main draining vein onto the side of the artery is performed; however the original side-to-side anastomoses described by Brescia; and Gracz fistulae (using the deep perforating veins) are alternatives (Konner, 1999; Allon & Robbin, 2002).

Following creation of the anastomosis, the low-pressure outflow vein is exposed to the higher flow rates, higher pressures and shear stresses of arterial blood and, with time, the vein too will become 'arterialised'. This process of arterialisation is referred to as maturation. The blood flow rate in the radial artery, which is typically 20-30mL/min prior to AVF creation, immediately increases to 200-300mL/min (as the blood flows into a low

resistance venous system) and, following complete maturation, flow rates of 600-1200mL/min will typically be established (Schuman et al. 2007). The immediate increase in laminar blood flow (with fast flow down the centre of the vessel and slower flow at the edges) results in increased shear stress within the vessel wall. In response to the shear stress, the vascular endothelium releases nitric oxide and prostacyclin, which promote vascular smooth muscle cell relaxation, vasodilatation and inhibit platelet aggregation and thrombosis (Riella & Roy-Chaudhury, 2013). Outward vascular remodeling then occurs as a homeostatic process (to reduce vascular shear stresses) and is responsible for the maturation process (Browne et al. 2015). Maturation typically takes between 6-8 weeks before the vein is suitable for cannulation for dialysis.

1.4.2. Complications of AVF

Unfortunately, a significant number of AVF fail to complete the maturation process and with never develop into an access suitable to sustain HD. This is the principal limitation to their universal use (Lok, 2007; Dember et al. 2008). Other complications associated with AVF occur less commonly than in other forms of vascular access.

1.4.2.1. Failure to mature (FTM)

Failure to mature (FTM) and early thrombosis is the 'Achilles' heel' of autologous fistula use (Riella et al, 2013, pp.348). Exact rates of non-maturation range from 10-50% depending on the definition of primary failure, with worse outcomes observed in contemporaneous cohorts (Miller et al. 1999; Dixon et al. 2002; Dember et al. 2008). Most authors will report an immediate thrombosis rate of approximately 20%, with a substantially larger proportion of patients having fistulae that mature suboptimally, never achieving functional patency (Allon & Robbin, 2002). For example, the widely cited randomised controlled Dialysis Access Consortium (DAC) study found that 60% of all AVF created had "failed to attain suitability for dialysis" (i.e. maintain a pump flow rate of >300mL/min during 8 of 12 dialysis sessions) five months after creation (Dember et al. 2008). Similarly the recently published Fish oil and Aspirin in Vascular access OUtcomes in REnal Disease (FAVOURED) study demonstrated a fistula failure rate of 50% at one-year in both control and intervention arms of the trial (Irish et al. 2017). A high early failure rate necessitates further attempts at AVF creation with associated morbidity and prolonged catheter dependence (Leake et al. 2015). This has latterly lead a number of authors to advocate the use of AVGs as an alternative to AVF (Allon & Lok, 2010; Lok,

2007), citing comparable cumulative patencies rates up to 2 years for the two access modalities when the early AVF failure rate is accounted for (Lok et al. 2013) (Figure 1.9). KDOQI guidelines advocate the use of objective criteria to assess the maturation of AVF and suitability for cannulation (NKF-KDOQI, 2006). They describe "the rule of 6s": fistulae must be able to support a blood flow of 600mL/min; be a maximum of 6mm from the skin surface; and have a diameter of >6mm to permit cannulation. In reality, as long as the Qa is at least 100mL/min greater than the pump speed on the dialysis machine, the AVF should be capable of sustaining haemodialysis without recirculation (American Society of Nephrology, n.d.) . Most clinicians will wait 6-8 weeks prior to attempting the first cannulation, however data from the DOPPS study indicate that, for suitably mature AVF, there was no significant difference in outcome between AVF cannulated within 15-28 days and those which had a longer maturation period (43-82 days) prior to initial cannulation (Pisoni et al. 2002).

A number of risk factors for FTM have been identified. Lok and colleagues (2006) identified that age >65 years old, coronary artery disease, peripheral vascular disease and non-Caucasian ethnicity were associated with high early failure rates of AVF. Many observational studies also show a higher FTM rate in diabetics (Feldman et al. 1996). Small, calcified vessels are also implicated in AVF failure, with most authors advocating minimum arterial diameters of 2mm and minimum venous diameters of 2.5mm before attempting AVF creation (Sidawy et al. 2008; Silva et al. 1998).

Successful maturation depends upon appropriate increases in blood flow through the fistula (Tessitore et al. 2014b), increased diameter of the vein (Allon et al. 2016) and vein wall thickness (Jaberi et al. 2011) following creation. Mean fistula diameters of >4mm are seen at day 1 in 85% and by 6 weeks in 87% upper arm AVF, but only 40% and 77% of forearm AVF respectively (Allon et al. 2016) . Similarly, access flow rates (Qa) <400-500mL/min are associated with an increased risk of thrombosis (Tessitore et al. 2014b). Studies of perioperative blood flow found brachial artery blood flow of <120-160mL/min to be highly predictive of early thrombosis (Saucy et al. 2010), highlighting the importance of the immediate blood flow through the fistula in the maturation process. In most successful AVF, the blood flow rates necessary to sustain dialysis are seen immediately, with one study of 602 AVF confirming that in at least 50% of AVF the six-week blood flow measurement was achieved at day 1 (Bay et al. 1998). Ladenheim and colleagues (2016) recently demonstrated a similar pattern in RCF with functional AVF having a mean blood flow of 753mL/min at 1 week compared to 121mL/min in non-functional AVF. No fistula

in this study with a blood flow <200mL/min after 1 week ever achieved functional patency. It may be that an inability of vessels to adapt and dilate to increase early flow rates explains the higher FTM rate observed in elderly patients and diabetics with high resistance, mediacalcinosis and heavily calcified vessels (Riella & Roy-Chaudhury, 2013)

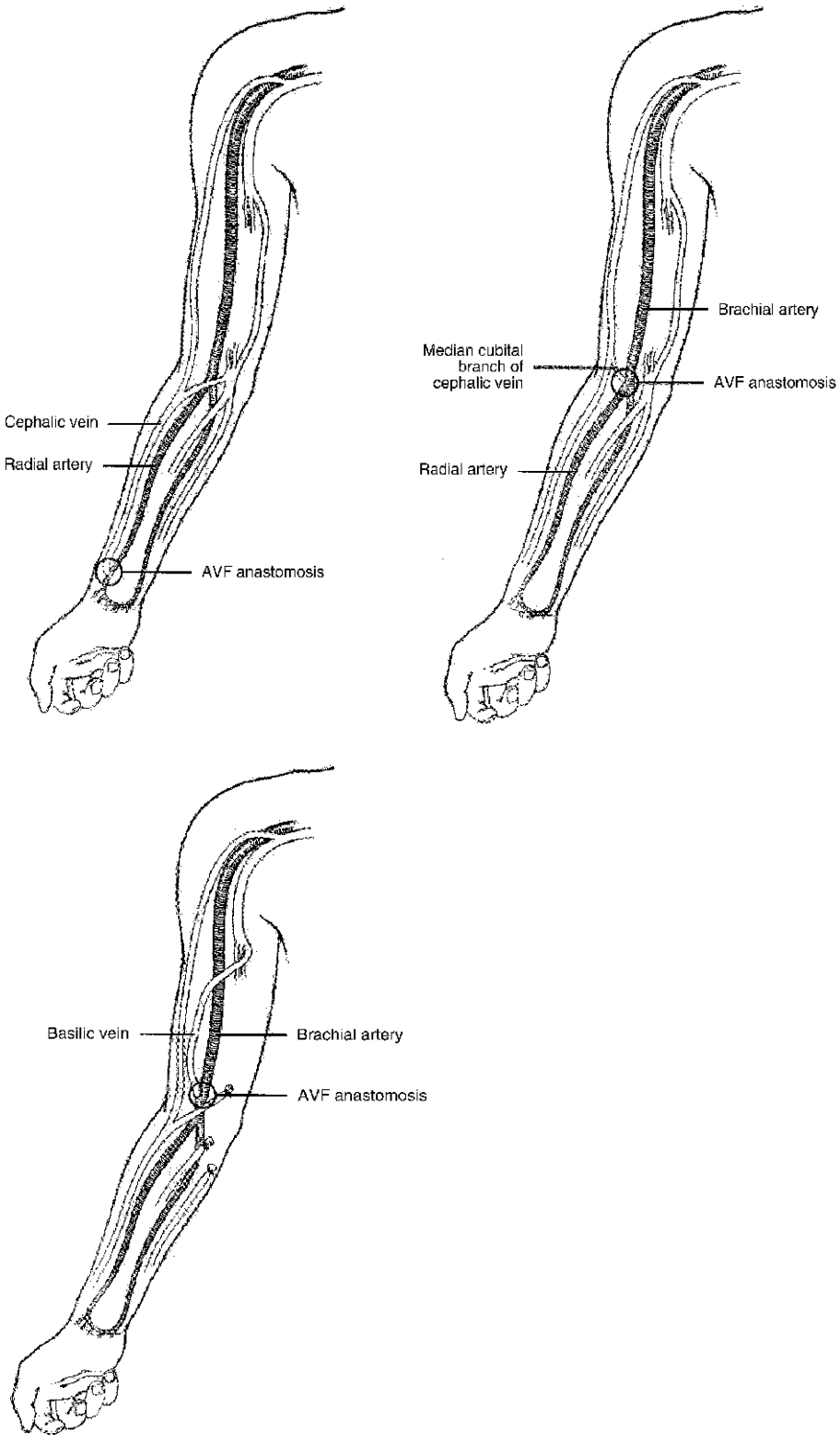


Figure 1.8: Diagram of radiocephalic (top left), brachiocephalic (top right) and brachiobasilic fistulae (bottom). Adapted from Allon and Robbin (2002).

Recent years have seen a plethora of ideas to try and improve poor early patency rates. Operative techniques that focus on modifying the flow dynamics of the anastomosis have shown theoretical promise, but have not yet translated into improvements in clinical outcomes (Rajabi Jagahrgh et al. 2013; Ene-Iordache et al. 2001). Similarly, attempts at topical treatment of the AVF anastomosis either with antispasmodics (e.g. papaverine) or enzymes to reduce intimal hyperplasia (e.g. PRT-201 pancreatic elastase) have not shown any improvement in early patency rates (Hye et al. 2014). Even in the DAC study, which did show a reduction in early AVF thrombosis with clopidogrel (12.2% versus 19.5%; P=0.018) (Dember et al. 2008), this was not translated into any meaningful difference in functional patency.

If a patent fistula can be established however, it may be that an angiographic procedure to dilate up the venous outflow of the AVF (balloon assisted maturation) can then be used to improve blood flow and permit maturation of a suboptimal fistula into one capable of sustaining dialysis (Roy-Chaudhury et al. 2012a). Early results with this technique appear promising with Miller and colleagues (2011) successfully maturing 118 of 122 suboptimal in AVF to the extent that they were capable of sustaining dialysis. This technique does, however, lead to intimal injury, recurrent intimal hyperplasia, rapid restenosis and need for additional interventions to maintain patency (Allon et al. 2016; Allon et al. 2013).

1.4.2.2. Stenosis and thrombosis

Long-term patency of AVF is superior to other forms of vascular access (Allon & Robbin, 2002). Primary unassisted patency rates in mature AVF of 75-90% at one-year are commonly quoted in the literature (Coburn, 1994; Silva et al. 1998). In their large study of nearly 500 patients, Huijbregts and colleagues (2008) found 6, 12 and 18 month secondary and functional patency of 75%, 70%, 67% and 90%, 88% and 86% respectively. Nevertheless, if AVF thrombosis does occur, thrombectomy/ declotting is often technically challenging and associated with poor outcomes (Aitken et al. 2012a).

Nearly all AVF thrombosis occurs on the background of a pre-existing stenosis. A stenosis is a narrowing of the blood vessel which will progress and limit blood flow through the fistula, ultimately resulting in occlusion. The stenosis can occur at any site in the fistula, but the outflow vein and juxta-anastomotic areas are most common. Stenoses tend to occur at the site of vascular injury (either surgical insult, injury from needling or at areas of the

outflow vein where turbulent blood flow exists e.g. the cephalic arch). The pathognomonic feature of AVF stenosis is neointimal hyperplasia (Rothuizen et al. 2013). In response to injury, there is an influx of proinflammatory cells and cytokines into the vessel wall. There is differentiation of fibroblasts into myofibroblasts and synthetic type vascular smooth muscle (VSM) cells, which in turn leads to smooth muscle proliferation within the media and neointimal hyperplasia (Lee & Roy-Chaudhury, 2009; Roy-Chaudhury et al. 2007; Li et al. 2007). When the rate of this process exceeds the rate of outward remodeling, the vessel will stenose and ultimately occlude (Rothuizen et al. 2013).

A number of antiproliferative drugs e.g. paclitaxel and sirolimus have been trialled in an attempt to reduce treat neointimal hyperplasia and prevent stenosis with some early promise (Kelly et al. 2006; Roy-Chaudhury et al. 2007; Iyem, 2011), however they have no routine role in clinical practice currently.

Given that the progression from stenosis to thrombosis is well recognised and angioplasty or stenting is very effective in treating stenosis to prevent subsequent thrombosis (unlike thrombectomy after thrombosis) (Miquelin et al. 2008; Roy-Chaudhury et al. 2012a), much attention has been focussed on surveillance of AVF. The hope is that by intervening early on an asymptomatic stenosis, future thrombosis will be prevented. Surveillance is advocated by most sets of clinical practice guidelines (Fluck & Kumwenda, 2011; NKF-KDOQI, 2006), however in reality, the majority of observational data fails to support this rationale (Tonelli et al. 2001).

1.4.2.3. Steal/ distal hypoperfusion ischaemic syndrome

Distal hypoperfusion ischaemic syndrome (DHIS) is a condition in which hand ischaemia occurs following vascular access placement. It affects between 5-10% of vascular accesses to varying degrees (Malik et al. 2008), presenting initially with pain and pallor in the hand and digits. In extreme cases it can result in tissue and even limb loss if not treated. The peripheral nerves as particularly vulnerable to ischaemia and an irreversible ischaemic monomelic neuropathy can rapidly develop (Thermann & Kornhuber, 2011). Many cases of DHIS result from distal arterial disease and inadequate inflow to the arm that is exacerbated by creation of a vascular access. However, true “steal syndrome” occurs in the absence of intrinsic arterial disease. The high blood flow within the fistula (commonly a BCF) leads to reverse blood flow in the distal (radial) artery and blood that is literally “stolen” from the hand. For this reason, steal is more common in elderly patients and in

female diabetics with small distal vessels (Tordoir & van der Sande, 2004). Diagnosis is made by ultrasound or angiography. Treatment strategies are principally operative, either by ligation of the fistula; proximalisation (to a large vessel e.g. axillary artery inflow) (Zanow et al. 2006); or distalisation (via either a distal revascularisation and interval ligation (DRIL) procedure or a revision using distal inflow (RUDI) procedure (Minion et al. 2005; Roh, 2012; Walz et al. 2007).

1.4.2.4. Infection

Infection accounts for approximately 20% of AVF complications, however the rate remains significantly lower than for TCVCs or AVGs (Stolic, 2012). Most infections are localised perivascular cellultis presenting as erythema and oedema that can be easily treated with antibiotics. Systemic infection is rare with a rate of 0.03 bacteraemic episodes per 1,000 access days commonly quoted (Taylor et al. 2002). It is postulated that systemic bacteraemia arising from fistulae may be the result of poor cannulation technique (NKF-KDOQI, 2006). In particular buttonhole cannulation (a technique in which two fixed tracts are created for repeated cannulation of the AVF at the same site) may be associated with a higher bacteremia rate (O'Brien et al. 2012).

1.4.2.5. Aneurysm

An aneurysm is a pathological, localised dilatation of a blood vessel. In AVF they occur for two reasons: upstream stenosis and repeated area cannulation and vessel trauma at the same site (Stolic, 2012). A true aneurysm involves all layers of the vessel wall. Conversely, pseudoaneurysms (false aneurysms) may only involve part of the vessel wall with haematoma lying outside the vessel, and almost invariably occur at the site of cannulation where an injury to the vessel wall has occurred. The skin over an aneurysmal area commonly is thinned and they carry a risk of rupture. Surgical revision or ligation is necessitated in such cases to prevent life-threatening haemorrhage (Stolic, 2012).

1.4.2.6. Impact on cardiovascular function

The Vascular Access Society defines “high-flow” AVF as those with Qa >1000-1500mL/min (Huijbregts et al. 2008). In actuality, much higher access flow rates commonly occur without complication. High vascular access blood flow (Qa) is believed to increase cardiac output and may (in rare cases) lead to high output cardiac failure

(MacRae et al. 2004). It is conjectured that creation of an AVF results in reduction in systemic vascular resistance (SVR), leading to compensatory increases in stroke volume (SV), heart rate (HR) and cardiac output (CO) in order to maintain blood pressure (BP) (MacRae et al. 2004; Válek et al. 2010; Korsheed, 2011); however the evidence for such theories comes principally from animal studies (Guyton & Sagawa, 1961) and a few small case series (Savage et al. 2002; Isoda et al. 1994). There is anecdotal evidence that high flow AVF can cause symptomatic heart failure with orthopnoea, paroxysmal nocturnal dyspnoea and peripheral oedema (MacRae et al. 2004; Isoda et al. 1994), however many patients tolerate very high Qa i.e.>5L/min with minimal symptoms.

1.5. TUNNELLED CENTRAL VENOUS CATHETERS

1.5.1. What is a tunnelled central venous catheter?

Tunnelled central venous catheters are dual-lumen catheters made from silastic or silicon elastomer, which are inserted percutaneously using a Seldinger technique into a large central vein either in the neck (internal jugular or subclavian), groin (femoral) or directly into the inferor vena cava via lumbar vessels (translumbar) (Klein et al. 2016). Unlike temporary catheters, a cuff is used to secure their position and reduce the risk of introducing infection. TCVCs are simple and easy to insert and can conveniently be used immediately for dialysis. For this reason, their use has revolutionalised acute HD and, in 2011, 59% of all incident patients in the England and Wales commenced dialysis via a TCVC (National Kidney Care Vascular Access Report, 2012). Conversely however, CVCs are the leading cause of healthcare-associated bloodstream infection and confer a significantly higher risk of bacteraemia than any other form of vascular access (Taylor et al. 2002).

1.5.2. Complications of central venous catheters

Patients dialysing via central venous catheters are more likely to be hospitalised as a result of access related complications than patients dialysing via another modality (National Kidney Care Vascular Access Report, 2012). UK data indicate that TCVC use confers a six-fold increased risk of systemic sepsis and three-fold higher all-cause mortality compared to AVF (Thomson et al. 2007; Bray et al. 2012), whilst DOPPS data report a 32% increased risk of death in HD patients with a CVC worldwide (Pisoni et al. 2009). Central vein stenosis can have significant and underrecognised long-term adverse

consequences (Agrawal, 2013). Furthermore, catheter use appears to be associated with a chronic catabolic state, malnutrition, weight loss and hypoalbuminaemia (Yeun & Depner, 2000).

1.5.2.1. Catheter-related bloodstream infection (CRBSI)

CRBSI is the most common infection in patients on HD with an estimated incidence 0.6-6.5 per 1,000 catheter days observed in most studies (Lata et al. 2016; Lok & Mokrzycki, 2011), although the exact rates vary with reporting and definition practices. A local study reports systemic bacteraemia rates of 1.77 per 1,000 catheter days for TCVCs, 6.3 per 1,000 catheter days for internal jugular NTCVC and 13.5 per 1,000 catheter days from femoral NTCVCs (Thomson et al. 2010). Healthcare associated bacteraemia is associated with an increased risk of death (HR 2.8 [95% CI 1.5-5.1]) (Lata et al. 2016) and increased length of hospital stay from an average of 7 to 21 days (Stone et al. 2005). An average CRBSI costs $37 000 to treat with catheter-related bacteraemia costing the healthcare system over $2 billion annually in the USA (Stone et al. 2005).

A patient on haemodialysis should expect to be hospitalised twice a year on average. 1 in 10 of these admissions will be due to vascular access infection (Ravani et al. 2013b). Whilst, the overall number of hospital admissions attributable to vascular access appear to have fallen in recent years, infection as a cause for hospital admission continues to rise (USRDS, 2014). In the USA, the number of hospital admissions due to vascular access infection more than doubled between 1993 and 2005 (Lok & Mokrzycki, 2011). This rise in infective admissions (to 903 admissions per 1,000 patient years) is disproportionate for patients on HD compared to the other RRT modalities and is widely attributed to catheter related-complications (USRDS, 2014). A prospective cohort study of over 100 000 patients in Canada found that the relative risk of bloodstream infection with TCVCs was 15.5 and with uncuffed CVCs was 22.5 compared to AVF (Taylor et al. 2002). Similarly within a local cohort, catheter use was found to be an independent risk factor for both bacteraemia and death compared to AVF (HR 5.4 and 2.8 respectively) (Thomson et al. 2007).

Most cases of catheter-related bacteraemia are uncomplicated and can be treated simply with antibiotics with or without catheter removal (Ashby et al. 2009; Lata et al. 2016), however others can result in metastatic infection. Approximately 10% of CRBSI in dialysis patients are associated with infective endocarditis (Lok & Mokrzycki, 2011). Endocarditis in this context carries a mortality rate of 25% (Lata et al. 2016). Discitis, spinal epidual

abscess, septic pulmonary emboli and osteomyelitis can all occur as secondary complications. Mortality rates from CRBSI in HD patients range between 6-34% in the literature (Lok & Mokrzycki, 2011). Whilst prevalent mortality on HD is reducing, incident death rates remain static (UK Renal Registry, 2016), at least in part explained by early catheter-related bacteraemia (Thomson et al. 2010).

Most catheter-related bacteraemic episodes are the result of infection from skin commensals e.g. *Staphylococcus aureus* or *Staphylococcus epidermidis*. *Staph.aureus* is normally methicillin sensitive (MSSA). However methicillin-resistant *Staph.aureus* (MRSA) is more common amongst dialysis patients and vancomycin forms the mainstay of treatment of both systemic and local exit site infection (Lata et al. 2016; Lok & Mokrzycki, 2011).

Given that infection is so costly, both in terms of the economic burden and morbidity for the patient (most cases necessitating line change), recent research has focussed on strategies to reduce infection. Education, strict asepsis, catheter care bundles and "scrub the hub" regimens with chlorhexidine skin cleansing and "no touch" technique have been very effective in reducing bacteraemia rates (Simmons et al. 2011). Topical antibiotics e.g. mupirocin/ polysporin (Lok et al. 2003), recombinant tissue plasminogen activator (tPA) (Hemmelgarn et al. 2006) and antimicrobial locks e.g. taurolidine/ sodium citrate have also proven effective. For example the Haemodialysis Infection Prevention with PolyspOrin (HIPPO) study demonstrated significant reduction in catheter-related bacteraemia rates with a combined topical antibiotic (polysporin) ointment, with bacteraemia rates <1 per 1,000 maintained out beyond 6 years (Lok et al. 2003; Battistella et al. 2011). In clinical practice, multimodal and combination preventative strategies have been employed with greatest effect.

1.5.2.2. Thrombosis and catheter malfunction

In reaction to vessel damage and platelet activation, a fibrin sheath will form around many TCVCs shortly after insertion (Napalkov et al. 2013). This fibrin sheath can complicate the line in several ways: it may become colonized with bacteria and form a biofilm or can directly occlude the catheter causing malfunction and poor flows through the catheter. The KDOQI guidelines define catheter dysfunction as the inability of achieve volumetric blood flow >300mL/min during the first 60 minutes of dialysis (NKF-KDOQI, 2006). Reported rates of catheter malfunction or thrombosis range between 0.6 and 33% or 0.06 to 21

episodes per 1,000 catheter days (Napalkov et al. 2013). In the event of catheter occlusion of malfunction, forceful flushing is contraindicated as it may lead to catheter rupture. Recombinant tPA and intraluminal lock or infusion of lytic enzyme (e.g. urokinase) may assist in dissolution of acute thrombosis (Hemmelgarn et al. 2006; NKF-KDOQI, 2006), and in some cases it is possible for the fibrin sheath to be stripped from the catheter under radiological guidance (Funaki, 2012). However in many cases the catheter cannot be salvaged as evidenced by local data demonstrating that 7% of TCVCs needed replaced due to occlusion during 1 year follow-up (Aitken et al. 2014a).

1.5.2.3. Central venous stenosis

Of all the catheter-related complications, central vein stenosis (CVS) or occlusion carries the greatest long-term morbidity and is the most difficult to manage (Agarwal et al. 2007). Trauma to the vein wall during and following TCVC insertion leads to upregulation of proinflammatory transcription factors and profibrotic genes, which in turn, cause smooth muscle proliferation, intimal hyperplasia, smooth muscle proliferation and subsequent thickening and fibrous changes within the intima of the central veins.(Agarwal, 2013) The resulting venous outflow stenosis and obstruction causes venous hypertension and presents with arm or facial swelling or access dysfunction of an ipsilateral fistula. In extreme cases, patients may present with bilateral central venous occlusion precluding both upper limb autologous access or further CVCs. Very rarely complete access failure may result with patients unable to dialyse as a result of access loss (Aitken et al. 2014b).

The prevalence of central vein stenosis varies depending on the diagnostic criteria (i.e. symptomatic versus angiographic), however most of the literature would suggest that between 10-40% of central lines are affected (MacRae et al. 2005). Risk factors for CVS include increasing number of TCVCs, longer duration of TCVC, a subclavian approach to vessel puncture and the presence of a cardiac pacemaker device (Agarwal, 2013).

Its widely accepted that asymptomatic CVS should not be treated (Agarwal, 2013; Agarwal et al. 2007). Symptoms may improve as venous collaterals develop (Agarwal et al. 2007). Symptomatic CVS can be managed by endovascular intervention (angioplasty or stenting) (Bakken et al. 2007), however it is notoriously difficult to treat. Lesions are susceptible to elastic recoil and commonly recur (Beathard, 1992).They require repeated intervention, the benefit of which is often short-lived (Bakken et al. 2007), and are associated with significant personal and economic burden (Jackson et al. 2014). 12-month

unassisted patency rates for angioplasty of CVS range from 12-50%, with cumulative patency rates as low as 13% in some studies (Beathard, 2015; Quinn et al. 1995; Dammers et al. 2003a). National Kidney Foundation-KDOQI (2006) guidelines recommend stenting of the central veins in cases of elastic recoil with significant residual stenosis following angioplasty or in cases of recurrence after < 3months. Patency rates of stenting vary and are improving as technology advances, however primary patency rates at 1-year remain approximately 50-60% (Rajan et al. 2007). In most cases, intervention for CVS is a temporising measure that will ultimately fail leading to access loss.

"End-stage" vascular access (ESVA) with imminent vascular access failure and the inability to dialyse is an uncommon but devastating problem (Aitken et al. 2014b). The exact prevalence of access failure is poorly described in the literature, however most clinicians involved in caring for patients with renal failure will be aware of a handful who have died as a result of complete access failure due to central venous occlusion (Jackson et al. 2014). Bilateral central vein occlusion precludes any future upper limb access (either peripherally or with further catheter into the neck vessels). Lower limb access or translumbar lines can be attempted, but the outcomes are suboptimal (Power et al. 2010) and ultimately occlusion of the iliac vessels and inferior vena cava will occur also. There are no good treatment solutions to this problem, which commonly affects younger dialysis patients, and can prove fatal. For this reason, perhaps more than any other, unnecessary catheter use should be avoided to prevent the initial occurrence of CVS.

1.6. ARTERIOVENOUS GRAFTS

1.6.1. Traditional arteriovenous grafts

Arteriovenous grafts (AVGs) are artificial conduits between artery and vein. A synthetic material is utilised to create the graft, which is implanted subcutaneously, and then cannulated for dialysis. AVGs in their modern-day guise were first utilised in 1972 (Konner, 2005). Three different graft materials were used at this time: one biological (bovine carotid artery) and two synthetic (expanded polytetrafluoroethylene (ePTFE) and Dacron® (Chinitz et al. 1972; Dunn et al. 1972)). Ultimately, ePTFE was found to be a more effective material of dialysis grafts than Dacron® due to its ease of handling, lower risk of aneurysm formation with repeated cannulation and lower infection rates (Konner, 2005).

An arteriovenous graft can theoretically be implanted at any site in the body between an artery and vein, however the most common configurations are brachio-basilic forearm loops and brachioaxillary in the upper limb (Figure 1.9) and common femoral artery to femoral vein in the lower limb (Akoh, 2009).

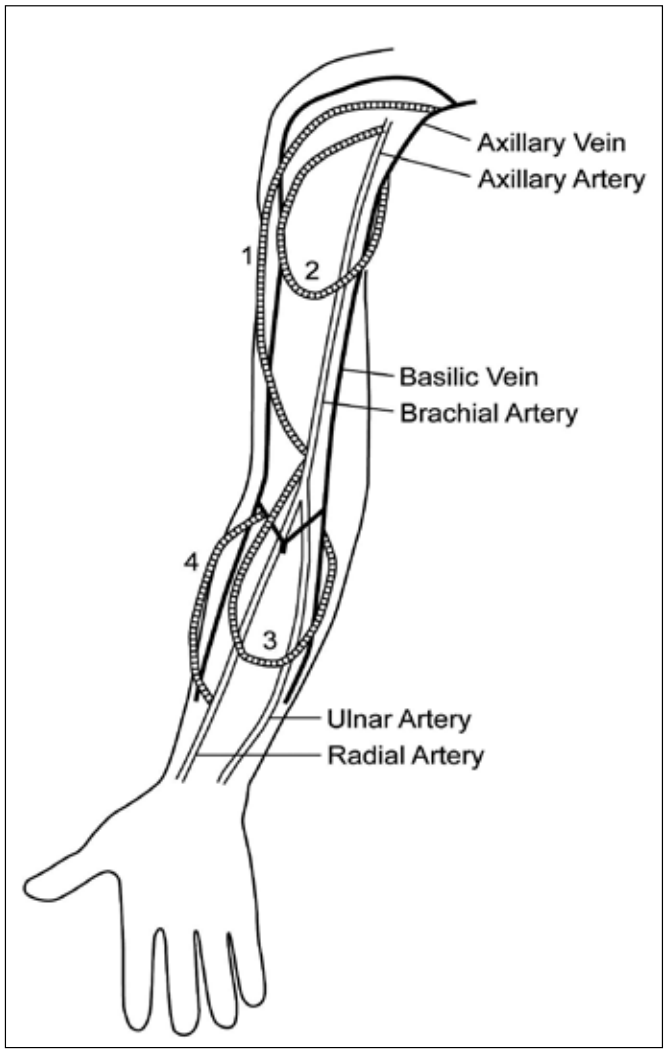


Figure 1.9: Common configurations of upper limb arteriovenous grafts.
1: brachioaxillary; 2: axillo-axillary; 3: forearm loop (brachiobasiic or brachiocephalic); 4: straight forearm (radial to median cubital or cephalic). Reproduced with permission from Wichtig Publishing (Akoh, 2009).

The benefits and limitations of an AVG lie somewhere between those of a TCVC and an AVF: they require significantly more initial cost in surgical expertise, time, and finance but have rates of complication and infection lower than a TCVC.

As previously described, systemic bacteraemia rates of AVGs are 0.5-0.6 per 1,000 dialysis days compared to 1.77 per 1,000 catheter days for TCVC and 0.3 per 1,000 dialysis days for an AVF (Taylor et al. 2002; Thomson et al. 2010).

It is well recognised that the long-term patency of a functioning AVF is significantly better than an AVG, with the need for fewer interventions to maintain that patency. In a large Canadian cohort study of 1,140 accesses created between 2000-2010, Lok and colleagues (2013) found that, once primary failures were excluded, median cumulative patency for AVFs was 61.9 months compared to 23.8 months for AVGs (HR 0.56, 95% CI: 0.43-0.74; P<0.001). They also concluded, however, that AVGs are more likely to establish initial function than AVF. The primary failure rate for AVGs in their series was half that of AVF (19% vs 40%; P<0.001). Furthermore, accounting for the high primary failure rate of autologous access, the cumulative patency did not differ between fistulae and grafts for either first or subsequent accesses (7.4 vs.15 months; P=0.85 and 7.0 vs. 9.0 months; P=0.39 respectively). In most contemporary series the primary patency rates for AVGs range from 40-60% (Schild et al. 2007). However with aggressive management of thrombosis and re-intervention, secondary patency rates of as high as 90% at 1 year have been achieved in some cases (Akoh, 2009).

Besides "failure to mature", AVGs obviate several other of the problems associated with autologous access use: lack of native vessels and prolonged maturation time (Allon & Lok, 2010; Lok, 2007). Standard ePTFE AVG can be cannulated two weeks after implantation (allowing just a short period of time for the graft to be incorporated into the surrounding tissue) (Akoh, 2009; Saran et al. 2005), avoiding the delays associated with prolonged or inadequate AVF maturation and the need for repeated interventions to achieve functional patency. In one observational study, only 16% of AVG required intervention to achieve functional patency, compared to 42% of AVF (Lee et al. 2007).

The Renal Association, NKF-KDOQI and European Best Practice Guidelines in Vascular Access advocate the use of AVG only as a second line vascular access in patients in whom no autologous options exist (citing poor patency rates and infectious complications associated with AVG usage). Despite this however, AVGs were still the most prevalent form of vascular access in the United States until the early 1990s, with 70-80% prevalence (Hirth, 1996).

1.6.2. Early cannulation arteriovenous grafts (ecAVGs)

Unlike standard AVGs, which need to be left approximately two weeks from insertion prior to first cannulation in order to allow them to incorporate into the surrounding tissue,

early cannulation arteriovenous grafts (ecAVGs) are suitable for immediate cannulation. This property of ecAVGs means that, instead of principally being used in patients with no native vessels for autologous access, these grafts can be marketed as an alternative to TCVC in patients requiring immediate haemodialysis (Ottaviani et al. 2016).

The first attempt at producing an early cannulation graft was in 1997 (Perma-Seal® (Possis Medical Inc., Minneapolis, MN, USA)). The role of and application of the graft was never recognised by the surgical community and the graft did not obtain FDA approval (Glickman, 2016). Since this time, an increased recognition of the mortality and morbidity associated with unnecessary catheter use (Thomson et al. 2007) and greater appreciation of the burden of AVF non-maturation necessitating TCVC use (Xue et al. 2010; Lacson et al. 2007; Dember et al. 2008) lead to a revival in interest of ecAVG as an alternative to TCVC. In fact the 2006 KDOQI Vascular Access Update advocates the use of arteriovenous grafts as a "planned bridge" to AVF creation in selected cases based on clinical need.

Initially the Vectra® (Bard, Murray Hill, NJ, USA) graft was licensed for early cannulation, and subsequently the three currently commercially available products (Rapidax™ (Vascutek Ltd, Renfrewshire, UK), Gore®ACUSEAL (W.L. Gore Associates, Flagstaff, AZ, USA) and Flixene™ (Maquet-Atrium Medical, Hudson, NH, USA) were developed. Both the Gore®ACUSEAL and Flixene™ grafts are made from ePTFE with unique tri-layer structures that give the grafts "low bleed" properties. The Gore®ACUSEAL graft is composed of two layers (outer and inner layer) of ePTFE separated by a central elastomeric membrane, designed to give the graft its self-sealing properties and limit pseudoaneurysm and seroma formation (Glickman, 2016) (Figure 1.10). The median time to first cannulation in most case series is 2 days (Tozzi et al. 2014a; Berard et al. 2015), however the grafts may be cannulated as early as 30 minutes post-operatively (Tozzi et al. 2014b; Al-Shakarchi et al. 2015a).

Published data on the outcomes of ecAVGs remains limited. Patency rates in observational studies of both Flixene™ and Gore®ACUSEAL are comparable to those of standard ePTFE (Tozzi et al. 2014a; Glickman et al. 2015; Berard et al. 2015; Chiang et al. 2014). Much of the data reflect small, single-centre experiences with short follow-up. Nevertheless secondary patency rates for Gore®ACUSEAL range from 60-90% at 12 months in every series (Table 1.2). In the only prospective multicentre study of early cannulation grafts, 1-year cumulative patency was 79% (95% CI: 71-85%), with a primary

unassisted patency rate of 35% (95% CI: 27-44%) (Glickman et al. 2015). Complications in this series were higher than in other cohorts with 6 patients experiencing haematoma formation, 15 graft infections and 15 cases of steal syndrome amongst 138 patients (Glickman et al. 2015). Overall infection rates for ecAVGs are comparable to those of standard AVGs, ranging from 0-18% in the published series (Al-Shakarchi et al. 2015b).

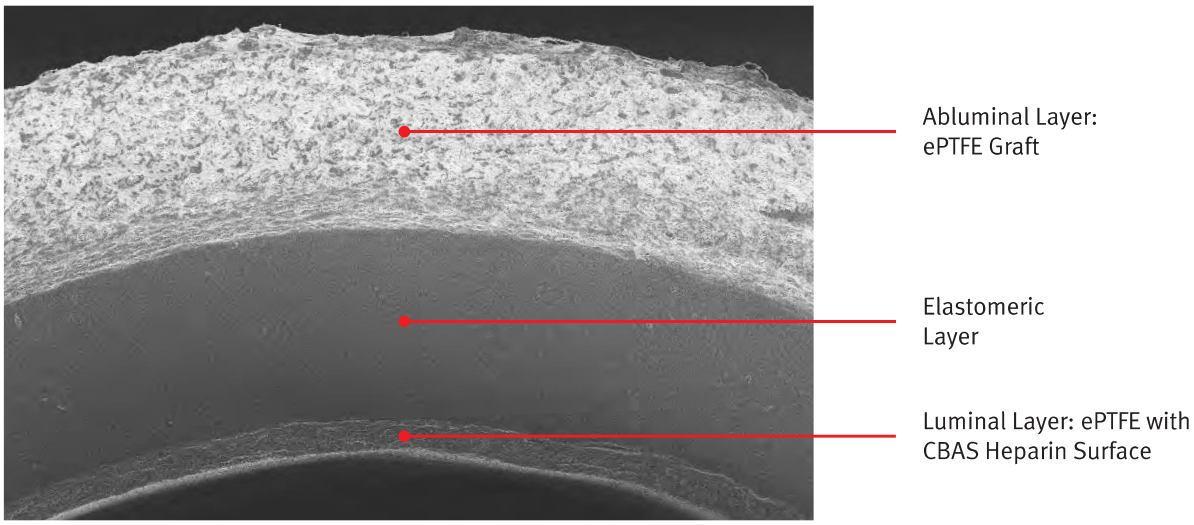


Figure 1.10: Trilayer construction of Gore®ACUSEAL early cannulation graft.
Magnification 500x. Reproduced with permission from W.L.Gore Associates.

Despite published data on over 1 000 ecAVGS (Al-Shakarchi et al. 2015b), the exact role of ecAVG in clinical practice remains unclear and poorly defined. This is reflected by the large variety and range of patients treated with ecAVG in the literature: patients with no autologous upper limb options for vascular access (Glickman et al. 2015; Berard et al. 2015); failure of previous vascular access (Tozzi et al. 2014b); need for urgent vascular access and TCVC avoidance (Berard et al. 2015; Aitken et al. 2014b) and complex or "end stage" vascular access solutions (Aitken et al. 2014b; Chemla et al. 2011). Chemla and colleagues (2011) present a series of early cannulation axillo-axillary grafts for patients with complex vascular access needs quoting 6 weeks and 1 year primary patency rates of 93% and 66% respectively. Due to the diverse patient populations and characteristics it is, however, difficult to draw direct comparisons between the existing series of ecAVGs.

Author	Number of patients	Multi/single-centre	Indications	Time to first cannulation	Median follow-up	Primary patency at 12 months	Secondary patency at 12 months	Infection rate
Tozzi et al..2014a	30	Single centre	Median age: 60+/-12 years "poor candidate for autologous access" 90% upper limb	Median: 2.4+/-1.2 days	6.3 months	68%	93.3%	0%
Aitken et al. 2014c	37	Single centre	Median age: 42+/-17 years "allcomers" 46% bilateral central vein stenosis 65% lower limb	Mean: 30.4+/-23.4 hours	6.5 months	32%	40%	16%
Maytham et al. 2015	55	Single centre	Median age: 64+/-17 years "native options not possible or exhausted"	73% within 24 hours	17.5 months	46%	61%	0.2 per 1,000 dialysis days
Glickman et al,.2015	138	Multicentre	Median age: 63+/-14 years "upper arm vascular access in patients not suitable for AVF"	Median 15 days	12 months	33%	78%	11%

Table 1.2: Summary of published studies of Gore®ACUSEAL early cannulation graft.

1.6.3. Novel arteriovenous grafts

The relatively poor outcomes in vascular access provide the prime opportunity for innovation to improve results. As a result, recent years have seen an explosion of new technologies, in many cases outpacing the current evidence or experience (Inston & Jones, 2014). This rapid expansion is largely driven by industry with novel interventions targetted to each of the clinical problems encountered. Graft geometry and flow modification e.g. spiral laminar flow grafts aim to counter the problems with venous outflow stenosis (Kokkalis et al. 2015); graft drug coatings e.g. heparin (Glickman, 2016), paclitaxel (Baek et al. 2012) and sirolimus (Paulson et al. 2012) have all been proposed as interventions to reduce in-graft stenosis and thrombosis (Allon et al. 2016); and new electrospinning technologies have been employed to control the size, density and orientation of graft fibres with the intention of giving them specific self-sealing properties to permit early cannulation (Ferraresso et al. 2013). The development of novel biological grafts more akin to autologous vessels may improve patency rates (Dukkipati et al. 2013; Peck et al. 2011), while devices such as the haemodialysis reliable outflow (HeRO) device have been designed to manage a specific clinical problem (central vein stenosis) (Glickman, 2011). The pace at which technology has developed and the overwhelming influence of industry has limited the head-to-head evidence available for any of these new products, most of which are described as case reports or small case series in the literature (Inston & Jones, 2014).

1.6.3.1. Biological grafts

Synthetic arteriovenous grafts are universally plagued by neointimal hyperplasia and stenosis leading to subsequent thrombosis and poor patency rates (Peck et al. 2011). The rationale for biological grafts therefore is that, by avoiding artificial material, the foreign body reaction is also prevented.

Biological grafts are not new. In fact, at the same time as modern era synthetic grafts were being developed, both xenogenic and allogenic biological grafts were also employed for vascular access. Bovine carotid artery, mesenteric vein and ureteric grafts (Darby et al. 2006; Katzman et al. 2005; Kaplan et al. 1976) were all found to form effective arteriovenous conduits with at least comparable patency to ePTFE. Unfortunately however, high rates of both pseudoaneurysm formation and rupture limited their long term use (Peck et al. 2011). Cryopreserved saphenous and femoral vein homografts remain commercially

available, however the hypothesis that such grafts would reduce infection rates was not supported in practice and cumulatively the clinical application of these grafts is limited to very niche situations (e.g. implanting into an area of existing infection) (Peck et al. 2011).

Recent work has focussed on developing scaffolds for biological grafts (either bioengineered resorbable scaffolds that permit cellular ingrowth (Shinoka et al. 2001) or completely biological in vivo tissue-engineered grafts (Campbell et al. 1999). Like the xenografts previously, bioengineered grafts form excellent bypass conduits, but concern regarding their ability to maintain sustainable integrity at cannulation sites is always a concern for dialysis vascular access (Tillman et al. 2012). The best-established biological graft is the biosynthetic Omniflow® graft (LeMaitre, Toronto, Canada), which utilises ovine collagen grown around a polyester mesh template. Retrospective analysis of 720 vascular accesses (59 ovine grafts) found the bioengineered grafts to have 1-year secondary patency comparable to autologous AVF (71%) and substantially better than ePTFE (54%). The infection rate of the ovine graft was 2% (Edwards & Ramshaw, 1995). More recently results of the multicentre phase II trial of the human acellular vessel (Humacyte® (Humacyte Inc., Morrisville, NC, USA)) have been published and show significant promise. Six-month primary and secondary patencies of 63% and 93% were observed, with no evidence of aneurysm formation and only one infection in 60 patients (median follow-up 16 months) (Lawson et al. 2016) . The decellularised collagen scaffold, has theoretical benefits of producing less inflammation and lower immune reactions. A phase III trial is underway. To date this has recruited 190 patients. One of the major limitations in the implementation of tissue bioengineered grafts into clinical practice is cost (Tillman et al. 2012). It therefore follows that a graft, such as Humacyte®, which could in the future be produced to be freely available off the shelf, might have significant benefit.

1.6.3.2. Haemodialysis Reliable Outflow (HeRO) Device

The Haemodialysis Reliable Outflow (HeRO) device is a unique innovation in vascular access, designed to manage the problem of central vein stenosis, in patients who have no venous outflow to drain a standard AVG, but in whom there is a desire to avoid TCVC. The device is a hybrid of a venous outflow component (akin to a central venous catheter) that is placed in the central vessels under image-guidance and drains much is a line would and an inflow graft component that is anastomosed onto the artery and tunnelled and cannulated as would be a standard graft. The graft component and outflow component then

connect together to permit venous drainage (Glickman, 2016; Glickman, 2011; Al-Shakarchi et al. 2015c) .

In an era where there is increased survival on haemodialysis, the number of patients who have exhausted all traditional vascular access options are increasing. Central venous occlusion poses a very difficult problem to manage. The HeRO device provides one potential solution for this complex patient cohort. Given the complexities involved in managing these patients and the lack of alternative treatment strategies, published outcomes from the HeRO device are commendable. A recent review of the literature (Al-Shakarchi et al. 2015c) identified eight studies with a total of 409 patients, mainly in North America. Pooled primary and secondary patency rates of 21.9% and 59.4% at one-year were obtained. Systemic bacteraemia rates of 0.13-0.7 per 1,000 dialysis days have been observed.

1.6.4. Complications of AVGs

The complication rates of AVGs lie somewhere between those of AVF and TCVC. Bacteraemia and local infection are more common in AVG than AVF, but less common then in TCVC. Similarly, graft thrombosis occurs more frequently than AVF thrombosis, however it is easy to treat and re-establish patency with a graft.

1.6.4.1. Venous stenosis and thrombosis

The majority of grafts occlude due to venous outflow stenosis. Like in AVF, a process of vascular injury, neointimal hyperplasia, stenosis and then thrombosis occurs. The process is particularly aggressive at the graft-vein anastomosis, although can also occur at sites of needle injury within the graft (Roy-Chaudhury et al. 2012b). The venous anastomosis is especially vulnerable to endothelial and smooth muscle cell injury due to a combination of haemodynamic stressors (non-laminar and turbulent blood flow and low shear stress) (Van Tricht et al. 2005) surgical injury and PTFE graft-induced macrophage accumulation (Roy-Chaudhury et al. 2001). Injury can also occur at the time of angioplasty (Lee et al. 2010). As a result, the rates of venous stenosis and subsequent thrombosis are higher in AVGs than autologous AVF, though it is easier to re-establish patency following thrombosis in prosthetic (Sgroi et al. 2013; Lok et al. 2013).

Twelve-month primary and secondary patency rates of AVGs range from 22-65% (Sgroi et al. 2013; Keuter et al. 2008) and 58-81% (Gibson et al. 2001; Kakkos et al. 2008) in historical series of standard PTFE. Secondary patency rates as high as 93% have been quoted in some contemporaneous series of ecAVG (Tozzi et al. 2014a). In their large 10-year cohort study comparing AVF and AVG, Lok and colleagues (2013) found that whilst overall cumulative patency for AVF and AVG did not differ, AVG had significantly poorer cumulative patency (23.8 vs. 61.9 months; $P<0.001$) after exclusion of primary failures. Thrombosis occurs in 50% of all grafts within 1 year of placement, necessitating a salvage procedure in 75% (Schwab, 1999; Miller et al. 2000).

Recent years have seen multiple interventions directed at attempting to improve graft patency. To date most have failed to convincingly or consistently reduce thrombosis rates (Diskin, 2003; Kaufman et al. 2003; Sreedhara et al. 1994; Moufarrej et al. 2016). Pharmacological therapies have been both local and systemic. A large multicentre randomised trial of dipyridamole plus low-dose aspirin demonstrated modest improvement in graft patency (28% vs. 23% primary unassisted patency at 1-year) but poor cumulative AVG survival (Dixon et al. 2009). The Cochrane review published in 2008 (Osborn et al. 2008) identified ten studies that evaluated the role of anti-platelet or anticoagulant drugs in maintaining patency of AVGs. A modest improvement in graft thrombosis was observed with anti-platelet agents (asprin, clopidogrel and ticlopidine), however the single study of warfarin (Crowther et al. 2002) was halted early due to an increased rate of haemorrhagic complications in the treatment arm. A recent randomised controlled trial of fish oil supplementation found lower rates of graft failure in the fish oil supplementation arm (3.43 vs. 5.95 per 1,000 access days; $P<0.001$), however was probably underpowered to detect any difference in the primary endpoint (proportion of patients experiencing thrombosis or need for intervention in the first 12 months) (Lok et al. 2012). Finally, there have been multiple attempts made at modifying the venous outflow of the graft in an attempt to improve the haemodynamics and minimise neointimal hyperplasia. These adaptations have been driven by industry and include a spiral graft aimed at inducing spiral laminar flow (Stonebridge et al. 2012); tapered grafts designed in an attempt to widen the venous outflow and control flow rates through the graft (Krueger et al. 2004); the Optiflow™ (Bioconnect Systems, Ambler, PA, USA) anastomotic connector to obviate the need for suturing and surgical trauma (Manson et al. 2013) and the Gore®Hybrid graft with nitinol reinforced stent to cross the venous anastomosis (Jones & Inston, 2015). The theoretical benefits of such products are evident, however to date there is no evidence that any one results in superior patency (Roy-Chaudhury et al. 2012b).

1.6.4.2. Graft infection

Systemic infection rates of AVGs are higher than AVF but significantly lower than TCVCs in most published series. The systemic bacteraemia rate for AVG is commonly reported as 0.06 per 1,000 access days (Schild et al. 2007). In actuality, the infection rates quoted in the literature vary significantly (Table 1.3) and there is no standardised definition of what constitutes an infection, making comparison of incidence, intervention and outcome difficult (Ryan et al. 2004). Most case series are small, involve heterogenous patient groups and variable sites for AVGs (upper and lower limb). Follow-up is poorly defined and there are no clear reporting methods for infection rates (Kingsmore, 2016). Some series report infection rates as a percentage of the total population at end of the follow-up period (Schild et al. 2007; Allemang et al. 2014), others report per year (Ram et al. 2010) or per 1,000 access days (Aitken et al. 2014b). As a result, widely variable infection rates are quoted (Kingsmore, 2016).

Although systemic bacteraemia is uncommon (and metastatic infection practically unheard of) localised infection and infected haematoma of AVGs is significantly more common, affecting 10-15% of all grafts (Al-Shakarchi et al. 2015b). The natural history and timing of infection is also important, with most infections occurring early (presumably the result of infected haematoma at the operative site) (Kingsmore, 2016). Such infections tend to result in local problems and may ultimately necessitate explant of the graft, but rarely result in a systemic bacteraemia. Later (secondary) infections commonly result from poor cannulation technique and lack of asepsis. The organism is normally a skin commensal and systemic bacteraemia is more common (Kingsmore, 2016; Harish & Allon, 2011) (Figure 1.11). Often a prolonged course of antibiotics will effectively treat these infections, although practice is variable and without an established evidence base (Ryan et al. 2004). Standardised definitions of graft infection including methods of quoting incidence, severity of local (i.e. degree of local cellulitis/ abscess formation) and systemic infection (i.e. positive blood cultures or suspected systemic infection), and need for intervention are required for effective comparison between products and centres and to facilitate future research (Kingsmore, 2016).

Table 1.3: Infection rates of arteriovenous grafts in published case series and randomised controlled trials

Author	Study type	Number of grafts	Follow-up	Graft type	Site of graft	Infection rate
Wang et al.1996	Case series	109	18 months	Omniflow Standard PTFE	63% upper limb	1%/yr 2.3%/yr
Glickman et al. 2001	RCT	142	12 months	Vectra PTFE	100% upper limb	5.6% 5.6%
Dammers et al. 2003	RCT	109	12 months	Tapered PTFE Standard PTFE	100% upper limb	0.12/ yr 0.03/ yr
Ryan et al. 2004	Case series	1441	-	Standard PTFE	100% upper limb	3.5%
Rooijens et al. 2005	RCT (vs RCF)	84	12 months	Standard PTFE	100% upper limb	0.13/yr
Schild et al. 2007	Case series	702	Median: 10 months	Standard PTFE	95% upper limb	9.5%
Kakkos et al. 2008	Case series	76	18 months	Vectra	100% upper limb	6.6%
Keuter et al. 2008	RCT (vs BBF)	51	325 days	Standard PTFE	100% upper limb	15%
Palumbo et al. 2009	Case series	38	Median:38 months	Omniflow	-	0%
Ko et al. 2009	RCT	89	2 years	Cuffed PTFE Standard PTFE	100% upper limb	4% 5%
Ram et al. 2010	Case series	268	-	Standard PTFE	79% upper limb 21% thigh	0.5/pt/yr 0.1/pt/yr
Sala et al. 2011	Case series	30	-	Standard PTFE	100% upper limb	10%
Mistry et al. 2011	Case series	48	-	Flixene	100% upper limb	6.25%
Lioupis et al. 2011	Case series	48	-	Flixene	100% upper limb	6%
Morosetti et al. 2011	RCT (vs BBF)	27%	2 years	Omniflow II	100% upper limb	0%
Harish & Allon, 2011	Case series	1309	-	Standard PTFE	78% upper limb 22% thigh	9% 14%
Kennealey et al. 2011	RCT	53	33 months	Standard PTFE Bovine carotid artery graft	100% upper limb	0.1/yr 0.13/yr
Bachleda et al. 2012	Case series	53	-	Standard PTFE	-	28.3%
Lok et al. 2012	RCT (fish oil)	201	12 months	Standard PTFE	95% upper limb	8.4%
Davoudi et al. 2013	RCT (vs BBF)	30	-	Standard PTFE	100% upper limb	17%
Allemang et al. 2014	Case series	265	Up to 4 years	Standard PTFE	92% upper limb	9%
Scarritt et al. 2014	Case series	78	-	Flixene	100% upper limb	9%
Harlander-Locke et al. 2014	Case series	17	18 months	Bovine carotid artery	Previous infection or high risk	6%
Tozzi et al. 2014a	Case series	30	6.3 months	Acuseal	90% upper limb	0%
Chiang et al. 2014	Case series	64	18 months	Flixene Standard PTFE	100% upper limb	20% 40%
Nassar et al. 2014	RCT	72	18.5 months	Standard PTFE HeRO	21% 20%	
Maytham et al. 2015	Case series	52	17.5 months	Acuseal	100% upper limb	16%
Glickman et al. 2015	Case series	138	12 months	Acuseal	100% upper limb	11%
Berard et al. 2015	Case series	46	Median: 223.5 days	Flixene	73% upper limb	2%
Shemesh et al. 2015	RCT	160	23.5 months	Standard PTFE Propaten	100% upper limb	3.8% 3.8%

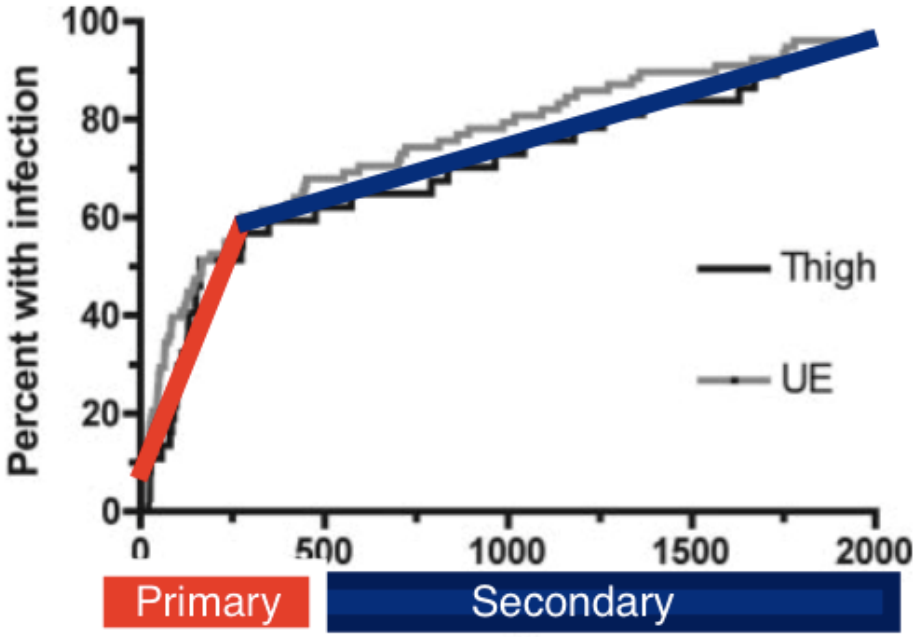


Figure 1.11: Time to graft infection in days (thigh and upper extremity (UE)), highlighting two distinct time periods for onset of infection- primary (likely the result of infected haematoma at the time of surgery) and secondary (likely resulting from inoculation of organisms due to poor cannulation technique. Adapted from Harish & Allon, 2011. Reproduced with permission from Mr David Kingsmore.

Graft infections are notoriously difficult to treat. Once prosthetic has become infected systemic antibiotics (even prolonged courses) and often ineffective and often operative drainage or explant of the grafts is the only treatment option (Ryan et al. 2004; Benrashid et al. 2017). Prevention therefore is the mainstay of management. Strict asepsis and good cannulation technique is vital (Bachleda et al. 2012; Parisotto et al. 2014); prophylactic antibiotic at the time of implant may be helpful (Kingsmore, 2016); and, finally, graft modifications (antibiotic impregnated or bioengineered grafts) may have a role in the future (Inston & Jones, 2014).

1.6.4.3. Other graft complications

Like AVF, AVG can also be complicated by pseudoaneurysm formation and steal (Al-Shakarchi et al. 2015b; Sgroi et al. 2013). As with graft infection, the reporting of other graft complications in literature is variable and non-standard. Quoted rates of pseudoaneurysm formation range from 0-17% (Al-Shakarchi et al. 2015b; Kakkos et al. 2008; Sgroi et al. 2013). They are commonly associated with clustering of cannulation sites (area cannulation) and rotation of needle sites can assist in preventing this complication (Tozzi et al. 2014b; Al-Shakarchi et al. 2015b).

Theoretically steal syndrome should be more common in patients with AVGs than AVFs due to the diameter of the graft (6mm internal diameter in most AVGs vs. 2-3mm outflow vein in AVF). In reality, rates reported in the literature (0-11%) (Glickman, 2016; Al-Shakarchi et al. 2015b) don't differ significantly from autologous access, though the clinical symptoms are more likely to manifest soon after surgery due to the fixed outflow of the AVG and higher flow rates observed immediately.

1.7. PROMOTING THE USE OF AUTOLOGOUS ACCESS

Conventional opinion supporting AVF as the 'gold standard' vascular access (Smith et al. 2012, pp.849) has led to a number of strategies, targets and initiatives promoting autologous access use.

1.7.1. "Fistula First"

The "Fistula First Breakthrough Initiative" (FFBI) is a multi-faceted, American, continuous quality improvement project that was established in 2003 with the aim of achieving the KDOQI targets of 50% incident and 40% prevalent AVF use by 2005 (Lok, 2007). The goal of 40% prevalent AVF use was rapidly surpassed with an increase in AVF use from 24% in 2000 to 52% in 2008 (Pisoni et al. 2002; Spergel, 2008; Lynch et al. 2011a; Lynch et al 2011b; Allon & Lok, 2010). The new target of 66% prevalent AVF use is fast approaching. The initiative has however failed to influence incident AVF use. Until last year (when DOPPS-5 observed slight improvements in incident AVF usage to 28%) incident AVF use in the US has been <15% compared to 60-70% in most of Europe (Pisoni et al. 2015; Ethier et al. 2008; Allon & Lok, 2010).

Furthermore, unfortunately the increase in prevalent AVF usage has unfortunately not been accompanied by a concomitant reduction in catheter use (Lok, 2007). Conversely, the rate of prevalent TCVC usage has actually increased from 17% to 26% (perhaps due to a high primary failure rate of AVF created through an aggressive fistula primacy policy necessitating prolonged TCVC dependence) (Allon & Lok, 2010; Pisoni et al. 2015). Instead of a switch from TCVC to AVF, the post-FFBI era has seen a switch from AVG to AVF with no, or in fact negative, influence on catheter usage (Figure 1.12) (Gomes et al. 2013; Vassalotti et al. 2012). Although reduction in CVC use was never a primary goal of the FFBI, many now recognise the need for 'a concurrent approach to AVF promotion and CVC reduction' (Lok, 2007, pp.1045). The KDOQI standard of ≤10% prevalent catheter

use has now been widely adopted into the FFBI campaign and latterly there has been a shift in focus from "Fistula First" to "Catheter Last" (NKF-KDOQI, 2006; Lacson et al. 2007; Fulton, 2009).

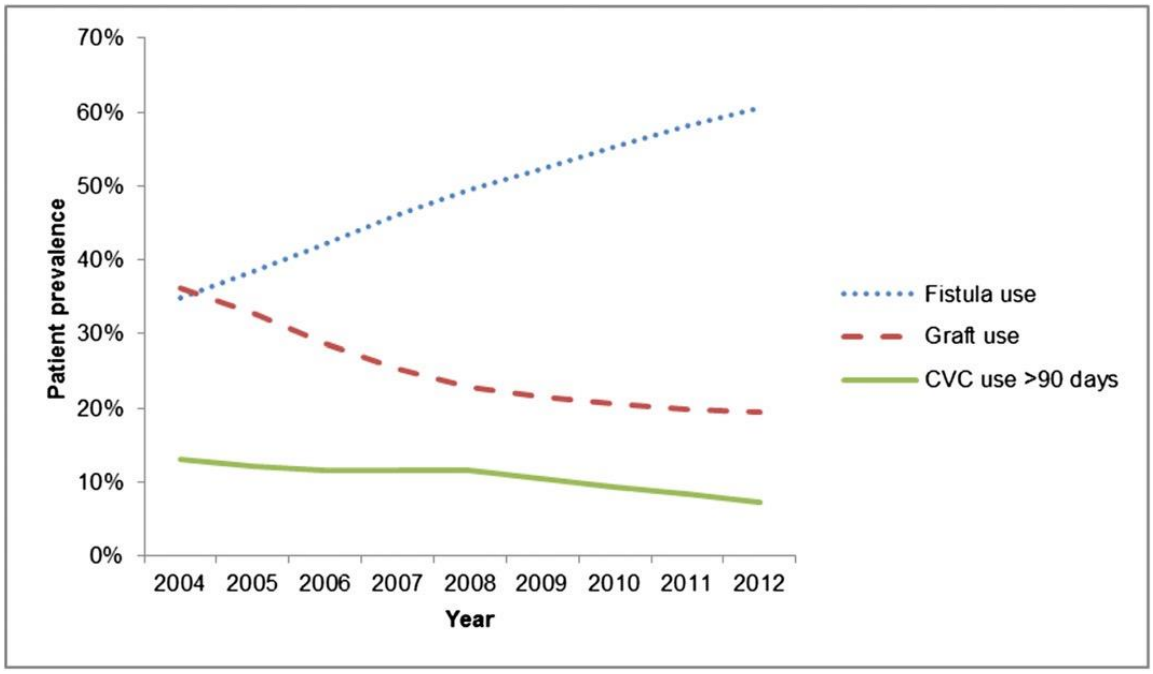


Figure 1.12: Prevalent vascular access use in the US highlighting the impact of the FFBI (increasing numbers of AVF, reducing numbers of AVGs and no significant change in TCVC use.) Reproduced with permission from National Kidney Foundation Fistula First Breakthrough Initiative**.** (Gomes et al. 2013)**.**

So has "Fistula First" actually achieved its aims? Certainly, the improvement in prevalent autologous access use must be commended, as should the heightened awareness of vascular access as a key determinate of outcomes for patients on HD that has been promoted by the campaign. However there is currently no evidence to suggest that the observed increase in AVF usage has actually resulted in any improvement in dialysis-related outcomes (either reduction in infection rate or improved survival) (Malas et al. 2015). Furthermore 'current incident practice [still] falls exceedingly short years after recommendations, [with] a change in current policies and structured multidisciplinary efforts needed to ameliorate this deficit' (Malas et al. 2015, pp.441). Additionally, whilst DOPPS data confirm that drives to improve autologous access use have resulted in more AVF being created (more than twice as many AVF were created per head of the dialysis population in 2012 compared to 2002), the proportion of those AVF that are subsequently used for dialysis has actually reduced in recent years (Rayner et al. 2003; Pisoni et al. 2009). These observations have led some to observe that perhaps the drive should not be simply to have 65% of patients on HD with a fistula, or even that 65% of patients on HD

have a “functioning” fistula, rather that 65% of patients on HD have an AVF capable of sustaining dialysis (Lok, 2007).

1.7.2. Targets in the United Kingdom

In the UK, The Renal Association has set even more stringent targets, advocating that 65% of incident patients and 85% of prevalent patients should have autologous vascular access (Fluck & Kumwenda, 2011). Recently a controversial best practice tariff was established in England and Wales with the aim of creating a rules-based framework that financially rewards efficiency and best practice (Department of Health, 2010). The Payment by Results (PbR) tariff was calculated based on 75% of prevalent haemodialysis occurring via an AVF or AVG in 2011/2012; 80% in 2012/2013 and 85% by 2013/2014, with trusts financially recompensed for achieving these goals (Department of Health, 2010; Sharif & Baboolal, 2011).

Although contentious, the best practice tariffs have rekindled the drive for definitive vascular access this side of the Atlantic. Like in the US, prevalent AVF rates have increased year-on-year with 67% prevalent AVF use in DOPPS-1, 74% in DOPPS-4 and 80% in DOPPS-5, with a corresponding reduction in catheter-dependence (unlike the US, baseline prevalent AVG use was low and therefore improvements in AVF use in the UK have resulted in concurrent reduction in TCVC use) (Robinson & Port, 2010; DOPPS Collaborators, 2012; Ethier et al. 2008; Pisoni et al. 2015). Practice around the UK is diverse however, with some units having upwards of 60% of patients dialysing via an AVF after only 6 months, while others have less than 10% (UK Renal Registry, 2014). Furthermore, like in the US, the incentivised practice has not translated into improvement in autologous access use in incident patients to date (UK Renal Registry, 2016). The recent DOPSS-5 data show that incident AVF use in the UK is only 53% compared to 85% in Japan (Pisoni et al. 2015).

1.7.3. The Local Problem

Healthcare in Scotland is a devolved power, therefore the best practice tariff does not apply within the National Health Service (NHS) in Scotland. There is now a significant discrepancy in autologous access rates North and South of the border (73% prevalent AVF rate in Scotland compared to 80% in England and Wales) (UK Renal Registry, 2016; Scottish Renal Registry, 2015), with concerns that the disparity will further increase without incentivisation in Scotland (Thomson 2015, personal communication).

There is also significant variation in prevalent vascular access use within Scotland (Figure 1.13) (Scottish Renal Registry, 2015). Units in the West of Scotland are falling well below the national average. In 2015, Glasgow's dialysis units only achieved 63% prevalent AVF use, compared to 81% in Edinburgh and 94% in Aberdeen (Scottish Renal Registry, 2015). These shortcomings have lead to a drive to improve vascular access provision locally.

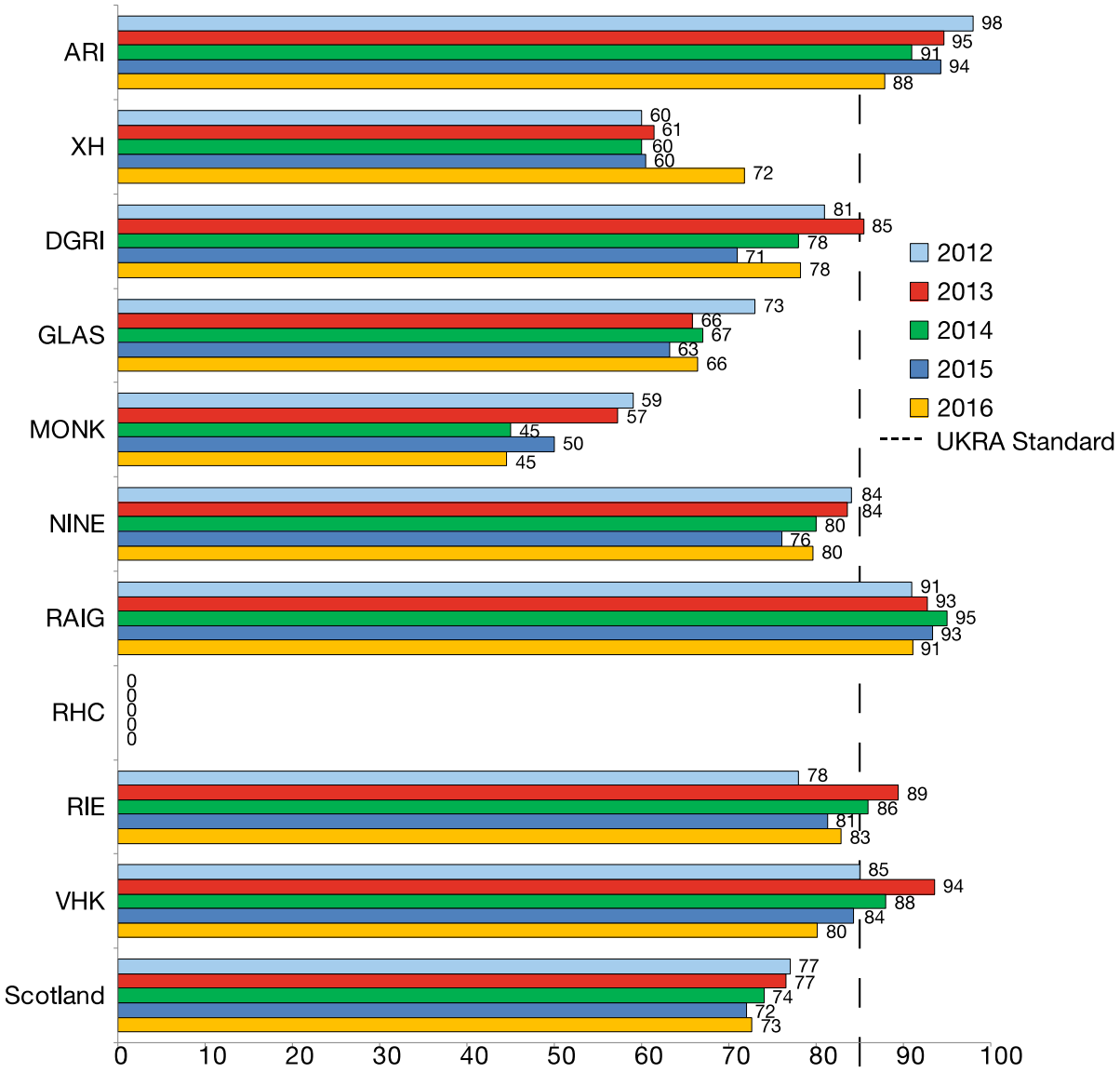


Figure 1.13: Percentage of prevalent haemodialysis patients in Scotland dialysing via autologous AVF 2012-2016. Reproduced with permission from Information Service Department (ISD), Scotland (Scottish Renal Registry, 2015).

1.7.4. How do you improve autologous access use?

Attaining a functioning fistula is a complex process 'akin to running a hurdle race' (Allon, 2007, pp. 786). There are multiple steps (referral to a nephrologist, surgical assessment,

creation of AVF, maturation and maintenance) that need to be performed in a sequential order. Failure in any of the steps results in the patient initiating dialysis via a catheter (Allon, 2007). Input is required from a range of specialists within the multidisciplinary team (nephrologists, surgeons, interventional radiologists, vascular access nurses) (Lok, 2007). It is therefore vital that a co-ordinated team-based approach is adopted with everyone working towards a common goal (Lok & Davidson, 2012).

The factors associated with a suboptimal start onto HD are both patient- and centre-specific. Each unit and every patient will present unique challenges and barriers to AVF creation that need to be addressed at a local level as well as through national targets (Wilson et al. 2013). Root-cause analysis of TCVC usage however repeatedly highlights common problems. Assuming that TCVC avoidance is the aim, a better understanding of the reasons for catheter usage can be used to inform a strategy to optimise autologous access (Wish, 2010). Lee and colleagues (2005) found that nearly half of patients (43.5%) dialysing via a TCVC did so as they were still awaiting AVF creation (either after starting HD or following failure of a previous AVF). 28.7% were waiting for an AVF to mature; 18.5% had no native option and 9.2% did so through patient choice (Lee et al. 2005). Nica and colleagues (2013) highlighted that patient factors and deficiencies in the systems and processes of vascular access provision were major determinants of TCVC use, with patient refusal, late referral, wait for surgery, lack of operating room space and poor cannulation quoted as relatively consistent problems. Good access outcomes require both reliable systems and attention to the human factors (National Kidney Care Vascular Access Report, 2012).

The strategies required to improve autologous vascular access rates differ between incident and prevalent patients. In prevalent patients, the aim must be to prevent access loss through thrombosis. Failure to recognise and treat dysfunctional access is the principal cause for loss of a functioning vascular access (Vassalotti et al. 2012). Although the role of radiological surveillance of fistulae remains controversial, clinical monitoring with prompt recognition of stenosis and timely intervention for failing AVF is essential to prevent thrombosis (Sharma & Ranjan, 2014; Polkinghorne, 2006; Salman, 2014; Allon & Robbin, 2002; Fluck & Kumwenda, 2011). Education of dialysis nursing staff and good cannulation practice is also vital to minimise complications. A single episode of infiltration prolongs TCVC dependence by 3 months (Allon & Lok, 2010; Lee et al. 2006). Finally, there is a growing body of evidence to suggest that pharmacological manipulation at various of stages in the stenosis-thrombosis pathway may assist in preventing access loss

(Jackson et al. 2012). Fish oils, clopidogrel, aspirin and dipyridamole have all been shown to have a modest benefit in prolonging patency of both AVF and AVG in clinical trials (Lok, 2012; Dember et al. 2008; Tanner & DaSilva, 2015). Whether or not this translates into clinically significant benefit to the patient remains a matter of debate. The Dialysis Access Consortium (DAC) trial of aspirin and dipyridamole only prolonged graft survival by 6 weeks (Dixon et al. 2009).

Incident patients should be the focus of efforts to improve autologous access creation (Lok, 2007). An optimal start on dialysis with functioning AVF is associated with better short- and longer term survival (Mendelssohn et al. 2006; Malas et al. 2015). Starting dialysis via a TCVC sets a precedent for ongoing future catheter use (Weber et al. 2009). 40% of patients who started on a line are still with TCVC (with or without AVF) after a year on HD (Lok, 2007; Ethier et al. 2008). The vestige of poor access planning and early line usage remains with the patient for their lifetime on dialysis in the form of lost access sites and central vein stenosis (Agarwal et al. 2007; Aitken et al. 2014a).

Late referral is cited as the commonest reason for failure to start dialysis via an AVF (Lok, 2007; Wish, 2010; UK Renal Registry, 2014.). The recommendation from the UK Renal Association is that referral for vascular access should occur when the patient enters CKD IV (taking into account comorbidities, rate of declines in renal function and the surgical pathway) (Fluck & Kumwenda, 2011). Similarly, the National Kidney Foundation advocates AVF creation at least 6 months before the anticipated need for dialysis (NKF-KDOQI, 2006). Despite this, even in patients known to nephrology services >90 days, only 50% were referred to the surgical team for autologous access creation prior to starting on HD (National Kidney Care Vascular Access Report, 2012). Of those assessed by a surgeon at least three months prior to starting dialysis, 70.4% started dialysis on an AVF whereas only 9.7% of those who had not seen a surgeon did (UK Renal Registry, 2014.).

A recent Dutch study identified a number of bottlenecks in the referral pathway for AVF creation: delayed referral (failure of nephrologist to recognise decline in renal function); delay to surgical assessment (suboptimal accessibility OF surgical clinic); delay to surgery (lack of surgical capacity) (van der Veer et al. 2015). Several years ago, a Joint Working Party Group of The Renal Association, Vascular Society of Great Britain and Ireland and British Society of Interventional Radiology (2006) identified minimum physical requirements that were required to provide a vascular access service. Despite this, many units still fall short of their recommendations of one theatre list per week for every 120 prevalent dialysis patients, a two-week waiting time for fistuloplasty and the ability to

perform thrombectomy within 48 hours.

In addition to these material requirements, integration of the individual components within vascular access service infrastructure is essential since 'fragmentation of care' has been identified as major barrier to AVF placement (Wish, 2010, pp.615). Clear referral pathways and processes are essential as lack of a structured referral pathway is recognised as an obstacle to autologous access creation (Lopez-Vargas et al. 2011). However rigid strategies can put unnecessary delays into the system (for example the recommendation of "Fistula First" that every patient must have a pre-operative vein mapping ultrasound) (Lok, 2007). A degree of flexibility, and perhaps redundancy, is required so that the process of care is fluid and can be adapted for the individual patient. Currently inherent delays created by a methodical surgical referral pathway in many centres (clinical assessment, then imaging, then wait listing prior to surgery) (Lok & Oliver, 2003) means that only 8% of patients who are referred for surgery "late" (i.e. after starting on dialysis) have a functioning AVF after 6 months on dialysis (UK Renal Registry, 2014).

Approximately one third of patients are known to a nephrologist for <90 days prior to the initiation of HD. Obviously it will not be possible to create and mature an AVF within this time period, therefore these "crashlanders" present unique management challenges. They are often critically unwell, grossly fluid overloaded or hyperkalaemic. Many have experienced a significant hypotensive insult to precipitate their renal failure and many have poor cardiac function. Repeated cannulation and venesection in this patient cohort will destroy native vessels and limit autologous options for the future. For these reasons, the default position for such patients is for TCVC, with nearly 90% starting dialysis via a line (Chao, 2013; UK Renal Registry, 2016). However, it is essential that autologous access planning begins at the initial recognition of acute kidney injury (AKI) with preservation of vessels for future vascular access. Despite the fact that the patient is acutely unwell and TCVC may be the simplest and easiest option, alternatives including urgent PD, ecAVG, and early cannulation of native AVF should be considered as means of avoiding damage to the central veins and compromising autologous options for the future (Ponce & Balbi, 2011; Blake, 2012; Tozzi et al. 2014b; Berard et al. 2015; Saran et al. 2005). Such options require a degrees of flexibility within the surgical service and cannot be managed on the "next available" theatre list. Locally, there has been some success with a policy of semi-urgent vascular access creation where required (Aitken et al. 2012C).

The best way to manage "crashlanders" remains to avoid them by identifying patients early enough to allow access planning prior to an urgent need to commence HD. Hughes and

colleagues (2013) found that 31.2% of patients classified as “crashlanders” actually had somewhat predictable acute-on-chronic renal failure in which a foreseeable trajectory of renal decline was not adequately anticipated or recognised, necessitating avoidable TCVC insertion for the start of HD.

Early identification of patients soon to require HD also allows for pre-dialysis education. Pre-dialysis education has a very important role in preservation of vessels for native access. Patients told to avoid phlebotomy from their non-dominant arm are twice as likely to successfully have creation of a native AVF (Lok & Oliver, 2003). Additionally, pre-dialysis education is important to influence and inform opinion about the value of autologous access (Lok, 2007). Nephrologists consider patient refusal to be one of the principal barriers to AVF creation and it’s well recognised that the longer a patient spends dialysing via a line, the harder it is to convince them as to the benefits of AVF (Xi et al. 2010.; Nica et al. 2013). Many patients who have a catheter enjoy the ease of dialysis (quicker to get on and off the machine, no needles etc.) and become reluctant for AVF creation (Xi et al. 2010.; Lacson et al. 2011).

Finally, non-maturation of AVF is a significant problem. If a fistula is created, but not matured by the time a patient starts on dialysis, the default is a TCVC. 81% of patients known to renal services have AVF surgery attempted prior to commencing on HD, but the number of patients actually starting HD via an AVF is less than 50% in the UK (Pisoni et al. 2015; UK Renal Registry, 2016; Scottish Renal Registry, 2015). Despite pre-operative vein mapping to choose the optimal site and balloon-assisted maturation, only about half of AVF created mature sufficiently for dialysis (Dageforde et al. 2013; Mendes et al. 2002; Roy-Chaudhury et al. 2012b; Zangan & Falk, 2009; Dember et al. 2008). As previously highlighted, the challenge is therefore not in creating an AVF, it is in creating a functioning AVF (Lok, 2007). Two-thirds of patients in the Dialysis Access Consortium (DAC) study of AVF maturation, had AVF that were patent but still unsuitable for use at the time the patient needed to commence of dialysis (Pisoni et al. 2009). It is therefore important that attention to access is maintained throughout pre-dialysis care (even after creation) as a culture of “create and forgot” can result in an otherwise adequate AVF being unsuitable for use at the start of dialysis because no one checked to ensure it was maturing adequately (Nica et al. 2013; Lok & Oliver, 2003). Ultimately every hurdle is of equal importance. The most complex system and robust infrastructure will fail if no-one remembers to check for a thrill in the Low Clearance Clinic. It is therefore essential that vascular access remains foremost in the mind of every clinician caring for patients with

ESRD and is considered at each and every consultation.

1.8. CHALLENGING THE 'GOLD STANDARD' ARTERIOVENOUS FISTULA

In recent years the doctrine of AVF primacy has been challenged. There is, in fact, no level I or II evidence to support the use of AVF over other access modalities, and international vascular access guidelines, which universally advocate AVF as the modality of choice (Fluck & Kumwenda, 2011; KHA-CARI, 2012; Tordoir et al. 2007; NKF-KDOQI, 2006), are based on data from large (albeit good quality), retrospective case series. The high primary failure rate of autologous accesses and increasingly frail, comorbid dialysis population have led a number of authors to question whether AVF really are the panacea that they are reputed to be or whether TCVCs are a necessary evil in some situations (Drew & Lok, 2014; Lok, 2007; Allon & Lok, 2010). "Fistula First" and other similar initiatives promote autologous access use at all costs. However, latterly some authors have questioned if failure to achieve a functioning AVF by the time of HD initiation really does reflect poor quality care? Or whether the well-recognised benefits of having an AVF need to be balanced against the burden of trying to achieve a functioning AVF and the likely gain that the patient is likely to obtain in terms of dialysis-years via that access? (O'Hare et al, 2010; Moist et al. 2012; Drew & Lok, 2014).

1.8.1. Evidence for AVF as 'gold standard'

1.8.1.1. Randomised controlled trials

There is minimal level I evidence comparing vascular access modalities. No randomised controlled trials (RCTs) exist comparing TCVC to either AVF or AVG. There are four RCTs comparing AVF and AVG. These are summarised in Table 1.4. The two multicentre studies were conducted by the same research team in the Netherlands, compare autologous AVF to prosthetic PTFE in very specific patient cohorts, and have differing conclusions. Rooijens and colleagues (2005) found forearm PTFE grafts superior to RCF in patients having primary AVF creation with suboptimal vessels (79% vs. 52% secondary patency at 1-year; p=0.001), while Keuter and colleagues (2008) found transposed BBF to have superior patency to forearm loop grafts (46% vs. 26% primary patency at 1-year; P=0.005) in patients unsuitable for or with failed RCF or BCF fistulae. In both studies the prosthetic arm required more interventions to maintain patency than the autologous arm. Both

studies are well-conducted RCTs, but their clinical applicability is limited by the fact that neither address the true dilemmas faced by the clinician in practice: BCF or forearm loop AVG following failed RCF? BBF or brachio-axillary AVG following failed BCF? Is there a role for lower limb prosthetic? (Allon & Lok 2010) For this reason, neither of the studies are mentioned in either the American or European Vascular Access Guidelines, which draw on large, observational cohort studies for evidence instead (Tordoir et al. 2007; NKF-KDOQI, 2006). The other two studies are small single-centre trials comparing AVG and BBF with conflicting results (Morosetti et al. 2011; Davoidi et al. 2013). Morosetti and colleagues (2011) found primary patency rates at 6, 12 and 24 months of 81%, 61% and 60% respectively in the BBF cohort and 55%, 32% and 21% in the AVG cohort, whilst Davoudi et al. (2013) found no difference in mean primary patency time in transposed BBF and AVG (244.13 ± 103.65 and 264.97 ± 149.28 days respectively). Both studies have fewer than 30 patients in each arm, no description of where the AVG were sited and add little to the existing body of evidence.

1.8.1.2. Observational cohort studies

All of the large registry studies show an association between AVF and improved survival compared to TCVC or AVG (Table 1.5) (James et al. 2009). Registry data is supported a plethora of single-centre, retrospective cohort studies that are summarised in two systematic reviews (Huber et al. 2003; Murad et al. 2008). For the most part these studies support, not only a survival benefit with AVF, but also lower infection rates, hospitalisation rates and improved cost-effectiveness (Huber et al. 2003; Murad et al. 2008; Lok, 2007; Pisoni et 2015) (Figure 1.14).

The retrospective registry studies carry inherent selection and indication bias (Allon & Lok, 2010). The data collected is often limited in breadth and missing data is not infrequent. For example, in the UK Registry Report (2014) six centres needed to be excluded as the data return for was less than 50%. Selection bias in large cohort studies systematically favours the outcomes of AVF over TCVC. Critically ill patients starting haemodialysis urgently and those too frail for AVF creation will be included for analysis in the TCVC cohort, increasing the risk of adverse outcome in this group (Quinn & Ravani, 2014). Patients who are not eligible for AVF creation have a 3-year survival of 26% vs. 81% in those deemed eligible for AVF creation (Blake et al. 2013). The eligibility criteria for AVF placement in the retrospective studies are poorly defined (Ravani et al. 2013a). Additionally, new starts onto dialysis (particularly “crashlanders”) are more likely to

dialyse via TCVCs. It is well recognised that individuals who start dialysis urgently have twice the risk of adverse events, including death (OR 2.09) (Mazonakis et al. 2009). In an analysis of incident patients Quinn and colleagues (2011) found that, although the hazard for death was 70% higher in patients treated with catheters compared to those with autologous access, when those starting dialysis urgently were removed there was no significant difference in outcome. Large registry datasets do not include such data and therefore their interpretation is limited by indication bias. Likewise, most authors will consider outcomes by 'access achieved' not 'access intention' (Windus, 1993, pp.460). Given that most failed AVF attempts occur in frail, elderly, diabetics, such a per protocol analysis will also favour AVF outcomes (Quinn & Ravani, 2014). Finally, it must be taken into account that, in many cases, retrospective data on patency rates and access outcomes are over 30 years old (Lok, 2007). The dialysis population has changed significantly during this time, as have access practices and outcomes (Scottish Renal Registry, 2016; USRDS, 2014; Fernstrom et al. 1988; Golledge et al. 1999; Dember et al. 2008; Lok et al. 2006). Inferences and recommendations based on historical data may not hold true in the contemporary dialysis population.

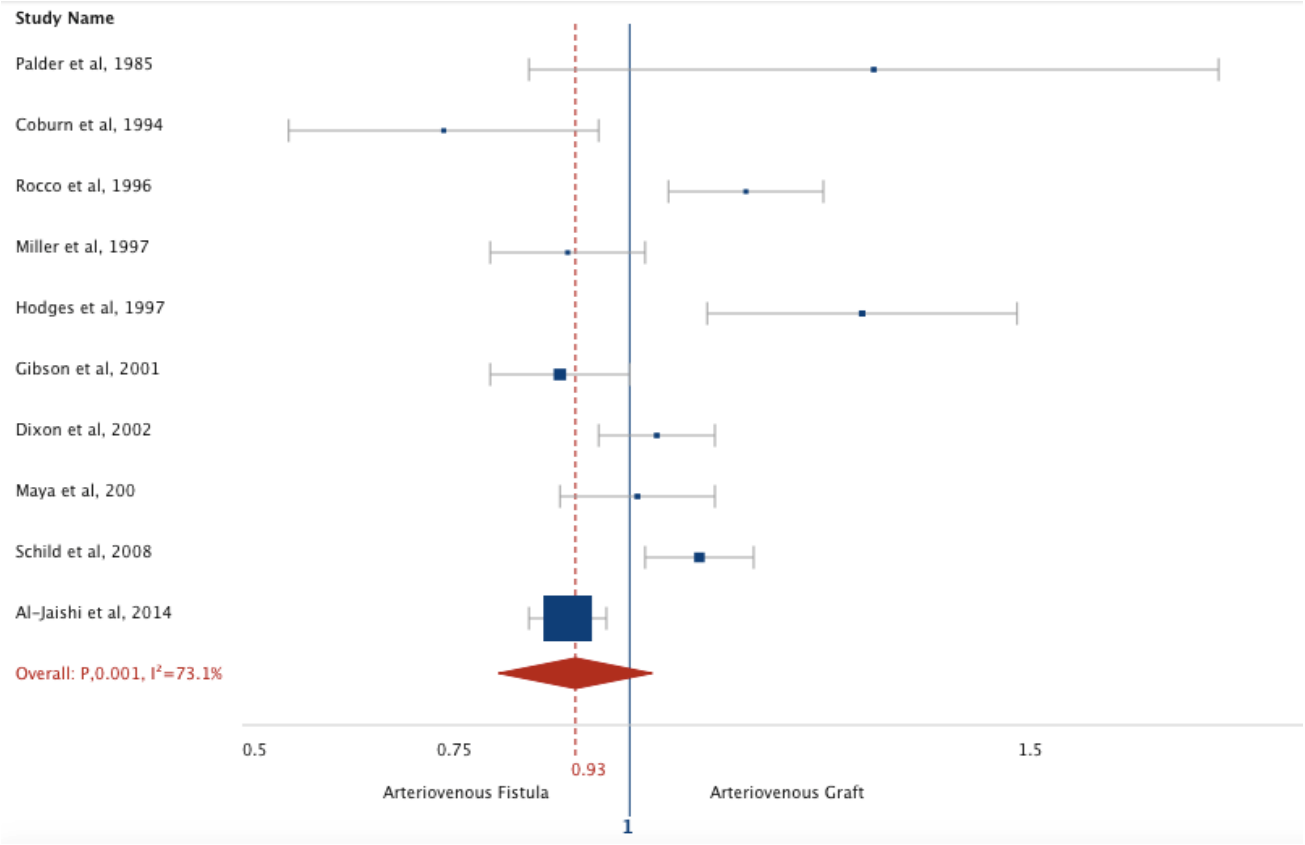


Figure 1.14: Forrest plot of 12-month cumulative access patency (from observational study data) comparing arteriovenous fistula and arteriovenous grafts (including primary fistula failures).

Author	Study design	Population	Comparison	Primary end point	Secondary end points	Primary outcome	Secondary outcomes	Conclusions
Keuter et al. 2008	Randomised, muticentre trial in Netherlands	Patients with failed RCF/ BCF or vessels unsuitable for either fistula type (n=105)	Transposed BBF vs. forearm loop graft	Primary patency at 1 year	Primary aand secondary patencies at 1 year Number of interventions necessary to maintain patency	Primary patency at one year was superior in BBF than forearm PTFE loop grafts (46% vs. 22%; P=0.005)	Primary assisted patency was also superior in BBF (87% vs 71%; ; P=0.04). Secondary patency at 1 year was comparable between the groups (89% vs. 85%; P=0.86) Fewer interventions were required in the BBF to maintain patency (1.7/ pt. vs. 2.7/pt)	BBF are superior to forearm PTFE loop grafts in patients unsuitable for primary RCF or BCF with superior primary and primary assisted patency rates and fewer interventions required to maintain patency.
Rooijen et al. 2005	Randomised, muticentre trial in Netherlands	Patients requiring de novo primary vascular access with marginal forearm vessels (radial artery diameter 1-2mm and/or cephalic vein at wrist <1.7mm) (n=383)	RCF vs. forearm graft	Primary patency at 1 year	Primary assisted and secondary patencies at 1 year Number of interventions necessary to maintain patency	Primary patency at 1 year was superior in prosthetic forearm grafts compared to RCF (44% vs. 33%; P= 0.03)	Primary assisted patency and secondary patency were also superior in forearm grafts (63% vs. 48%; P=0.03 and 79% vs. 52%; P=0.001 respectively). Fewer interventions were required in the RCF cohort for access salvage(0.5/ pt./yr vs. 0.94/pt/yr; P=0.08)	Forearm PTFE grafts are superior to RCF in patients with poor forearm vessels with better primary, primary-assisted and secondary patency rates. More intervention were required to maintain this patency however.
Morosetti et al. 2011	Single centre randomised controlled trial in Italy	'Complex' patients (failed RCF/ BCF, exhausted superficial veins or suitable vessels) (n=57)	BBF vs, Omniflow Ii Vascular prosthesis	Primary and secondary patency (time-point for primary outcome unclear)	Operation time, length of hospital stay, rescue procedures	Primary patency at 6, 12 and 24 months for BBF were 81%, 61% and 60% and for AVG were 55%, 32% and 21% respectively. Secondary patency at 6, 12 and 24 months for BBF were 86%, 76% and 66% and for AVG were 72%, 52% and 34% respectively.	Total operation time was 91+/- 15minutes in the AVG arm and 105+/- 28minutes in the BBF arm. Mean length of hospital stay was 4+/-1 days in the AVG arm vs. 5+/- days in the BBF arm	BBF should be the first choice in patients with good life expectancy who can rely on a temporary vascular access. However, given the shorter time to use AVG could be used in those with shorter life expectancy or who can't have temporary vascular access.
Davoudi et al. 2013	Single centre randomised controlled trial	No suitable forearm veins (n=60)	BBF with transposition vs. AVG	Primary patency time	Secondary patency at 1 year; access related complications	Mean primary patency times in the BBF and AVG groups were 244.13 ± 103.65 and 264.97 ± 149.28 respectively	Access failure rates at 1 year 23.3% in BBF cohort vs. 30% in AVG cohort	AVG offer similar patency and complication rates to BBF, thus they should be considered the preferred haemodialysis access when there are no suitable forearm veins.

Table 1.4: A summary of randomised controlled trials comparing AVG to AVF.

Author	Registry	Population	Access status	Crude mortality	Adjusted mortality	Confounders adjusted for
Dhingra et al. 2001	USRDS	Random sample of prevalent haemodialysis patients in the United States December 1993 (n=5507)	At study start date	NR	Diabetics: AVF: reference; AVG: RR 1.41; TCVC: RR 1.54 Non-diabetics: AVF: reference; AVG: RR 1.08; TCVC: RR 1.7	Age, gender, race, BMI, smoking, CAD, PVD, cancer, ability to walk, education level
Pastan et al.. 2002	ESRD Network 6	All prevalent haemodialysis patient in North Carolina, South Carolina and Georgia April 1998 (n=7,497)	At study start date	AVF: 7.3% AVG: 9.1% TCVC: 15.2% NTCVC: 16.8%	AVF: reference; AVG: OR 1; TCVC: OR: 1.4	Age, gender, race, diabetes, functional status, serum albumin, angina, CHF, MI, delivered time, blood flow, URR, time since onset of ESRD
Xue et al. 2003	Medicare	All Medicare incident haemodialysis patients >66y.o. commencing haemodialysis 1995-1997 (n=66,595)	At time of first dialysis	1 year mortality: AVF: 24.9% AVG 28.1% CVC: 41.5%	AVF: reference; AVG: RR 1.16; TCVC: RR 1.7	Age, gender, race, diabetes, initial access type, BMI, days from first access placement to initial dialysis date, albumin and creatinine
Polkinghorne et al. 2004	ANZDATA	All adult patients starting haemodialysis in Australia and New Zealand 1999-2002 (n=3,749)	At time of first ANZDATA study	Deaths per 1,000 access days: AVF: 86 AVG: 146 CVC: 261	AVF: reference; AVG: HR 1.39; CVC (by duration of dialysis): <60 days: HR: 2.53; 60-120 days: HR: 1.66; >120 days: HR: 2.77	Age, gender, late referral, PVD, CAD, PRD, smoking, hypertension, lung disease, geographical location, year of entry
Astor et al. 2005	CHOICE study	Subpopulation of incident HD patients in the United States who were recruited for the CHOICE study (n=616)	Access treated as a time dependant variable	Annual mortality AVF: 11.7% AVG 14.2% CVC: 19.9%	AVF: reference; AVG: HR: 1.2; TCVC: HR: 1.5	Age, gender, race, PVD, cardiovascular disease, diabetes, index of coexisting disease, BMI, smoking, education, timing of referral to a nephrologist, insurance
Bradbury et al. 2007	DOPPS I and II	Selected incident HD patients in the United States , Europe, Japan, Australia, New Zealand and Canada 1996-2004 (n=4,802)	At time of first dialysis	1 year mortality: AVF: 11.0% AVG 11.8% CVC: 19.9%	AVF: reference; AVG: HR: 0.97; TCVC: HR: 1.49	Age, gender, race, BMI, PRD, comorbid conditions, albumin, calcium, haemoglobin, phosphate, pre-ESRD nephrology care
Pisoni et al. 2009	DOPPS I and II	Selected prevalent HD patients in the United States , Europe, Japan, Australia, New Zealand and Canada 1996-2004 (n=3,786)	At date of study sample	NR	AVF: reference; AVG: RR: 01.15; TCVC: RR: 1.32	Age, gender, race, BMI, PRD, comorbid conditions, albumin, calcium, haemoglobin, phosphate, pre-ESRD nephrology care, dialysis centre
Grubbs et al,.2013	USRDS	Incident haemodialysis patients in the United States aged 67-90 years 2005-2007	At time of first dialysis	NR	AVF: reference; AVG: HR: 1.2; TCVC: HR: 1.95	Age, gender, health status, functional health status, place of residence
DeSilva et al. 2013	USRDS Medicare	Selected incident haemodialysis patients in the United States aged ≥ 67y.o. (n=115,425	At time of first dialysis	NR	AVF: reference; AVG: HR: 1.05; TCVC: HR: 1.77	Age (stratified), gender, race, diabetes, initial access type, BMI, CAD, PVD, PRD
Hicsk et al. 2015	USRDS	All prevalent haemodialysis patients in the United States 2006-2010 (n=507,791)	At time of first dialysis	NR	TCVC reference; AVG: HR: 0.83; AVF: HR:0.63 Age 18-48y.o.: TCVC reference; AVG: HR: 0.92; AVF: HR:0.53 Age 49-89y.o. TCVC reference; AVG: HR: 0.81; AVF: HR:0.63 Age >89y.o.: TCVC reference; AVG: HR: 1.24; AVF: HR:0.76	Age (stratified), gender, race, diabetes, initial access type, BMI, comorbidities

Table 1.5: Summary of Registry Data comparing mortality on dialysis between AVF, AVG and TCVC.

1.8.1.3. The evidence in context

Many of the more recent registry studies acknowledge the significance and implications of an aged, co-morbid dialysis population on vascular access choice. The conclusions of these latter series differ with regards to the role of AVF. For example, DeSilva and colleagues (2013) demonstrated no survival benefit of AVF over AVG in incident patients over 67 years old (HR 1.05) and several authors have actually shown superior patency of AVGs in the first 18 months after insertion (Chan et al. 2007; Moist et al. 2012). Such observations have led some to advocate for an approach of preferential graft placement in those patients with a life expectancy of less than 2 years on dialysis (Moist et al. 2012; Lee et al. 2005).

Contrary to widely held belief, the 1-year cumulative patency is actually comparable for AVF and AVG, with the caveat that grafts need additional interventions to maintain patency (Allon, 2007; Allon & Robbin, 2002). After exclusion of primary AVF failures, the perceived improved access survival of AVF over AVG is nullified, with comparable patencies for both AVF and AVG out to 10 years (Lee et al. 2006; Allon & Lok, 201; Lok & Foley, 2013; Lok et al. 2013) (Figure 1.15). Rosas and colleagues (2012) found a strategy of AVF primacy to be cost-effective over prosthetic only if the AVF maturation rate was >69%. A recent systematic review found the pooled AVF maturation rate in contemporaneous studies to be only 59% (Al-Jaisji, 2013).

Perhaps patency is the wrong end-point with which to compare access modalities altogether? AVG are associated with a less frequent need for early intervention (Roy-Chaudhury et al. 2012) and earlier catheter removal than AVF (Leake et al. 2015). In a recent retrospective series, Disbrow and colleagues (2013, pp.680) question: 'Is a reappraisal of the Fistula First Initiative indicated?' after finding that in patients dialysing via a catheter at time of definitive access placement (AVF or AVG), the maturation time, risk of non-maturation and number of interventions required to achieve a functioning AVF negated its potential benefits. The authors suggest that the aim of definitive vascular access should be to minimise the number of catheter-dependent days.

Finally, interpretation of the literature must be undertaken within the context of local resources and practice. For example, Kumbar et al. (2012) concluded that, with appropriate surveillance, AVGs have similar long-term primary-assisted patency to AVFs. Even TCVCs, with appropriate care and maintenance, have been shown to have excellent outcomes in the right setting. The West London group recently published enviable catheter

outcomes with 1-year patency rates of 76% and a bacteraemia rate of 0.34 per 1,000 catheter days (Power et al. 2011) (lower than that quoted for many studies of AVF) again illustrating the role of a "horses for courses" approach to vascular access.

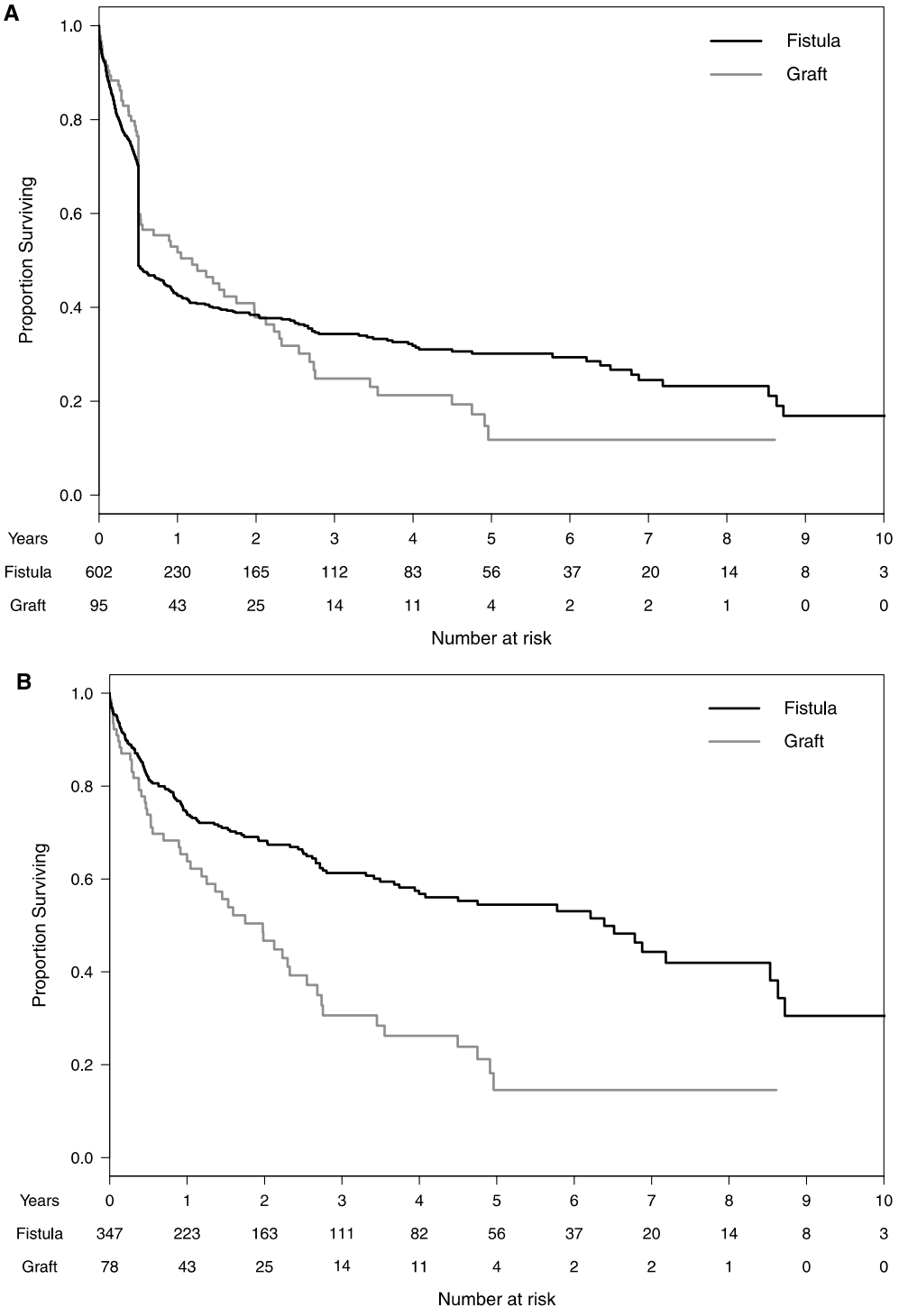


Figure 1.15: Survival curves of cumulative access patency of AVF and AVG in haemodialysis patients with forearm access. A. AVF vs. AVG after including primary failures. B. AVF vs. AVG excluding primary failures. Reproduced with permission from The Clinical Journal of the American Society of Nephrology (Lok et al. 2013)**.**

1.8.2. Are arteriovenous fistulae right for everyone?

As previously discussed, the dialysis population is changing. Elderly, diabetic patients have poor AVF outcomes, shorter survival on HD and increased risk associated with access creation (Scottish Renal Registry, 2015; Lok et al. 2005; Miller et al. 1999). The utility and benefit of a functioning AVF must be weighed against the futility and morbidity associated with multiple failed attempts at access creation. Whilst a functioning AVF may well be preferable to a functioning AVG, a non-functioning AVF isn't (Allon, 2007). Three factors need to be taken into account when considering whether "Fistula First" is really the right approach:

1. The likelihood of successful AVF maturation.
2. The morbidity associated with attempted AVF creation.
3. The benefit that is likely to be gained from having AVF creation (i.e. anticipated survival on dialysis or likelihood of needing dialysis).

Access planning requires an understanding and balance of these factors.

1.8.2.1. Balancing the risks and benefits of AVF creation (likelihood of maturation versus morbidity)

The likelihood of successful maturation must be balanced against the morbidity associated with AVF creation or, perhaps even more importantly, the morbidity of failed AVF creation. An elderly and increasingly comorbid dialysis population means that the 10% FTM rate quoted a decade ago is obsolete and now approaches 50% (Drew & Lok, 2014). Despite a 2-3-fold increase in AVF and AVG creation noted in the most recent Dialysis Outcomes and Practice Patterns Study (DOPPS) study, initial feedback indicates that this does not appear to have translated into more usable accesses (Pisoni et al. 2015)

AVF created in obese patients are less likely to be successfully cannulated, with the patient often subjected to multiple revisional and superficialisation procedures in an attempt to achieve functional patency (Evans et al. 2015; Chan et al. 2008). Advancing age, coronary artery disease, peripheral vascular disease and diabetes are all associated with increased chance of FTM (Lin et al. 1998; Lok et al. 2006; McGrogan et al. 2015a). Lok and colleagues (2006) found advancing age to confer a 2-fold greater chance of non-maturation. Lazarides and colleagues (2007) concluded from their meta-analysis that the

non-maturation rate of RCF in the elderly was so high, that distal AVF should not be considered in those >70years. Similarly a recent meta-analysis found small (<2mm) vessels, low intra-operative arterial blood flow and late referral for access creation were also associated with non-maturation (Smith et al. 2012). However, despite multiple predictive tools, it remains very difficult to acutely predict whether an individual fistula will mature (McGrogan,et al. 2015b).

Diabetics, especially women, have small, diseased arteries. (Chen & Moe, 2003) This is associated, not only with a high primary failure rate of autologous access (Jankovic et al. 2015), but also a higher than average risk of steal syndrome (Malik et al. 2008). The balance of risk-benefit in this patient cohort in therefore altered. Furthermore, the median survival of a 65 year-old diabetic commencing on dialysis is only 1.6 years (Scottish Renal Registry, 2013), leading some to question the value of AVF in this patient cohort (Lee et al. 2007).

AVF creation is not a benign procedure: 5-10% of patients will develop steal syndrome (Malik et al. 2008); high output cardiac failure is a recognised complication (Wasse et al. 2007); severe chronic neuropathic pain occurs in 3.2% whether or not the fistula ever successfully matures (Aitken et al. 2013). Given that most patients who undergo AVF creation have not yet started dialysis and the procedure is being performed prophylactically, the need to minimise unnecessary complications is paramount (O'Hare et al. 2007).

Perhaps more significant than complications (and commonly overlooked), is the burden of failed or suboptimal maturation. Less than half of AVF created are suitable to use for HD five months after creation (Dember et al. 2008). The rest either fail early necessitating a second or subsequent surgery with diminishing returns from each attempt (Aitken et al. 2014a; Gibyeli Genek et al. 2015; Lok et al. 2006), or require multiple interventions e.g. balloon assisted maturation to promote development (Roy-Chaudhury et al. 2012a). Multiple interventions are associated with the need for repeated hospitalisation and negatively impact on QoL (Afsar et al. 2012). Again, many of these interventions are performed on patients not yet on dialysis, increasing the burden of disease in an otherwise relatively asymptomatic cohort of patients. Furthermore, surgical fatigue can also result in reluctance for second or subsequent attempts at access creation, which are perceived to be futile (Gibyeli Genek et al. 2015). The costs associated with an unused fistula are much higher than perceived (Malas et al. 2015). Some authors advocate AVG as an alternative to

multiple failed AVF attempts to obviate this problem (Allon & Lok, 2010; O'Hare et al. 2010).

1.8.2.2. Predicting the decline to end-stage and survival on dialysis: the benefit of fistula creation

Aside from the access itself, two major factors influence the benefit, or otherwise, that a person might obtain from an AVF:

1. The likelihood of that patient ever requiring dialysis.
2. The anticipated life expectancy on dialysis.

These factors are heavily influenced by co-morbidity, nature of the primary renal disease and age, therefore they are constantly changing with the evolving demographic of the ESRD population (Toussaint et al. 2015).

AVF creation in the pre-dialysis setting differs from any other any other preventative or preparatory healthcare intervention (O'Hare et al. 2010). Unlike vaccination it does not confer public heath benefits, nor is it a potentially life-saving procedure akin to elective abdominal aortic aneurysm repair. More like purchasing a life insurance policy, the benefits of AVF placement are only accrued if the event (i.e. dialysis initiation) actually occurs (O'Hare et al. 2010). Prior to this, the burden and morbidity associated with attempting to achieve functioning vascular access is incurred without any tangible gain.

One of the most challenging aspects of pre-emptive access placement is determining when, or if, a patient is likely to need dialysis. Vascular access planning guidelines fall into two categories: those which suggest that an absolute eGFR should be used for referral for access creation e.g. a creatinine clearance <15-20ml/min (Canadian Society of Nephrology, 2006) and those which advocate that time to need for dialysis should be predicted and utilised to determine referral i.e. within 6 months of anticipated need for dialysis (NKF-KDOQI, 2006). They all assume linearity of progression in renal function decline (Rosansky, 2012). In reality, prediction of the trajectory of renal function decline is poorly understood and very difficult to forecast.

O'Hare and colleagues (2012) identified four different patterns of decline to end-stage. The majority of patients had a persistently low level of eGFR <30mL/min/1.73m^2 (mean eGFR

slope 7.7 ± 4.7 mL/min/1.73m^2/ year). However 9.5% had accelerated loss from eGFR >60 mL/min/1.73m^2 (mean eGFR slope 32.3 ± +/-13.4 mL/min/1.73m^2/year) and 3.1% demonstrated catastrophic loss (Figure 1.16), highlighting the difficulties both in predicting when dialysis might be required and in applying a fixed cut-off for any intervention (Schell & O'Hare, 2013). Nearly half of patients with CKD stage V will have stable renal function at 2 years follow-up (O'Hare et al. 2012) and over a quarter of elderly patients (average age 75 years) with stage IV CKD showed no decline in eGFR after 10 years follow-up (Eriksen & Ingebretsen, 2006), making many pre-emptive AVF creation attempts in these patients extraneous.

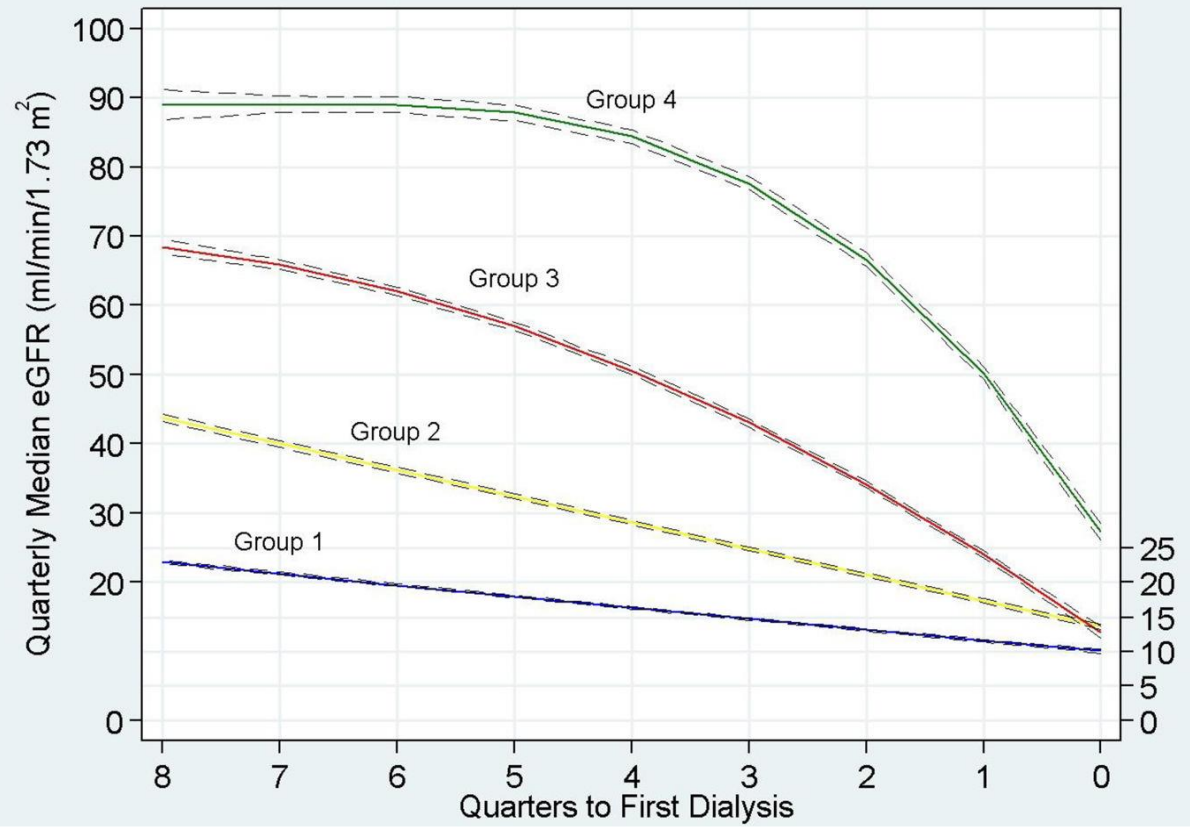


Figure 1.16: Estimated glomerular filtration rate (eGFR) trajectories in patients approaching end stage renal disease.
Trajectory group 1 (63%): persistently low eGFR (<30 mL/min/1.73m^2);
Trajectory group 2 (25%): progressive loss from baseline 30-59 mL/min/1.73m^2;
Trajectory group 3 (9%): accelerated loss in eGFR from levels >60 mL/min/1.73m^2;
Trajectory group 4 (3.1%): catastrophic loss from levels >60 mL/min/1.73m^2 within 6 months or less.
Reproduced with permission from National Institute of Health. (O'Hare et al. 2012)

It is well recognised that elderly patients will have a slower rate of decline in renal function (Van Pottelbergh et al. 2012; Vachharajani, 2011; O'Hare et al. 2007) and a shorter life expectancy (Kurella et al. 2007), therefore the potential for unnecessary vascular access procedures in this cohort is particularly salient. O'Hare et al. (2007)

evaluated a US Department of Veterans Affairs population and created a hypothetical model in which all patients with advanced CKD were assumed to received vascular access surgery. They used their model to calculate the proportion of patients in whom AVF creation would be necessary (the patient initiated dialysis within 2 years) or unnecessary (the patient died prior to starting dialysis or remained alive and dialysis free). They observed that in patients >85 years with eGFR <15ml/min/1.73m^2 only 25% of patients started dialysis within 6 months and only 1 in 3 started within a year. The authors extrapolated this data to calculate that among 85 year old patients referred for access surgery at an eGFR <15ml/min/1.73m^{2,}, with predicted 6 months survival, three accesses have to be created for every one used for dialysis (O'Hare et al. 2007).

The rate of decline of renal function and likelihood of needing dialysis also needs to be balanced against the likelihood of dying prior to ever requiring dialysis. Figure 1.17 highlights this problem, demonstrating the relative frequency by which ESRD exceeds that of death by patient age. For example, the likelihood that a 70 year-old man will survive to commence dialysis does not exceed the risk that he will die from other causes until his eGFR falls below 15mL/min/1.73m^2 (O'Hare et al. 2010).

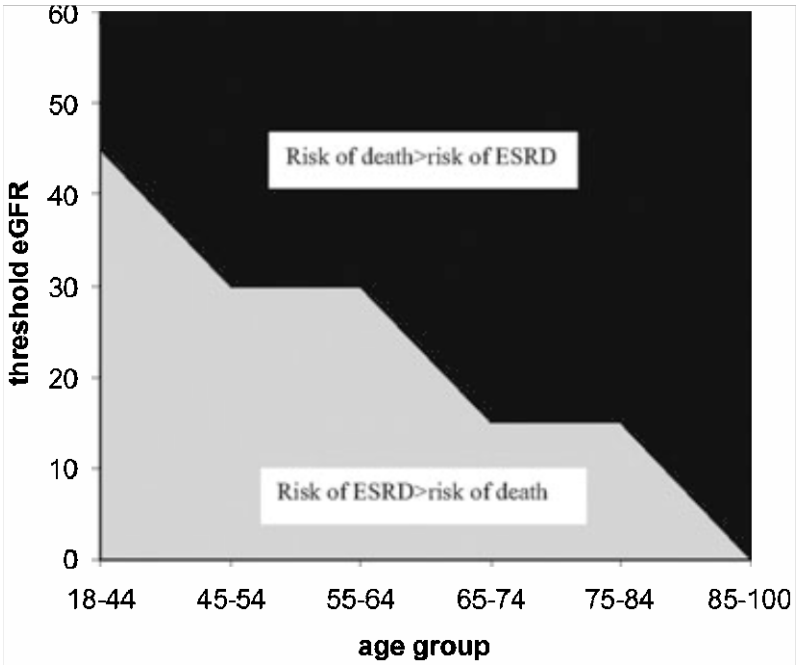


Figure 1.17: Graphical representation of the eGFR at which the relative frequency of ESRD exceeds that of death by patient age. Reproduced with permission from John Wiley & Sons Ltd. (O'Hare et al. 2010).

More than one percent of patients will die within 30 days of access creation (Jorna et al. 2016) and almost 30% of patients >74 years do not survive 12 months after AVF creation (McGrogan et al. 2014). Nearly two-thirds of patients over 80 years old die within 18 months of commencing on dialysis (Vacharanjani et al. 2014), with the median survival of patients aged 65-79 years at initiation of maintenance haemodialysis only 2 years (Kurella et al. 2007). There is however considerable heterogeneity and variation around this observation with an interquartile range of 8.3 months to more than 4 years (Kurella et al. 2007), which (like the prediction of decline in renal function) makes prediction of survival on HD difficult, with few good objective measures to help prognosticate. Moss and colleague (2008) describe the utility of the "surprise question" i.e. 'would I be surprised if this patient died in the next year?' for predicting short-term mortality. In practice, this subjective measure is likely to prove just as valid as more complex algorithms in determining where the futility of unnecessary access procedures is likely to lie (McGrogan et al. 2014).

Approximately 30% of patients remain pre-dialysis one year following creation of their AVF (Morsy et al. 2011) and a recent Canadian study found that 9% of incident patients who had AVF created died before the AVF was ever used (median follow-up 8 months) (Oliver et al. 2012). Recently several authors have utilised analytical models in an attempt to minimise gratuitous AVF creation. Shechter and colleagues (2014) used a Markov model to calculate that referral 15 months prior to initiation of dialysis would result in 34% of patients starting dialysis via a TCVC with 14% unnecessary AVF, while referral at eGFR threshold of <20mL/min/1.73m^2 would result in 38% incident TCVCs and 20% unnecessary AVFs. Similarly, Hiremath and colleagues (2011) found a policy of watchful waiting until dialysis started was associated with better life expectancy (66.6 vs. 65.9 months) and quality adjusted life expectancy (38.9 vs. 38.5 quality adjusted life months) than immediate AVF creation in all patients with CKD stage IV. Data from our own centre demonstrates that one-third of brachiobasilic fistulae are never used for dialysis (Hameed et al. 2016), a finding that needs to be considered in the context of the morbidity (rehospitalisation and reintervention to achieve patency particularly in BBF). Some authors would advocate that, in this patient cohort with no simple autologous option, an AVG at the time a patient requires to start HD is favourable to pre-emptive AVF creation (Allon & Lok, 2010; Moist et al. 2012; Lok, 2007).

1.8.2.3. Elderly patients

Recently published Italian vascular access guidelines acknowledge that, in the context of shorter life expectancy and slower decline to end-stage disease, elderly patients must be considered as a unique patient cohort (Lomonte et al. 2016). As a patient group they provide a useful example to highlight a number of the issues already described and the need to consider these factors in individualised vascular access planning.

Increasing age is associated with a higher chance of non-maturing fistula, with patients >65 years having a more than doubling of the chance of primary non-function (OR 2.23; 95% CI 1.25, 3.96) (Lok et al. 2006). A recent observational study found cumulative fistula survival at 12 months to be 68% in patients ≤70 years old compared to 39% in patients over the age of 70 (Olsha et al. 2015). Similarly in their meta-analysis, McGrogan and colleagues (2015a) found pooled 12-month primary and secondary patency rates in the elderly of 53.6% and 71.6% respectively. Vascular calcification, oxidative stresses and poor endothelial function limit the ability of vessels to vasodilate and are postulated to be responsible for the higher failure rate of AVF that is observed in the elderly (Moist et al. 2012) with distal radiocephalic fistulae most likely to fail (OR 1.52 at 12 months) (Lazarides et al. 2007).

Vascular access procedures and their complications represent an important cause of morbidity and mortality in the elderly haemodialysis population (Feldman et al. 1996). Age greater than 65 years has also been identified as a risk factor for dialysis-associated steal syndrome (Zamani et al. 2009), and elderly patients require more frequent endovascular interventions to assist in achieving and maintaining access patency (Lok et al. 2005). Furthermore, frailty and malnutrition often lead to thin skin that bruises and tears easily. Such “minor” complications and the morbidity associated with them are often not documented or reported in studies (Moist et al. 2012).

The median life expectancies for a 65 year old and an 80 year old patient commencing haemodialysis are 2.5 and 1.3 years respectively (Cherukuri et al. 2016). In the United States, a quarter of octogenarians starting dialysis never return to independent living (Vacharanjani et al. 2014) and commencing dialysis is associated with significant decline in functional status such that only 13% of elderly patients starting on dialysis will have a preserved functional state after 1 year (Combs & Davison, 2015). More than a third of elderly patients who commence dialysis opt to discontinue within the first six months

(Rosansky, 2012). In patients over the age of 70, survival is comparable with haemodialysis and conservative care (Lazenby et al. 2016).

As earlier described, many elderly patients with significant reduction in their eGFR will never go on to initiate dialysis, therefore efforts to secure a functioning fistula prior to commencing dialysis may result in harm of a procedure from which they will never benefit (O'Hare et al. 2010; Schell & O'Hare, 2013; Oliver et al. 2012). A recent study found that, following AVF creation, up to two-thirds of elderly patients died before their fistula was ever used for dialysis (Richardson et al. 2009). Lee and colleagues (2015) recently published a large cohort study of over 3,000 elderly patients (>70 years) with access placed in the predialysis stage. They found that 67% of patients with AVF and 71% of patients with AVG commenced dialysis in the two year follow up period, however only half of these patients started dialysis via a functioning AVF/ AVG. Catheter dependence was more common in patients receiving predialysis AVF than AVG (46.0% vs. 28.5%; P<0.001) (Lee et al. 2015). The rate of decline in renal function needs to be balanced against life expectancy and quality of life. Conservative care and palliation should always be considered as a treatment option in older patients (Combs & Davison, 2015).

An individualised approach to vascular access is essential (Moist et al. 2012). Perhaps more than any other patient cohort, the heterogeneity that exists amongst life expectancy and functional status in the elderly, highlights the need for tailored decision-making (Cherukuri et al. 2016). For example, a fistula may be most appropriate for an elderly patient with minimal co-morbidity who is seen in the pre-dialysis clinic with anticipated dialysis start six months in the future, whilst an AVG (or TCVC) may be more appropriate in an elderly patient with multiple comorbidities and life expectancy <2 years (Moist et al. 2010).

There has been considerable debate in recent literature around the issue of whether AVF or AVG should be favoured in the elderly (Moist et al. 2012; Tordoir et al. 2015; Allon & Lok, 2010). Certainly, the initial operative procedure to create an AVF is simpler, associated with a shorter hospital stay and minimal morbidity (Swindlehurst et al. 2011). Despite poorer maturation rates, many elderly patients do still benefit from receiving dialysis via an AVF. In the UK more patients >60 years than <60 years start dialysis via an AVF (UK Renal Registry, 2016) (though this is likely to be the result of a slower rate of decline in function, rather than better AVF outcomes per se). And it must be remembered that the infective complications of TCVCs are most marked in the elderly and co-morbid.

Most European clinicians would still favour trying to create an AVF in a co-morbid 75 year old rather than seeking alternative access (van der Veer et al. 2015).

Conversely, elderly patients are likely to have a short life expectancy and unpredictable start to dialysis, factors that may favour the use of an AVG over AVF. A recent large observational study has demonstrated comparable survival from AVF and AVG in patients aged over 67 years (DeSilva et al. 2013). Survival was found to be comparable for all access types (including TCVC) in patients >80 years old. Likewise, Tamura and colleagues (2011) estimated the remaining lifetime absolute risk reduction in vascular access bacteraemia attributable to the use of preferred versus non-preferred access e.g. AVF vs. AVG and AVG vs. TCVC for patients with different life expectancies. AVF conferred a very modest risk reduction over AVG especially in the elderly e.g. in patients >85 years with life expectancy in the 25th percentile, more than 200 AVF would be required to prevent one episode of graft related bacteraemia. Similarly, whilst the number of AVGs required to prevent an episode of catheter-related bacteraemia was much less, the relative benefit of AVG versus TCVC also declines with age and life expectancy (Cherukuri et al. 2016). Accounting for primary failures, the cumulative patency of AVG and AVF are comparable for the first 18 months (Xue et al. 2003; Astor et al. 2005; Lee et al. 2007), therefore many authors now advocate AVG in elderly patients with a life expectancy less than 2 years to avoid the need for a TCVC (Allon & Lok, 2010; Lok, 2007; Moist et al. 2012).

Autologous AVF take longer to mature in the elderly (Viedma et al. 2005; Ravani et al. 2013b) with delayed maturation having the inadvertent consequence of prolonged catheter use. DeSilva and colleagues (2013) found that nearly half of elderly patients who had planned to start dialysis via an AVF ended up starting with a TCVC, compared to only 25% of patients who had planned start via an AVG. Given that infective complications of line use are more significant in frail, elderly patients (Thomson et al. 2007), Moist and colleagues (2012, pp.647) reflect that:

> 'the need for prolonged catheter use during AVF maturation may be considered harm if the patient will not live long enough to reap the benefits'

With the survival benefits of autologous access deferred, many now question the benefit of AVF in those with a short life expectancy instead advocating a policy of "watch and wait"

to see if dialysis is actually going to be required and then consider AVG as an alternative to AVF as first line vascular access (Drew & Lok, 2014; Tordoir et al. 2015).

1.8.3. An individualised approach

Recent literature (and clinical practice) reflects a gradual shift away from "Fistula First" towards a "patient first" approach to vascular access (Moist et al. 2012). There is increasing recognition of the need for an individualised approach, rather than a disease-based model of vascular access provision (Cherukuri et al. 2016; O'Hare et al. 2010; Bowling & O'Hare, 2012). The relative advantages and disadvantages of various access types are well documented at a population level, however the benefits and harms will also vary between individuals as a function of their need for dialysis and life expectancy (Cherukuri et al. 2016). Moist and colleagues (2014, pp.645) highlight that:

> 'Quality improvement initiatives in end-stage kidney disease care advocate for quality benchmarks, but fail to identify patients who may not benefit from 'standard of care' applicable to a 'standard patient''

1.9. SO WHAT IS "BEST PRACTICE" FOR VASCULAR ACCESS?

An inherent tension exists between best practice guidelines and the optimal care of an individual patient (Drew & Lok, 2014). Benchmarking and targets can fail to meet the unique needs of a specific individual. The "standard of care" can only be applied to a standardised patient and fails to take into account the significant heterogeneity within the ESRD population. A fistula primacy at all costs approach will inevitably lead to inadvertent surgical fatigue and prolonged catheter dependence (Lok, 2007). As such there are calls for the Fistula First Breakthrough Initiative target of 65% of patients with AVF to be revised to achieving 65% of patients with *functioning* AVF (Lok, 2007).
Patient-centred care must therefore be considered "best practice" for vascular access provision (Drew & Lok, 2014). A "one size fits all" approach is not effective (Lok, 2007). Personalised and bespoke vascular access planning is required to meet the individual's needs (Drew & Lok, 2014). It is essential that the focus is placed on the patient, not the access and that a "package of care", rather than a single intervention, is delivered (Lok et al. 2012). Lee and Allon (2012, pp.6) highlight that:

> 'clinicians should exercise their clinical judgement, experience and interpretation of

the literature….(rather than following) mindlessly rigid guidelines' .

The aim is to achieve the right access, for the right patient, at the right time (Lok & Foley, 2013).

A number of authors have developed predictive models in an attempt to inform clinical practice and determine which patients should have autologous access placed (Lok et al. 2006; Drew & Lok, 2014; Lee & Allon, 2012).

In their Risk Equation Determining Unsuccessful Cannulation Events and Failure to Maturation (REDUCE-FTM I) study, Lok and colleagues (2006) evaluated patient characteristics associated with AVF failure to mature, developing and validating a predictive scoring system. Age ≥ 65years, peripheral vascular disease, coronary artery disease and non-White ethic origin were identified as risk factors for FTM and a score (-3 to +3) assigned according to the presence or absence of each. This score is then used to predict a risk category of FTM, from which the authors extrapolate clinical advice for access planning. For example, a 40 year-old white male with no other risk factors confers a score of 0 and low risk (<25%) of FTM, so the authors advise clinical assessment ± pre-operative vein mapping and AVF creation. Conversely, a 70 year-old AfroCaribbean man with coronary heart disease scores 7.5 and is classified as very high risk (>70%) of FTM. The authors recommend consideration of another form of permanent access e.g. graft.

This model of Lok and colleagues (2006) has been heavily criticised in the literature (Beathard 2015; Lilly et al. 2012). In their study utilising a large US-administrative dataset, Lilly and colleagues (2012) failed to demonstrate the same risk stratification for FTM as did Lok, highlighting the importance of validating any predictive scoring system within the local population. Others criticise the inflexibility of such models and protocols. Beathard (2015) warns against excluding patients for autologous access creation based on the prescriptive instruction derived from demographic risk stratification alone, without surgical and radiological assessment of the vessels. It is crucial that any risk stratification scores for AVF maturation are exercised only as a guideline to inform practice rather than as a substitute to clinical judgment (Lee & Allon, 2012).

Latterly there has been recognition of the importance of assessing the needs of the whole patient rather than just the likelihood of attaining a functioning vascular access. Several authors have devised a decision tree to inform clinicians on the choice between AVF or

AVG (Allon & Robbin, 2002; Lee et al. 2005; Drew & Lok, 2014). The likelihood of fistula success is balanced against the perceived benefit to the patient of AVF creation and a recommendation made as to whether it is worth attempting autologous access or whether the patient would be better off with an AVG. Lee and colleagues (2012) propose a model that takes into account time on dialysis, predicted life expectancy and whether or not the patient has had prior failed attempts at AVF creation (Figure 1.18). Based on the likelihood of successful maturation, the authors then advise AVF or AVG as the most appropriate access for the individual patient (Lee & Allon, 2012). Drew and Lok (2014) recently proposed a similar, but somewhat simpler, model (Figure 1.19) derived from three fundamental questions: Is the patient on haemodialysis? What is the likelihood of long-term survival? And does the patient's age, co-morbidities etc. make them a good candidate for AVF creation? Their model favours AVG over AVF for all but the optimal fistula candidate and advocates adopting a watch-and wait approach to pre-dialysis patients with poor life expectancy is an attempt to avoid unnecessary surgeries in these patients. Whilst, individualised care must take precedent over any predictive modelling (Lok & Foley, 2013) and no patient should be deprived the opportunity for autologous access based on predictive modeling alone (Beathard, 2015), models such as those of Drew and Lok (2014) highlight an increasing trend towards patient-centred rather than access-focussed care (Drew & Lok, 2014; Lok & Foley, 2013; Allon & Robbin, 2002).

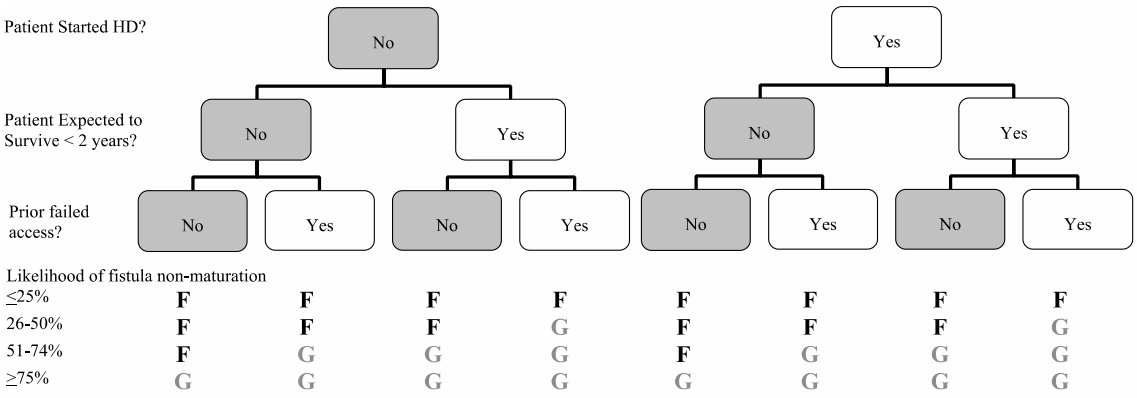


Figure 1.18: Algorithm to assist in the most appropriate choice of vascular access for an individual patient. The protocol requires nephrologist and access surgeon to consider three important clinical factors: timing of access surgery relative to initiation of dialysis; life-expectancy and prior failed access attempts. This information is used to determine the likelihood of fistula maturation and therefore the most appropriate access for the patient: fistula (F) or graft (G). Reproduced with permission from John Wiley and Sons Ltd. (Lee & Allon, 2012)**.**

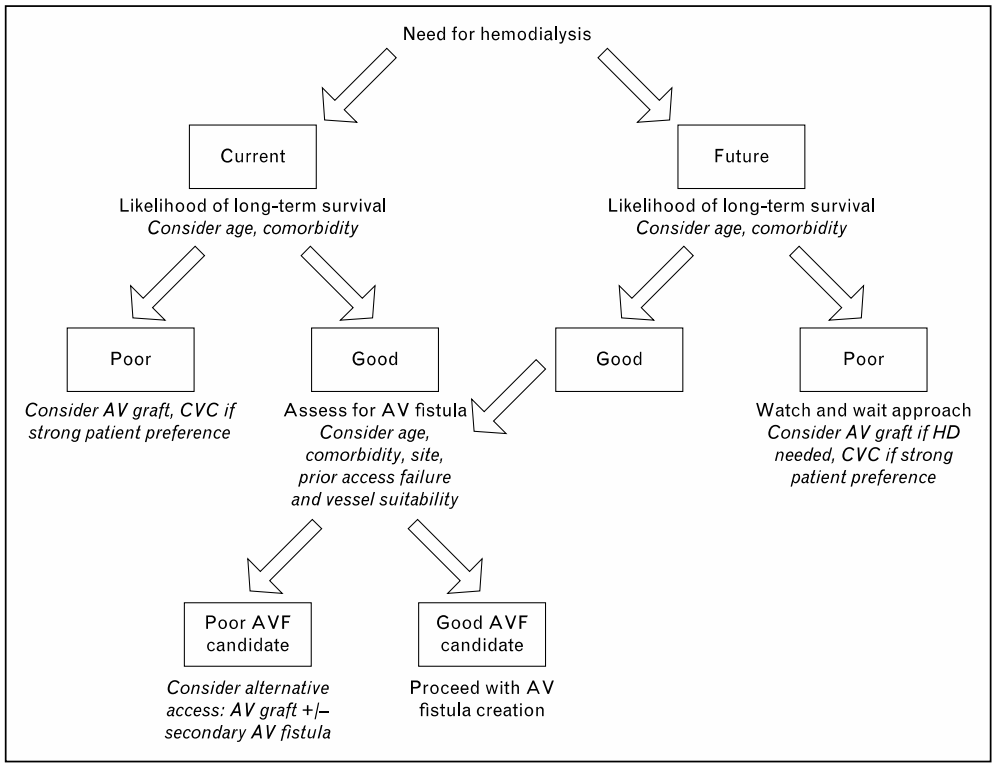


Figure 1.19: Flow diagram outlining a strategy for choosing the optimal vascular access for an individual patient. Reproduced with permission from Lippincott, Williams & Wilkins (Drew & Lok, 2014)**.**

The provision of individualised patient-focussed care necessitates input from an extended multidisciplinary team. It is vitally important that every member of the team is aware of the bigger picture and is focussed on a achieving a 'lifelong ultilisation strategy' (Lok & Davidson, 2012, pp.532) for vascular access. This forward-thinking begins in pre-dialysis education with vessel preservation and TCVC avoidance to prevent central vein stenosis and surgical fatigue in the future, and ends with a dialysis exit strategy e.g. transplantation, which must be the ultimate aim wherever possible. It is the success of the strategy rather than a single vascular access procedure which should be the goal of the vascular access service (Drew & Lok, 2014). Co-operation between healthcare professionals and an integration of the various elements of vascular access care is essential to ensure than there is unity between the 'prescribers of care (nephrologists), providers of care (access surgeons) and providers of cure (transplant surgeons)'(Kingsmore, 2016).

1.10. RATIONALE

Vascular access is the 'key modifiable risk factor' (National Kidney Care Vascular Access Report, 2012, pp.6) for mortality in patients on HD. Despite this, it remains a 'Cinderella' speciality (Konner, 1999, pp.2094) and is often overlooked in service development and

provision of care for patients with ESRD. Good quality research into vascular access is also limited. Fewer than 3,000 articles have been published in the past 15 years and, of these, only 59 studies were randomised controlled trials (RCTs) (Kian & Asif, 2010).

Despite the relative successes of strategies such as "Fistula First" and the best practice target in England and Wales, and the simultaneous improvement in rates of prevalent autologous access, there has been no associated improvement in incident vascular access rates (Fistula First Breakthrough Initiative, 2013; Sharif & Baboolal, 2011; Department of Health, 2010; Pisoni et al. 2015; Ethier et al. 2008).The importance "getting it right from the start" cannot be overemphasised (Lok, 2007).

Patients who start dialysis via a line are more likely to stay on a line (Weber et al. 2009; UK Renal Registry, 2016). Data from the UK Renal Registry (2014) indicate that 59.8% of patients starting on a TCVC remain dialysing via a TCVC at 3 months. Similar figures from the National Kidney Care Vascular Access Report (2012) suggest that this figure could be as high as 90% (Table 1.6). DOPPS data indicate that >40% will remain with their TCVC for more than a year (Ethier et al. 2008; Moist et al. 2012). The presence of a CVC at the time of dialysis commencing is associated with poorer AVF maturation (Brunori et al. 2005). Similarly, although underpowered for the secondary end-point, Weber and colleagues (2009) demonstrated a trend towards improved patency in AVF created when the patient was pre-dialysis. Patient refusal of AVF is also higher in those who had previously experienced dialysis via a line (Nica et al. 2013). The legacy of poor access planning and inappropriate line usage in the early days of HD follows a patient for life. Central venous stenosis can occur with just a few days of line exposure and has significant impact on both positioning and longevity of future vascular access (Agarwal et al. 2007; Moist et al. 2012; Jackson et al. 2014). Finally, mortality amongst dialysis patients is highest in the first year after starting HD (UK Renal Registry, 2016; USRDS, 2014). Catheter-related infection (which peaks between 3 and 6 months after starting dialysis) is the principle cause of death (Ravani et al. 2013a; Thomson et al. 2010; Collins et al. 2009). The risk of early sepsis episodes is higher in patients with delayed autologous access creation (>4 months after starting HD), independant of catheter use (Oliver et al. 2004). Likewise, in their study of 510,000 patients, Malas and colleagues (2015) found that patients commencing dialysis via an AVF had a 35% lower mortality than those starting via a TCVC (even accounting for confounding factors). Optimisation of incident vascular access is therefore vital, both to improve early patient survival, but also to reduce long-term morbidity and the exhaustion of access options for the future.

Table 1.6: Comparison of vascular access at first dialysis and vascular access at 3 months after commencing haemodialysis. Reproduced with permission from the Health and Social Care Information Centre. (National Kidney Care Vascular Access Report, 2012).

	Access at 3 months								
Access at first dialysis	**AVF**	**AVG**	**TCVC**	**NTCVC**	**PD catheter**	**Death within 3 months**	**Transplant**	**No data**	***Total***
AVF	748	1	27	3	2	28	3	29	*841*
AVG		13	2		1				*16*
TCVC	76	5	595	1	30	55	6	41	*809*
NTCVC	34	5	246	19	19	43	2	44	*412*
PD catheter	4		4	1	148	4	5	2	*168*
No data			4			2		5	*11*
Total	**862**	**24**	**878**	**24**	**200**	**132**	**16**	**121**	***2257***

Within this thesis, I will focus on incident patients and evaluate methods for improving vascular access within the incident patient cohort. I will take a multifaceted approach focusing on five main themes:

1. Line complications and central vein stenosis: avoiding problems for the future.
2. Predicting maturation: is the incident patient different?
3. Promoting maturation: are there strategies to optimise maturation?
4. Right access, right patient: how do you provide individualised, patient-centred care?
5. 'Crashlanders': how do you manage patients who present without prior warning?

The emphasis of this work is directed towards finding pragmatic, patient-focussed solutions to clinically relevant problems.

TUNNELLED CENTRAL VENOUS CATHETERS (TCVCs): THE EXTENT OF THE PROBLEM

2.1. INTRODUCTION

It is widely accepted that AVFs are the optimal method of achieving vascular access for haemodialysis for most patients, with fewer complications and lower mortality than TCVCs (UK Renal Registry, 2016.; McGee & Gould, 2009). As previously discussed, the use of TCVCs is associated with a six-fold increased risk of systemic sepsis and three times increased risk of all cause mortality compared to AVF, in addition to the long-term morbidity from central vein stenosis (Thomson et al. 2007; Bray et al. 2012). Given that the complications of vascular access account for 20% of all hospital admissions and one-third of in-patient bed usage for patients with ESRD (USRDS, 2007), AVFs are also a more cost-effective means of providing haemodialysis (Leermakers et al. 2013). For these reasons the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Vascular Access (NKF-KDOQI, 2006) in the USA and The Renal Association (2011) in the UK advise that AVF should be the access modality of choice wherever possible.

The Fistula First Breakthrough Initiative has been very effective at improving AVF usage in the United States (Massoud et al. 2006).The financially incentivized, multifaceted approach to encouraging optimal vascular access has resulted in a steady, incremental increase in the use of AVF (from 32.2% in 2003 to 60.4% in 2012) (Lynch et al. 2011a). The target of 66% of prevalent haemodialysis patients dialysing via an AVF is fast approaching.

In the UK, the Renal Association has suggested even more optimistic goals, advocating that 85% of prevalent and 65% of incident haemodialysis patients should be dialysing via an AVF (Fluck & Kumwenda, 2011). Recently the controversial best practice tariff in England and Wales has rekindled the vascular access debate and drive for definitive access this side of the Atlantic. The aim of Payment by Results (PbR) is to provide a rules-based framework that financially rewards efficiency and best practice (Sharif & Baboolal, 2011). Best practice tariffs were calculated based on 85% of prevalent haemodialysis occurring via an AVF or AVG by 2013/2014 (Department of Health, 2010). Healthcare trusts are financially recompensed for achieving these targets. Obviously this has heightened the

drive to achieve definitive vascular access, but many units have struggled to meet such stringent goals.

An increasingly elderly and comorbid dialysis population has led some to consider whether AVFs are in fact the best option for all patients. The peak age of prevalent haemodialysis patients in England and Wales is now 70-79 years, with the number of extreme elderly patients (>85 years old) on haemodialysis doubling in the past 5 years (UK Renal Registry, 2014). Life expectancy and quality of life may influence the optimal choice of vascular access (Latos, 2002). The Fistula First Breakthrough Initiative states that AVFs should be attempted first in all "suitable" dialysis patients. (Massoud et al. 2006) However, defining those suitable, or perhaps more importantly those unsuitable, for AVF is often difficult. It is important that national targets do not compromise individualised care and patient-centred vascular access solutions.

In 2010, despite national targets, only 75% of prevalent patients and 42% of incident patients were dialysing via autologous access (Scottish Renal Registry, 2013). Locally in the West of Scotland, prevalent AVF usage rates were even lower with significant variation between units (63-75%) (Scottish Renal Registry, 2013). We sought to embark on a multifaceted Quality Improvement (QI) project, of which the research studies described in this thesis were an integral part.

The study outlined in this chapter reflects the initial "fact-finding" element of the QI project, in which we attempted to characterise the scale of the problem, the causes of TCVC usage and to assess the impact of our first intervention (a surgically aggressive approach to definitive access creation).

2.2. METHODOLOGY

Approval for the study was obtained from the Clinical Effectiveness Department at the Western Infirmary, Glasgow. Formal ethics committee approval was not required for this service improvement project.

In November 2010, the Scottish Electronic Renal Patient Record (SERPR) was interrogated for all prevalent haemodialysis patients in the West of Scotland (n=636). SERPR is a computerised patient record system that allows prospective collection of data on all aspects of renal patients' illness (including dialysis status, dialysis parameters, vascular access, blood results). It can be searched as a database of audit purposes. The

volume of TCVC usage, reasons for line use and complications arising from TCVCs were recorded. Data pertaining to previous AVF and failed attempts at AVF creation were also obtained.

All patients dialysing via a TCVC were subsequently visited on haemodialysis by a clinician experienced in vascular access. Options for creation of definitive access in the form of AVF or AVG were explored. Over the subsequent year, aggressive operative attempts were made to achieve definitive vascular access in all patients who were fit and had a suitable anatomical option.

Patients were then visited 1 year later (November 2011) with re-evaluation of all prevalent haemodialysis patients (n=634). TCVC usage and reasons for this were again recorded. The fate of those patients dialysing via a TCVC in 2010 and all incident patients was evaluated.

Statistical analysis was undertaken using SPSS Statistics for Windows Version 19.0 (IBM Corp., Armonk, NY, USA). Continuous data are presented as mean (standard deviation (SD)) and categorical data are presented as median (interquartile range (IQR)). Otherwise results are presented as a percentage of the total population. Chi-squared test and paired sample t-test were used to compare outcomes between the two years. P-value <0.05 was significant.

2.3. RESULTS

2.3.1. Baseline demographics

The total number of patients on haemodialysis in the West of Scotland was similar in 2010 (n=636) and 2011 (n=634), with 267 new incident patients, 92 renal transplants and 177 deaths. There was no significant difference in the overall number of patients dialysing via a TCVC in 2010 (pre-intervention) compared to 2011 (post-intervention) (30.3% (n=193) vs. 31.7% (n=201) respectively; P=0.56). There was, however, a substantial flux and attrition of patients dialysing via a TCVC so that the majority of those on TCVC in 2011 were not those on TCVC in 2010 (Figure 2.1). Of the 267 incident patients, 125 (46.8%) began haemodialysis via an AVF; 108 patients (40.4%) commenced dialysis via a TCVC and 34 patients (12.7%) began haemodialysis via a temporary line.

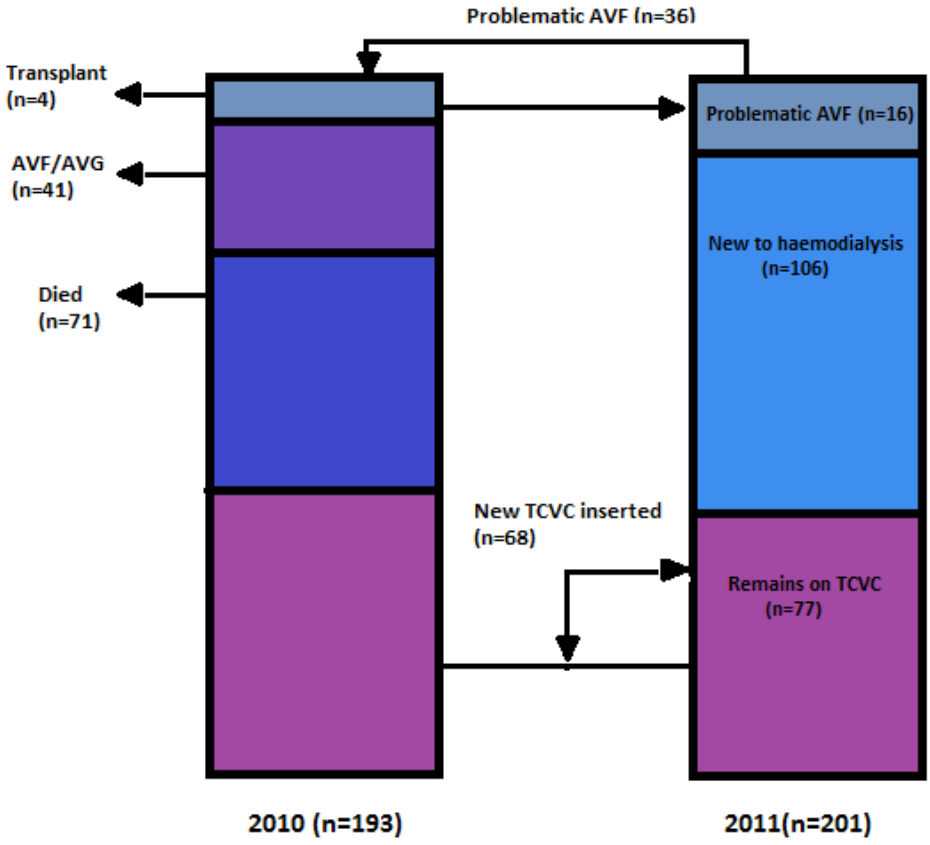


Figure 2.1: Fate of patients dialysing via a TCVC between 2010 and 2011 and reasons for TCVC usage in 2011

Table 2.1 highlights the demographics of the patients dialysing via TCVCs. The majority of patients were dialysing via internal jugular lines (Table 2.2). There was no significant difference in the mean number of previous TCVCs or AVF attempts per patient between years 2010 and 2011. However, following aggressive attempts at trying to achieve definitive vascular access, there were fewer patients dialysing via a TCVC who had never had an attempt at AVF creation (21.2% vs. 13.9%; P=0.02) (Table 2.3).

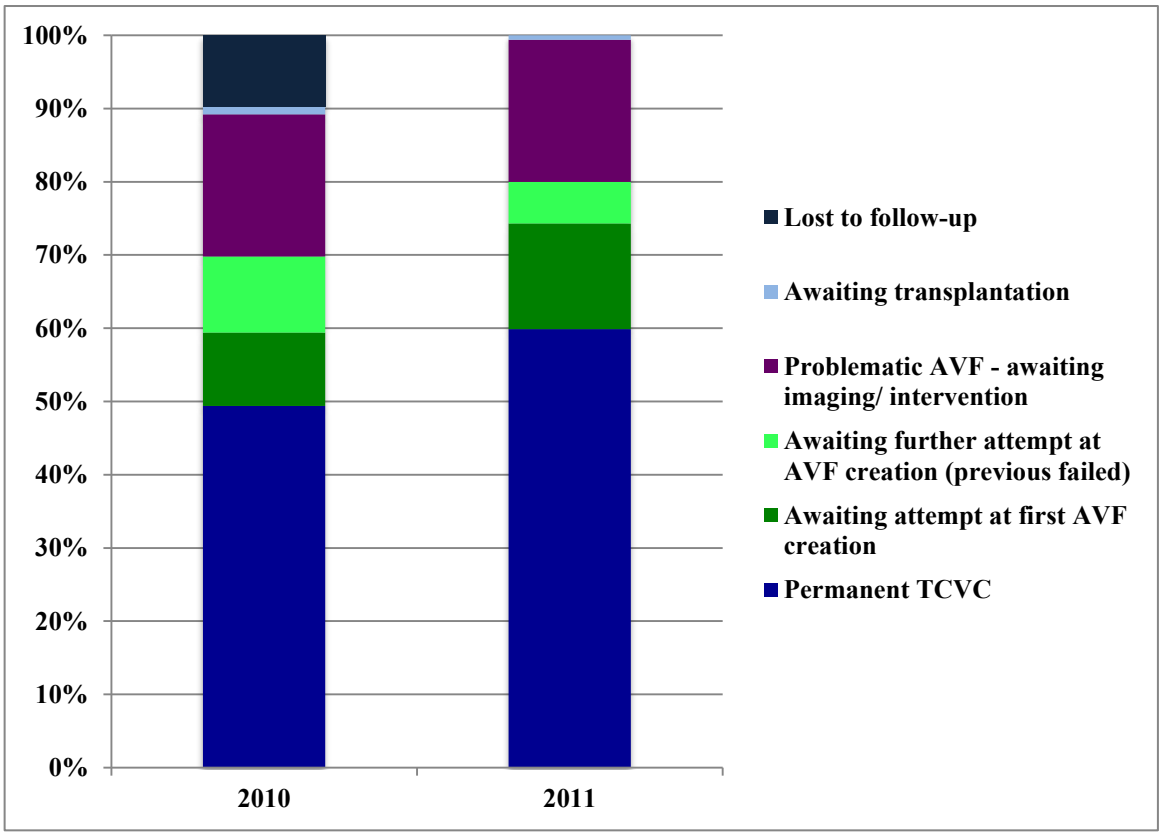
Table 2.1: Demographics of patients dialysing via a TCVC in 2010 and 2011. Results are presented as mean (SD) unless otherwise stated.

	2010	**2011**
Age (years)	65.5 (6.5)	62.3 (6.3)
Sex (percentage male)	48%	46%
Time on haemodialysis (years)	5.7 (3.4)	5.1 (5.4)
Number of previous TCVCs	3.06 (range: 1-15)	2.95 (range: 1-13)
Number of previous AVF attempts	1.9 (0.7)	2.2 (0.6)
Percentage of patients with at least 3 previous AVF attempts	23.3%	27.9%
Percentage of patients with no previous AVF attempts	21.2%	13.9%

Table 2.2: Site of tunnelled central venous catheter.

	2010	2011
Internal jugular	92.7% (n=197)	95.0% (n=192)
Subclavian	3.1% (n=6)	2.0% (n=4)
Femoral	3.1% (n=6)	1.5% (n=3)
Translumbar	1.0% (n=2)	1.5% (n=3)

Table 2.3: Reasons for TCVC use in 2010 (pre-intervention) and 2011 (post-intervention). Following the intervention more patients had a decision made not to attempt further definitive vascular access either due to comorbidities or exhaustion of anatomical options. Groups were compared using a paired-sample t-test.



	2010	2011	P-value
Permanent TCVC			
Unfit	28.2%	32.8%	0.08
Non anatomical option	9.8%	19.4%	<0.001
Patient choice	11.4%	7.9%	0.13
Awaiting new AVF creation/ maturation			
Awaiting maturation	8.8%	5.4%	0.05
Awaiting surgery to create AVF	12.6%	14.4%	0.45
Awaiting imaging/ review	12.6%	9.5%	0.23
Awaiting intervention for problematic AVF	7.8%	9.9%	0.35
Awaiting transplantation	1.0%	0.6%	0.06
Lost to follow-up	9.8%	-	

2.3.2. Complications of TCVCs

Culture-proven *Staph.aureus* bacteremia rate during the period November 2010 to November 2011 was 1.6 per 1,000 catheter days; 32 patients (16.6%) required their TCVC removed for infection within the year. One patient died from line sepsis. 13 patients (6.7%) required TCVC replaced for occlusive problems or poor flow in the period 2010-2011. A further 12 patients (6.2%) had difficulties with poor flows in their line which were managed conservatively. 24 patients (12.4%) had previously had >5 TCVCs replaced for complications and 24 patients (12.4%) had evidence of symptomatic or previously symptomatic central vein stenosis.

2.3.3. Indications for TCVC use

Table 2.3 outlines the reasons for TCVC use at the time of the initial clinical review in November 2010. 25.6% (n=49) of patients were deemed unfit for any further definitive access options; one-third of patients (n=64) were awaiting imaging or operative intervention and 10.5% (n=20) of patients did not wish AVF creation. A further 9.8% (n=19) of patients were found to be dialysing via a TCVC for no reason other than they appeared to have been lost to follow-up and plans for definitive access not made. Following the initial review, a plan for vascular access was created in each patient. A decision was made to keep the TCVC in 51.8% of patients (n=99). 7.8% (n=15) required imaging and/or intervention (either surgical or angiographic) for a problematic fistula. No patient was suitable for or willing to consider a switch to peritoneal dialysis (11.4% (n=22) had previously failed peritoneal dialysis). All other patients were at various stages of work-up for surgery (25.3% (n=49) were awaiting preoperative imaging; 2.1% (n=4) were awaiting clinical review; 12.4% (n=24) were on the waiting list for surgery).

2.3.4. Outcomes following aggressive intervention for definitive access

A year later, following aggressive attempts to achieve definitive access, the fate of the original TCVC patients is outlined in Figure 2.2. Of the 193 patients dialysing via a TCVC in November 2010, 37% (n=71) had died by November 2011. An active decision had been made for 22% (n=43) to remain on a long-term TCVC; 20% (n=39) had undergone successful AVF creation; 1% (n=2) were dialysing via an AVG and 2% (n=4) had received a renal transplant. A total of 34 patients (17.6%) were still trying to achieve definitive access 1 year on.

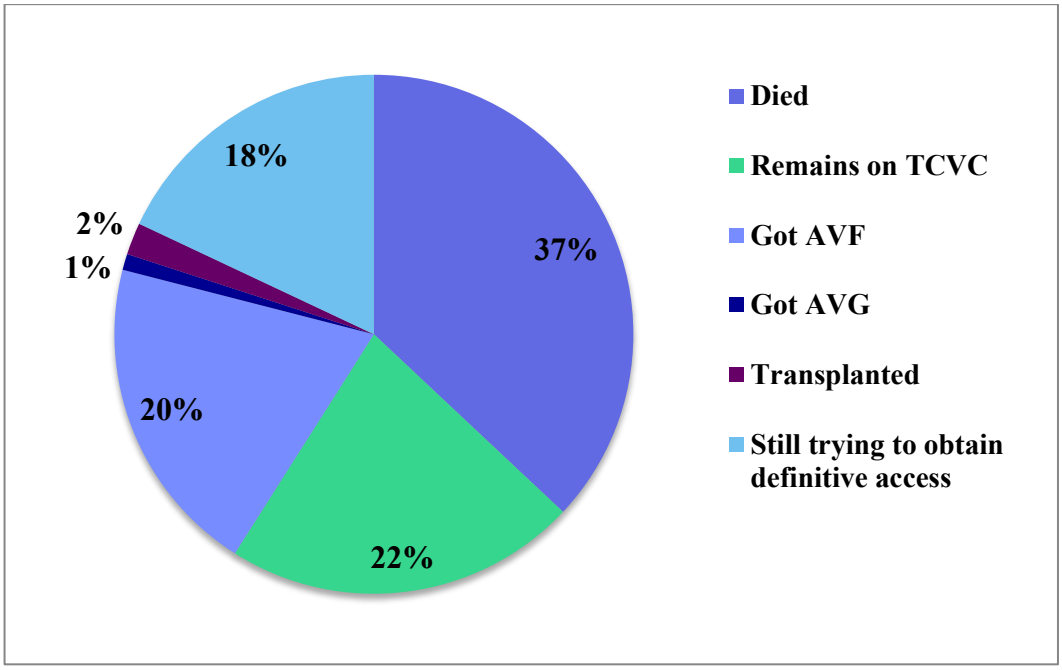


Figure 2.2: Outcome of those patients who were dialysing via a TCVC in November 2010 (first audit cycle) at the time of the second audit cycle.

Seventy-seven patients (39.9%) had 91 attempts made at creating definitive access during the follow-up period. 50.6% (n=39) of patients had successful AVF created at the first attempt (two were subsequently transplanted) and 2.6% (n=2) had an AVF successfully secured at the second attempt. In this patient group the success of AVF creation declined with the number of previous attempts at AVF creation and the length of time a patient had been on haemodialysis (Table 2.4). 44.2% (n=34) of patients had significant difficulties or complications following attempted AVF creation. A total of eight patients (10.4%) required ligation of a functioning AVF (two for venous swelling secondary to central vein stenosis; four for steal; two with calciphylaxis at the operative site). Five patients (6.5%) died within 28 days of surgery to create AVF. Two patients successfully had AVF created but have subsequently had stenotic complications and were again dialysing via TCVC awaiting reintervention. A total of 17 patients (22.1%) had undergone imaging and failed attempts at AVF creation in the subsequent year and continued to await further attempts at definitive surgery. 9 patients (11.7%) with bilateral CVS had attempts at achieving lower limb access via a thigh graft.

All patients had a documented "vascular access plan" at the time of the second clinical review. Reasons for TCVC use differed in 2011 (following the intervention) compared to 2010 (Table 2.3): 61.9% of patients (n=125) had an active decision made to continue dialysis via a TCVC at the time of second review (November 2011). A total of 40.1%

(n=81) had a new decision to dialyse via a permanent TCVC after imaging confirmed no suitable anatomical option for definitive vascular access or the patient had additional unsuccessful attempts at AVF creation. 21.8% (n=44) remained on a TCVC following the initial review. 15.8% (n=32) of patients were still trying to achieve definitive access 1 year on. A total of 7.9% of the patients (n=16) required TCVC insertion due to new problems (stenosis, occlusion etc.) that developed with their AVF and 13.9% of patients (n=28) were incident dialysis patients who commenced haemodialysis without definitive access and were dialysing via TCVC until AVF creation or maturation. Following aggressive intervention, significantly more patients had an active decision made to dialyse via a permanent TCVC either due to comorbidities or exhaustion of native options (19.4% vs.9.8%; P<0.001). There was no significant difference in the number of patients awaiting surgery or intervention either for first AVF, after multiple unsuccessful attempts, or for problematic AVF (Table 2.4).

Table 2.4: Success of subsequent AVF creation in patients dialysing via TCVC who have had previous attempts at AVF creation.

	Total number of attempts at definitive access creation	Percentage of patients with successful AVF creation	P-value
Number of previous attempts at AVF creation			
0	16	81.2% (n=13)	
1	13	69.2% (n=9)	
2	24	66.7% (n=16)	
3	15	6.7% (n=1)	
4	15	13.3% (n=2)	
>4	8	0% (n=0)	
Total	91	45.1% (n=41)	<0.001
Length of time on haemodialysis			
<1 year	20	80.0% (n=16)	
1-2 years	6	66.7% (n=4)	
2-5 years	24	50.0% (n=12)	
5-10 years	29	17.2% (n=5)	
>10 years	12	33.3% (n=4)	
Total	91	45.1% (n=41)	0.02

2.3.5. Incident patients

During the same time period, 142 incident patients commenced haemodialysis via a central venous catheter (CVC) (108 TCVC; 34 temporary). 82 of these patients (57.7%) had attempted AVF creation prior to commencing haemodialysis via a TCVC; 30 patients (21.1%) were deemed unsuitable for definitive vascular access attempts and 30 patients (21.1%) were not referred for access creation prior to starting haemodialysis. A total of 50% of these (n=15) were "crashlanders". 18.3% (n=26) had late referral for vascular access creation (within 6 weeks of the need to commence haemodialysis) and therefore did not yet have a mature AVF. A total of 38 patients (26.7%) had AVF created more than 6 weeks prior to starting haemodialysis that were inadequate to sustain dialysis and a further 18 patients (12.7%) had AVF which had adequately matured but subsequent thrombosis had gone unrecognised until the need to commence dialysis, also necessitating TCVC insertion.

2.4. DISCUSSION

Aggressive surgical attempts to achieve definitive access in prevalent patients resulted in 20% of patients previously dialysing via a TCVC having successful AVF creation. Due to the high turnover of patients and persistent difficulties in achieving AVF for incident patients, there was no reduction in the absolute number of TCVCs required one year after the initial intervention. Perhaps more importantly, as a result of active management, all patients obtained a formal "vascular access plan". Aggressive intervention certainly benefited some patients but this was offset against high background mortality and significant morbidity and complication rates among others in this relatively high-risk patient group.

The study represents a local service improvement initiative and, as such, results may not be generalisable to other units. However, our practice is comparable to that observed in other units in UK and the problems highlighted in this study are those encountered within the "real world" of vascular access. Furthermore, with the recent implementation of a PbR strategy in England and Wales, the findings are timely to illustrate the difficulties (central vein stenosis, lack of native vessels and comorbid patients) that clinicians are likely to encounter in trying to achieve inflexible targets in a complex patient group of long-term prevalent haemodialysis patients.

This study highlights the importance of a "personal vascular access solution" and targetted "vascular access plans". Some patients derived significant benefit from aggressive attempts at AVF creation. 20% of prevalent patients who were dialysing via a TCVC had a functioning AVF after 1 year, including several patients who had been on haemodialysis for over 10 years. Others did not obtain similar benefit with a high complication rate and poor functional patency derived from access procedures performed in complex patients who had multiple previous access attempts. Following several additional failed attempts at AVF creation, a number of these patients had an active decision to continue dialysis via a TCVC documented in their "vascular access plan". The vascular access plans were individualised, taking into account comorbidities, life expectancy, anatomical options and patient preference. Failure to achieve a functional AVF does not always reflect poor care, just as it is not always appropriate to assume that autologous access is the measure of good quality care. Additionally, maintaining a high proportion of such complex patients on AVF may become increasingly challenging (Mendelssohn et al. 2006; Thomson, 2009). AVF will inevitably suffer complications including stenosis and thrombosis. CVCs are likely to remain an essential stop-gap measure from time to time in patients with problematic vascular access. It is important to recognise that patients' "vascular access plans" are not a once-off, all-or-nothing decision, rather they will evolve, require fluidity and will need regular revision.

Unique complex vascular access problems occur in patients with bilateral central vein stenosis. The prevalence of bilateral central vein stenosis in our patient group was significant (11.7%) and higher than in other similar series (Antoniou et al. 2009). A recognised complication of long-term TCVC use, bilateral central vein stenosis makes it difficult to achieve upper limb venous access (Agarwal et al. 2007). Attempts at upper limb AVF creation in patients with unrecognised central vein stenosis were associated with venous swelling of the limb necessitating abandonment of the AVF in this study. Thigh grafts were attempted in a number of patients and provided good quality dialysis with avoidance of TCVCs in patients who had few other access options. A number of patients with bilateral central vein stenosis had significant comorbidities precluding them from general anesthetic and thigh graft creation however. As such they were subsequently recorded as having no further anatomical options for definitive access.

Just over half of patients in whom AVF was attempted had a functioning fistula after one year. The other half had significant difficulties either with complications of the AVF or with multiple unsuccessful attempts at achieving fistula maturation. 25% continue to have

ongoing attempts at definitive access creation beyond 1 year after the initial intervention, demonstrating the high failure rate of AVF in this population. These findings are consistent with data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), which found that the risk of AVF failure was increased in patients with prior CVC (OR1.8) (Rayner et al. 2004). Our findings also support those of Lawrence et al. (2002), confirming a law of diminishing returns with each subsequent vascular access attempt (81.2% functional patency for first AVF vs. 13.3% functional patency in patients who have had four previous attempts at AVF creation). Repeated admissions for unsuccessful AVF attempts and significant morbidity associated with definitive access attempts in this complex patient group justify the pragmatic approach taken during the second clinical review, with an increase the number of patients with a "vascular access plan" to remain on TCVC due to lack of anatomical options after several further unsuccessful attempts at achieving definitive access.

The number of haemodialysis patients in Scotland over the age of 75 years has doubled in the past 10 years (Scottish Renal Registry, 2015). Similarly, in the USA, the average age of a patient commencing haemodialysis is now 63 years (20 years older than 15 years ago) (USRDS, 2014). As previously described, definitive vascular access creation in an increasingly elderly, comorbid population presents unique challenges. In this study over one-third of patients who were dialysing via a TCVC at the time of initial review were dead within a year, illustrating the importance of considering life expectancy in the decision-making process for vascular access. There is a high mortality in extremely elderly haemodialysis patients, with a mean survival of only 386 days in patients over 80 years old (Vachharajani et al. 2011). This illustrates the futility of blindly creating an AVF in every octogenarian. Patency and success rates of AVF in older patients should also be considered when planning vascular access. Many authors have not shown any significant difference in AVF outcome in elderly dialysis patients (even at the extremes of age) and would argue that age, in isolation, should not be a contraindication to AVF creation (Morsy et al. 2011; Lok et al. 2005). However, the combination of advancing age and other comorbidities, including diabetes and PVD, is likely to be associated with poor AVF maturation (Lok et al. 2006). This risk of poor AVF maturation in patients with diabetes and PVD requires to be offset against an increased number of catheter-related bacteremia in comorbid patients (Thomson et al. 2007).

Both the Fistula First Breakthrough Initiative and PbR (Massoud et al. 2006; Department of Health, 2010) focus on minimising prevalent TCVC usage. However, this study has

highlighted the difficulties associated with a "one size fits all" approach to obtaining definitive vascular access in this population. Universal targets at the expense of individualised care may compromise outcomes in this complex patient group. It is vital that national targets and PbR do not jeopardise personal solutions. Conversely, incident patients would provide an appropriate target group, in whom definitive access is likely to be easier to create (Rayner et al. 2004) and prevention of TCVC-related complications, for example, central vein stenosis, would minimise the number of patients with complex, end-stage vascular access and no anatomical options for AVF creation in the future (Agarwal et al. 2007). During the time period of this study, only 46.8% of incident patients in the West of Scotland commenced haemodialysis via an AVF. It is essential that government initiatives to minimise prevalent TCVC usage do not occur at the expense of incident patients.

In conclusion, this study clearly demonstrates the need for accurate data collection and highlights the role that research can play in QI projects. It has illustrated that prevalent haemodialysis patients, previously dialysing via a long-term TCVC, are a high-risk and challenging group in whom to obtain vascular access. They have high background mortality and definitive vascular access is both difficult to achieve and associated with significant morbidity. Targetting resources towards the simpler incident patients, with higher likelihood of success, may provide better return and avoid patients with complex vascular access needs in the future. Furthermore, the study serves as a root-cause analysis to identify the main reasons for TCVC use in our practice and highlight areas requiring additional work both for service improvement and future research: the difficulties associated with non-maturation and associated consequential TCVC use; the need to identify patients in whom attempts at AVF creation may be futile and alternative vascular access may be more appropriate; and the importance of an individualised approach to vascular access. These are areas that have subsequently been targetted for development both in our clinical practice and research. They provide the basis for the main questions and themes of this thesis.

THE BURDEN OF CENTRAL VEIN STENOSIS AND "END STAGE" VASCULAR ACCESS

3.1. INTRODUCTION

Vascular access dysfunction is the leading cause of healthcare expenditure and second most common cause for mortality in patients on haemodialysis (Fluck & Kumwenda, 2011). Choice of vascular access modality is strongly associated with survival on haemodialysis (Malas et al. 2015). TCVCs are associated with greater all cause mortality, increased risk of systemic bacteraemia and long-term morbidity as a result of central venous stenosis (CVS) compared to alterative forms of vascular access (Thomson et al. 2010; Bray et al. 2012). Whilst infection and *Staph.aureus* bacteraemia rates are very tightly audited and regulated adverse outcomes, CVS is rarely considered as a marker of quality of care.

Central vein stenosis is a delayed complication of TCVC insertion (Agarwal, 2013; NKF-KDOQI, 2000), with a published incidence ranging from 25 to 40% amongst patients who are dialysing (or have dialysed) via a TCVC (Suroweic et al. 2004; Quinn et al. 2003). It can cause debilitating symptoms of upper limb and facial swelling, vascular access dysfunction and, once advanced, life-threatening loss of vascular access (Dammers et al. 2003a; NKF-KDOQI, 2006). Little is understood about the pathogenesis of CVS (Dammers et al. 2003a), however our own recent work suggests that prolonged duration of line use is a risk factor for CVS and there is a negative correlation with line infection. In this study, either CVS and/or line sepsis was found to be an inevitable consequence of every TCVC not removed for another reason (Aitken et al. 2015b). Treatment strategies are suboptimal, and affected patients suffer with frequent hospitalisation and deterioration in quality of life.

Notwithstanding the well-recognised complications associated with their usage, TCVCs remain fundamental in delivering HD to patients with no other functioning vascular access (Thomson et al. 2010; Aitken et al. 2014a; Schwab, 1999). They can be inserted quickly and easily to permit immediate access for HD, making them the default, stock choice for incident dialysis patients without a working AVF. Despite aggressive attempts to minimise usage, nearly 50% of incident patients and 25% of prevalent patients in Scotland continue to dialyse via a TCVC (Scottish Renal Registry, 2015). In the USA, nearly 80% of patients still commence haemodialysis via a line (Lok & Foley, 2013). However, the choice (or

necessity) for TCVC in incident dialysis patients can have significant negative long-term repercussions.

The clinical manifestations of CVS (vascular access dysfunction and/or limb swelling) are well recognised and the healthcare burden of CVS experienced by clinicians and patients is subjectively high, however the true cost to both patients and healthcare services has not been defined. The natural history and optimal treatment strategy of CVS is not known. Furthermore, due to the temporal separation between line insertion and CVS, there is often lack of awareness and accountability for the complication and it is rarely factored into the clinical and economic arguments driving high rates of provision of autologous vascular access.

Central vein stenosis is notoriously difficult to treat (Dammers et al. 2003a). Management presents two, often dichotomised, challenges: to both preserve vascular access and reduce symptoms. Attempts at autologous vascular access creation or rescue on the side affected with the CVS are doomed to fail without robust management of the stenosis itself, and patients have frequently already exhausted multiple alternative potential vascular access sites (Dammers et al. 2003a). There is no well-defined universal treatment algorithm for maintaining vascular access in this context (Lumsden et al. 1997). Symptomatic relief and maintenance of any autologous AVF is the optimum outcome of intervention for CVS. Endovascular intervention, by either angioplasty or stent insertion, has become the mainstay of treatment, providing a method that can potentially relieve symptoms and preserve access (Suroweic et al. 2014). Current data suggests that primary 12 month patency of angioplasty ranges from 23-63% (Suroweic et al. 2014; Quinn et al. 2003; Dammers et al. 2003b) and 31 to 91% for endovascular stenting (Suroweic et al. 2004; Dammers et al. 2003b; Quinn et al. 2003; Kovalik et al. 1994; Günther et al. 1989). When endovascular treatment fails to preserve existing autologous access, subsequent steps for further access provision must be taken. In patients with unilateral CVS, this normally involves creation of contralateral AVF or AVG.

Patients with bilateral central vein occlusion provide a uniquely challenging patient group for the vascular access surgeon as they have no upper limb options for vascular access (either native or prosthetic) (Ayarragaray, 2003). In severe cases it can lead to absolute loss of vascular access for dialysis. The true incidence of complete access failure is unknown, however most clinicians responsible for caring for patients with ESRD will recall the occasional patient who dies from loss of vascular access.

Case reports of exotic, last-resort procedures for end-stage vascular access are found throughout the vascular literature (Zanow et al. 2005; Zamani et al. 2012; Hamish et al. 2006). Considerable time and resources may be invested in heroic attempts at providing vascular access. Such attempts are costly and often only provide a short-lived solution (Yevzlin, 2008).

Many patients with bilateral central vein occlusion can be managed with a combination of a relatively limited number of second line access options. These treatment options include tunnelled catheters (femoral (Falk, 2007) and translumbar (Power et al. 2010)), HeRO grafts (Glickman, 2011), lower limb access (native long saphenous vein loop (Pierre-Paul et al. 2004; Gilbert & Gibbs, 2011) or prosthetic (Cull et al. 2004; Chemla et al. 2005)), peritoneal dialysis (Chemla et al. 2005; Kumbar & Besarab, 2013) and renal transplantation. The infection and occlusion rates of these second line access procedures (particularly those in the lower limb) are recognised to be higher than autologous upper limb fistulae (Cull et al. 2004) however they can provide effective access for haemodialysis, either in isolation or in combination with another modality, in patients with limited alternative options. There are no comparative data on which procedure offers the best options for long-term haemodialysis in these patients. Ranking of these options could provide a decision-making framework for intervention, generally leading to a "personal vascular access solution" on an individual patient basis (Aitken et al. 2014a).

The aims of this study were two fold: firstly to describe the burden of central vein stenosis, both to the patient (in terms of vascular access provision, hospitalisation and quality of life) and to the healthcare system (with associated costs of treating CVS and maintaining vascular access); and secondly to compare outcomes of the various treatment modalities (femoral tunnelled catheters, translumbar catheters, native long saphenous vein thigh loops, prosthetic thigh grafts, peritoneal dialysis and renal transplantation in patients with bilateral central vein occlusion. By demonstrating the significant affliction caused by ESVA, the importance of 'getting it right from the start' (Lok et al. 2013, pp.812) with TCVC avoidance in incident patients is highlighted.

3.2. METHODOLOGY

3.2.1. Study design and participants

The Vascular Access Service at the Western Infirmary, Glasgow serves a haemodialysis population of 700 patients in the West of Scotland, with approximately 170 incident patients commencing HD each year. Patients with symptomatic central vein stenosis (defined as CVS causing disabling limb or facial swelling, AVF dysfunction or loss of vascular access) were identified via a weekly Multidisciplinary Team (MDT) vascular access meeting attended by renal surgeons, interventional radiologists and nephrologists. All patients with problematic vascular access were referred to the surgical team via this MDT. A prospectively maintained database of patients with symptomatic central vein stenosis was created.

This was an exploratory study with the aim of comprehensively characterising and describing the central vein stenosis population in the West of Scotland: natural history, risk factors, impact on the patient and the healthcare system etc. For this reason, several different patient cohorts were evaluated:

1. All patients with symptomatic CVS referred to the Vascular Access MDT between 1st January 2011 and 31st December 2014 (4 years). This patient cohort was followed up until 1st September 2016
2. A subgroup of these patients deemed to have "end stage" vascular access (ESVA), defined as bilateral central venous stenosis/occlusion diagnosed as symptoms and/or access failure with no further options for upper limb access plus angiographic evidence of stenosis or occlusion which was no longer amenable to radiologic intervention. Recruitment occurred over the same time period outline above.
3. A subgroup of patients with ESVA considered eligible for renal transplantation. (This population is described in greater detail below).
4. 500 consecutive patients undergoing TCVC insertion between 1st January 2008 and 22nd October 2011. Follow-up on this patient population ended on 31st December 2014.

Approval for the study was obtained from the Greater Glasgow and Clyde Clinical Effectiveness Department. Formal ethics committee approval was not required for this

evaluation of existing clinical practice.

3.2.2. Data collection

The main prospective CVS database was maintained by two researchers (EA, AJ), Data entry was cross-checked to ensure accuracy. Basic patient demographic data were recorded weekly following the MDT, including age, sex, comorbidities, smoking status, medication history, vascular access status and central venous catheterisation history. Presenting clinical problems were also documented. The location of lesions was determined by central vein angiography. Patients were categorised into unilateral CVS and those with bilateral or superior vena cava stenosis. Patients with ESVA were considered separately. Prospective data were recorded on: treatment strategies (described below); treatment outcomes including access patency (primary, secondary and primary-assisted patency); complications (stenosis, occlusion, infection); re-interventions and hospitalisation episodes. Vascular access status (i.e. AVF, AVG, TCVC, PD, renal transplant) was recorded at 6 monthly intervals from diagnosis.

Primary assisted patency was defined as the time from access creation to thrombosis (or occlusion in the case of catheters). Secondary patency was defined as the time from access creation to access occlusion or loss (including any salvage procedures). "Loss of patency" has also been used to describe graft loss in the case of transplantation to permit comparison between cohorts.

Quality of life was also recorded. This was determined from self-reported EQ-5D (Szende et al. 2007; Brazier et al. 2004) questionnaires recorded at the time of diagnosis of CVS and 6 and 12 months post-diagnosis.

Additionally, data was retrospectively collected on 500 consecutive patients undergoing TCVC insertion. The Scottish Electronic Renal Patient Record (SERPR) was interrogated to obtain data on basic patient demographics, the date of each catheter insertion and number of preceding/ subsequent TCVCs. The number and date of culture-proven catheter-related blood stream infection (CRBSI) and CVS were recorded. Culture-proven catheter-related bacteraemia was defined as the presence of positive blood cultures associated with a systemic inflammatory response (e.g. pyrexia, raised white cell count (WCC) or C-reactive protein (CRP)) in the absence of clinical or radiological signs of a non-catheter-related source. Local exit site infections in the absence of systemic bacteraemia were

excluded. This approach is in keeping with the definition of CRBSI commonly used in the literature and consistent with that used in routine clinical practice (Thomson et al. 2010). Where patients were found to have developed CRBSI, the date of first positive blood culture was entered as the event date and time to event subsequently calculated. All TCVCs were removed following culture-proven CRBSI. For the purposes of this cohort, CVS was defined as typical symptoms (including limb swelling and access dysfunction or failure) along with radiographic evidence of central vein stenosis or occlusion. The date of diagnostic venography was used to calculate time to event. Patients in this cohort were followed prospectively to completion of the study or death.

3.2.3. Treatment strategies

Treatment strategies were selected based on the consensus of the multi-disciplinary team, adhering to the concept of a "personal vascular access solution" (i.e. the vascular access/ dialysis modality most likely to provide long-term successful RRT) and a philosophy of ranking autologous vascular access first, prosthetic vascular access second, and TCVC third. PD and transplantation were considered if appropriate. With failure of treatment, patients were again discussed at the MDT meeting, and a further treatment strategy agreed and implemented.

The procedures described below reflect standard practice within our institution:

3.2.3.1. Angioplasty and/or stenting to maintain autologous access

Theses procedures were mainly performed on an out-patient basis with few requiring hospital admission. Procedures were performed under local anaesthesia with or without intravenous sedation as required.

Balloon angioplasty was considered the treatment of choice, with stenting only employed if there was immediate elastic recoil following angioplasty, or of the stenosis recurred within the first three months.

Ultrasound-guided puncture of the basilic or brachial vein was performed and a 7-10F vascular sheath placed. Angiographic assessment of the central veins was performed. The length and diameter of the stenosis measured and the balloon/ stent size selected to over-estimate the vessel size by 10-20% in order to prevent migration. The stenosis was then

crossed with a standard hydrophilic guidewire. The hydrophillic wire was then exchanged for a stiffer non-hydrophilic 0.035mm guidewire and the stricture dilated with a balloon catheter placed over the stiff guidewire. The vein is dilated to the diameter of the subclavian or brachiocephalic vein immediately proximal to the stenosis. Generally balloon diameters between 10 and 20mm were required. If a balloon diameter >20mm was required a larger sheath was first inserted.

In the event that stenting was required, a standard Wallstent (Boston Scientific, Boston, MA, USA) or Viabahn (W.L. Gore Associates, Flagstaff, AZ) was used. The stent was oversized by 10-20% compared to the normal vessel to prevent migration. Balloon angioplasty of the stent was employed after deployment.

3.2.3.2. Prosthetic thigh grafts

In this study, mid-thigh loop grafts were performed under general anaesthesia. An 8-10cm diagonal incision was placed on the medial aspect of the right thigh at the anterior border of the sartorius muscle. The sub-sartorial femoral vein and superficial femoral artery were exposed and controlled. A separate small incision was made laterally to permit tunnelling of the graft. Both standard and early cannulation PTFE grafts were used at the discretion of the operating surgeon. An arteriotomy and venotomy were made on the superficial femoral artery and femoral vein respectively. End-to side anastomoses were performed with or without Miller cuffs. Vancomycin was routinely used as antibiotic prophylaxis.

3.2.3.3. Native long saphenous vein thigh loops

Under general anaesthesia, and again after vancomycin antibiotic prophylaxis, the long saphenous vein was mobilised through a series of incisions in the leg and divided distally. The common femoral artery was mobilised and controlled. A longitudinal arteriotomy was performed. The vein was brought through a subcutaneous loop tunnel and then an end-to-side anastomosis of long saphenous vein to common femoral artery was performed.

3.2.3.4. Tunnelled femoral catheters

Catheters were inserted under local anaesthesia with ultrasound-guidance. A short subcutaneous tunnel was created. The common femoral vein was cannulated with the

micropuncture needle and a Seldinger technique used to insert a 16F Split AshCath® (MedComp, Harleysville, PA, USA) catheter.

Our standard catheter care protocol was employed throughout the observation period. This demanded complete sterile precautions during catheter insertion and upon manipulation of the hub. Following catheter hub manipulation, the skin surrounding the insertion site was soaked with chlorhexidine solution prior to a sterile dressing being applied. An interdialytic lock with heparin 5,000iU/ml to the internal volume of the catheter was employed.

3.2.3.5. Tunnelled translumbar catheters

Catheters were inserted into the inferior vena cava (IVC) under local anaesthesia and moderate sedation with fluoroscopic guidance. The common femoral vein was punctured to permit guidewire insertion as a fluoroscopic target. A micropuncture needle was then used to gain access to the IVC and a Seldinger technique used to insert a 14F Translumbar AshSplitCath® (MedComp, Harleysville, PA, USA). The exit site was tunnelled across the lumbar region.

3.2.3.6. Peritoneal dialysis

Under general anaesthesia a 5-7cm mini-laparotomy was performed and a 15F Curl Cath® (Covidien, Dublin, Ireland) peritoneal dialysis catheter was inserted into the peritoneum. The laparotomy wound was closed and use of the catheter delayed for 7-10 days. Intravenous antibiotic prophylaxis was given.

3.2.3.7. Haemodialysis reliable outflow (HeRO) device

The HeRO device (Hemosphere Inc., Minneapolis, MN, USA) is a standard 6mm ePTFE graft attached to a 5mm nitinol-reinforced silicon outflow component. The outflow component was inserted under radiographic screening by an interventional radiologist in a similar fashion to a standard TCVC. The tip of the outflow component was placed in the right atrium and position confirmed radiologically. The inflow component/ graft was routinely replaced with Gore®ACUSEAL (W.L. Gore Associates, Flagstaff, AZ, USA) 6mm graft to permit early cannulation. This was anastomosed end-to side to the brachial artery and tunnelled in the standard fashion to a separate incision at the deltopectoral

groove. The two components are then brought together at this counter incision with a titanium connector as is described by Katzman and colleagues (2009).

3.2.3.8. Priority allocation of renal transplants from donation after circulatory death (DCD) donors

In the United Kingdom, cadaveric kidneys are allocated for transplantation according to the National Health Service Blood and Transplant (NHS-BT) Deceased Donor Organ Allocation Policy (Kidney Advisory Group, 2016). This complex matching algorithm attempts to provide equity of access to renal transplantation by prioritising based on factors such as waiting time, HLA-match, blood group and age difference. The median waiting time for a deceased donor kidney transplant is 3 years via this system (Hudson & Curnow, 2013).

Locally we recognised that there was a small cohort of patients with precarious vascular access whose lives were threatened by potential access loss and were likely to require transplantation more quickly than could be provided via the NHS-BT Deceased Donor Organ Allocation Policy. A strategy was devised within our unit for prioritise allocation of certain cadaveric kidneys to patients with failing vascular access. We describe our early (four year) experience with this approach.

Cadaveric kidneys donated after circulatory death (DCD) in the UK were, at the time of this study, allocated locally. Individual transplant units could allocate these kidneys to recipients based on local policies. Generally units choose to allocate such kidneys similarly to donation after brain death (DBD) kidneys, based on the national matching scheme. However within our unit it was agreed that patients with ESVA would be given priority to receive DCD kidneys if blood group compatible and cytotoxic (CDC) cross-match negative. Such patients were offered the first suitable available kidney. The full details of this strategy are described in more detail below.

3.2.4. Data analysis

Patient demographics, presenting symptoms and risk factors for CVS were evaluated. Thereafter, the aim of data analysis was four-fold. Firstly to define and describe a "standard" CVS patient pathway; secondly to outline the success of individual treatment strategies for CVS; thirdly to describe the personal burden in terms of quality of life,

hospitalisation etc. for patients living with CVS; and finally to describe the financial cost of CVS. The success of individual access modalities (prosthetic thigh grafts, native long saphenous vein thigh loops, tunnelled femoral catheters, tunnelled translumbar catheters, peritoneal dialysis). in patients with ESVA was considered separately, as was the role of expedited renal transplantation.

3.2.5. Statistical analysis

Statistical analysis was undertaken using SPSS Statistics for Windows Version 19.0 (IBM Corp., Armonk, NY, USA). Continuous data is presented as mean and standard deviation (SD). Categorical data is presented as median and interquartile range (IQR) or as a percentage of the total population. Event rates are presented per 1,000 dialysis days. Primary, primary-assisted and secondary patency rates at 3, 6 and 12 months for each RRT modality/access are provided. Vascular access/ RRT modality was recorded as a percentage of the total population at 6 monthly intervals from the time of diagnosis. Parametric testing with student's t-test and non-parametric testing with Mann-Whitney U-test were used in the assessment of continuous variables, while catergorical variables were assessed using Pearson chi-squared test. Kaplan Meier survival analysis was used to compare patencies for the various access modalities (log-rank). Finally, multivariate analysis of all patients undergoing TCVC insertion was performed using a Cox-proportional hazards model with stepwise conditional entry to test for independent risk factors for the development of central vein stenosis. Linearity and normal distribution of the relationship between TCVC insertion and the occurrence of CVS were evaluated and confirmed. Variables with $P<0.1$ on univariate analysis were considered for entry to multivariate analysis. $P<0.05$ on multivariate analysis was considered significant.

Healthcare costs were estimated from hospital practice and unit costs were taken from Personal Social Service Research Unit (PSSRU5) figures, NHS Reference Costs, 2013-2014) and published literature (Curtis, 2012; Hockenhull et al. 2008; Department of Health, 2015). All costs are quoted in pounds Sterling (£). Healthcare costs in each of the first three years following diagnosis were calculated, both for the individual patient and the overall population of patients with CVS treated locally. Healthcare costs were combined with EQ-5D data to calculate the cost per quality adjusted life year (cost per QALY) in patients with quality of life data available, using the National Institute of Clinical Excellence (2014) framework. The cost-per QALY represented the cost of the treatment philosophy, rather than a specific intervention.

3.2.6. Expedited renal transplantation

The West of Scotland Renal Transplant Unit, based at the Western Infirmary, Glasgow, serves a population of approximately 2.6 million people. There are approximately 230 patients active on the renal transplant waiting list. 152 renal transplants were performed at our institution last year (April 2015-March 2016) (NHS Blood and Transplant, 2016).

On 1st January 2011, our centre implemented a strategy of "expedited renal transplantation" for patients with ESVA. At the time, a policy of local allocation of all DCD kidneys existed within the UK. This permitted individual transplant centres to choose 'the most appropriate means of allocating [DCD] kidneys to patients on their lists' (Kidney Advisory Group, 2014a, pp.1) and determine locally which patient received the offer of a DCD kidney outwith the national matching algorithm. (Since then the policy has been revised so that one of the two DCD kidneys is retained locally and the other offered regionally for donors aged 5-50 years old) (Kidney Advisory Group, 2016).

It was agreed that patients with failing vascular access should be prioritised above all others to receive DCD kidneys from donors ≥ 50 years old or with other adverse prognostic features (e.g. prolonged cold ischaemic time (CIT) or poor perfusion) or tier E DBD kidneys retained at the local centre after failure to find another named recipient (as advised by NHS-BT)). ESVA was defined as bilateral central venous occlusion, failed or contraindication to peritoneal dialysis and survival deemed by the MDT to be <1 year on haemodialysis as a result of predicted access failure.

The clinical team of nephrologists and vascular access surgeons identified potentially eligible patients. All patients were discussed at our monthly Renal Transplant MDT Meeting comprised of nephrologists, transplant surgeons, vascular access surgeons, dialysis and transplant nurses and transplant coordinators and a consensus decision was reached as to whether the patient fulfilled the criteria to be listed for priority/ expedited transplantation. If deemed suitable, the patient was approached and the concept of the priority waiting list explained to them. If agreeable, the patient's name was added to a "priority transplant" waiting list held by the Histocompatibility and Immunogenetics Department responsible for tissue typing and crossmatching. The clinical team identified suitable donors and a crossmatch was performed for any blood group compatible donor/recipient pair.

Prior to implementation of the strategy, it was discussed locally at the Multidisciplinary Team Meeting and all satellite and feeder units were written to advising them of the allocation policy and rationale. Stakeholders were encouraged to respond and unanimous agreement regarding the policy was reached prior to its implementation. Nephrologists in feeding units were also encouraged to identify and bring to MDT any patient that they thought might be eligible or benefit from the new allocation strategy.

Basic demographic data was collected for both donor and recipient e.g. age, sex, cause of renal failure, vascular access history, waiting time, cRF (calculated reactive frequency), type of donor, cause of death. Additional data on specific aspects of the transplant, for example immunology (mismatch, match score, match points, immunosuppression) and technical/ anatomical challenges and difficulties was also collected. The match score is a hypothetical score calculated by NHS-BT based on recipient HLA-type and blood group (it reflects the number of patients out of a standard cohort of 10,000 patients who are blood group identical, HLA-compatible and 000 or favourably [100, 010, 110] matched). Match points convert the match score into a points score for the matching algorithm based on ease of transplantation (Kidney Advisory Group, 2016). A standard post-Symphony immunosuppressive strategy (Ekberg et al. 2007) with tacrolimus, mycophenolate and prednisolone was employed for all patients. Basiliximab (20mg day 0, day 4) was the standard induction agent. Anti-thymocyte globulin (ATG) induction (2mg/kg day 0, day 4) was considered for patients deemed to be of higher immunological risk (cRF >90% and/or pre-formed donor specific antibody (DSA)) in the absence of contraindication. Outcome measures include delayed graft function (DGF), biopsy-proven acute rejection (BPAR), primary non-function, 1-year graft and patient survival, estimated glomerular filtration rate (eGFR) at 6 and 12 months, in-patient bed days and number of admissions. Additionally a "chance of transplant" at 1, 2, 3, 4 and 5 years was calculated from the NHS-BT Chance of Transplant Calculator (NHS Blood and Transplant, 2014). This online calculator uses patient age, ethnicity, blood group and immunological profile to predict the likelihood of receiving a cadaveric kidney transplant through the national matching algorithm.

Patients with ESVA receiving a priority allocated kidney were compared to (where appropriate) one of: the entire cohort of patients receiving a renal transplant at our institution over the same time period (n=452) (1st January 2011-31st December 2014); patients with ESVA transplanted via the national matching algorithm over the same time period (n=6); or an age and sex-matched control cohort (n=18). All patients were followed up for 1 year post-transplant.

Results for this patient cohort are presented as either mean (SD), median (IQR) or as a percentage of the total population. Continuous data were compared using either student's t-test or one-way analysis of variance (ANOVA). Categorical data were compared using chi-squared or Fischer's exact text. $P<0.05$ is considered statistically significant.

3.3. RESULTS

3.3.1. Patient demographics

155 of the 1,192 patients on haemodialysis in the West of Scotland between 1st January 2011 and 31st December 2014 were identified as having symptomatic CVS, giving a period prevalence of 13.0%. Mean patient age was 59.0 years (range: 17-93) (Table 3.1). Most patients had multiple preceding TCVCs (median 3; IQR 2,6), however there was one patient who developed symptomatic CVS after only 4 days with a single left internal jugular non-dialysis CVC 12 years previously.

Table 3.1: Patient demographics of the central vein stenosis population. Results are presented as mean (SD) or percentage of total. ††Vasculitides include vasculitis, systemic lupus erythematosus (SLE)/ scleroderma and Henoch-Schönlein purpura (HSP)

Characteristic	Value
Age (years)	59.02 (15.72)
Male	56.1%
Cause of Renal Failure	
Glomerulonephritis	11.2%
APKD	8.0%
Unknown	21.0%
Pyelonephritis	5.4%
Hypertensive disease	5.2%
Diabetic nephropathy	19.0%
IgA nephropathy	6.4%
Renovascular disease	6.8%
Vasculitides††	3.2%
Unknown	21.0%
Other	12.0%
Diabetes mellitus	31.8%
Cardiac event	49.6%
Length of time on haemodialysis (days)	1712.41 (77.457)
Number of previous lines	
1	32.8%
2-4	45.2%
5-7	14.2%
8-10	4.4%
11+	3.4%

60% (n=93) of patients had unilateral stenosis, with 62% of these being left sided. 40% (n=62) of patients had bilateral or caval stenosis/occlusion. In patients with unilateral CVS 41% affected the subclavian vein; 9% affected the subclavian/ brachiocephalic junction; 35% affected the brachiocephalic vein and 15% affected the brachiocephalic/ caval junction. In patients with bilateral CVS 12% had lesions in both subclavian veins; 20% had lesions in both brachiocephalic veins; 32% had a lesion in the superior vena cava and 36% had lesions at multiple sites.

The predominant clinical presentation was of vascular access loss rather than limb or facial swelling. Isolated facial or arm swelling only occurred in 8% of patients (n=12). 36% of patients (n=59) presented with loss of autologous vascular access and a further 32% (n=50) presented with a dysfunctional AVF in isolation. A further 32% (n=50) presented with both access loss/ dysfunction and arm/facial swelling.

3.3.2. Risk factors for central vein stenosis

23.6% of TCVCs (n=118) inserted between 1st January 2008 and 22nd October 2011 resulted in the development of CVS (median follow-up: 1,967 ± 567 days). Central vein stenosis was an inevitable consequence of any TCVC not removed for alternative reason e.g. bacteraemia or alternative access. Table 3.2 outlines risk factors for the development of CVS. Number of line days (OR 1.02, p=0.003), age (OR 1.04, p=0.04) and culture-proven line infection (OR 0.59, p=0.014) were all independently associated with CVS on multivariate analysis. (Table 3.3).

3.3.3. The patient pathway and access status

Patients experienced frequent intervention and hospitalisation beginning soon after the time of diagnosis and increasing exponentially over the subsequent three years. Table 3.4 describes interventions and hospitalisations and their associated healthcare costs during the first 3 years after diagnosis. A high number of TCVC insertions are required despite concurrent attempts to maintain vascular access through central vein angioplasty and creation of alternative vascular access.

Table 3.2: Risk factors for central vein stenosis. †Early infection is culture-proven bacteraemia within 90 days of line insertion. ††Vasculitides include vasculitis, systemic lupus erythematosus (SLE)/ scleroderma and Henoch-Schönlein purpura (HSP). * <0.001 comparing vasculitides in isolation.

Risk Factor	Central Vein Stenosis	No central vein stenosis	P value
Age (years)	54.8 (1.3)	61.9 (1.2)	0.001
Male	51.6%	48.9%	NS
Cause of Renal Failure			
Glomerulonephritis	17.9% (n=10)	82.1% (n=46)	NS
APKD	20.0% (n=8)	80.0% (n=32)	
Unknown	15.2% (n=16)	84.8% (n=89)	
Pyelonephritis	18.5% (n=5)	81.5% (n=22)	
Hypertensive disease	19.2% (n=5)	80.8% (n=21)	
Diabetic nephropathy	20.8% (n=20)	79.2% (n=76)	
IgA nephropathy	18.7% (n=6)	82.3% (n=24)	
Renovascular disease	17.6% (n=6)	82.4% (n=28)	
Vasculitides††	75% (n=12)*	25.0% (n=4)	
Unknown	15.2% (n=16)	84.8% (n=89)	
Other	23.3% (n=14)	76.7% (n=46)	
Diabetes mellitus	30.5% (n=36)	24.1% (n=92)	0.17
Cardiac event	47.5% (n=56)	50.0% (n=191)	NS
Mean number of lines	5.4 (2.3)	2.9(1.7)	<0.001
Number of line days	1488.7(135.2)	1268.4 (103.4)	<0.001
Length of time on HD (days)	2313.7 (189.6)	1677.75(129.2)*	<0.001
Culture-proven bacteraemia rate	2.6 (1.4)	2.35 (0.5)	NS
Early infection†	22.8%	5.9%	<0.001

Table 3.3: Logistic regression analysis for risk factors of central vein stenosis.

	B	SEM	P-value	Odds ratio (95% CI)
Age	0.21	0.007	0.003	1.02 (1.00, 1.03)
Length of time on haemodialysis	0.00	0.00	0.26	1.04 (1.04,1.04)
Number of line days	0.00	0.00	0.04	1.04 (1.04,1.04)
Culture proven infection	-0.56	0.23	0.014	0.59 (0.37,0.93)

Table 3.4: Number of interventions per patient per annum and estimated cost per patient and overall to the local service. Costs estimates reflect both the costs of the interventions and additional bed days. * Healthcare costs were estimated from hospital practice and unit costs were taken from Personal Social Service Research Unit (PSSRU5) figures, NHS Reference Costs, 2013-2014 and published literature (Curtis, 2012; Hockenhull et al. 2008; Department of Health, 2015).

Intervention	Year 1 (n=155)		Year 2 (n=102)		Year 3 (n=93)		Cost per procedure*
	Total	Per Patient	Total	Per Patient	Total	Per Patient	
TCVC	208	1.34	105	1.13	70	1.2	£614
Angioplasty	93	0.59	48	0.51	30	0.51	£2 882
Angiogram	27	0.18	19	0.2	19	0.32	£2 389
Central Venous Stent	13	0.08	0	0	1	0.02	£3 829
AVF Creation/Ligation	56	0.36	14	0.15	0	0	£1 368
Endovascular Declot	45	0.28	30	0.32	0	0	£2 769
Surgical Declot	30	0.09	0	0	0	0	£1 368
Thigh/Arm Graft	30	0.19	22	0.24	18	0.29	£1 998
Peritoneal Dialysis Catheter	3	0.02	1	0.02	1	0.02	£1 366
Translumbar Line	3	0.02	13	0.13	19	0.3	£720
Additional bed days	1391.6	8.9	741.8	8.0	681.9	12.5	£1 865
Total Costs (£)	**3.6m**	**22k**	**1.8m**	**19k**	**1.6m**	**27k**	

Patients required frequent intervention, with a mean of 3.87 interventions per patient in the first year of diagnosis. Frequent hospitalisation also featured, with patients accruing between 8 and 12 bed days per year per patient in addition to those required for specific interventions. For those with bilateral central vein stenosis, the requirement of intervention and hospitalisation was significantly higher. Patients with unilateral central vein stenosis utilised a mean 6.2 (2.3) bed days per annum in the first year after diagnoses; 3.2 (3.4) in the second year; and 6.9 (2.3) in the third year. Patients with bilateral central vein stenosis utilised 11.3 (3.4) bed days per annum. This was consistent across all of the first three years after diagnosis. In the first year following diagnosis patients with unilateral CVS had a mean of 2.9 (1.6) interventions/ year to maintain vascular access; in the second year this reduced to 1.2 (0.9) interventions per year. There were no interventions in the unilateral cohort in the third year after diagnosis. In the bilateral CVS cohort, the number of interventions/ year was: 4.0 (1.9), 3.2(1.5), 3.9 (2.3) for years 1,2 and 3 respectively.

The primary vascular access for haemodialysis changed as time passed following the diagnosis of CVS (Figure 3.1). 12 months following diagnosis, 29% (n=45) of the patents were dialysising via their AVF and 54% (n=81) were dialysing via TCVC. Conversely by 5 years following diagnosis, only 13% (n=20) of patients were using an AVF and 24% (n=37) were using a femoral line for dialysis. The majority of the cohort was utilising/ had utilised one or more complex forms of vascular access. 17% (n=26) of patients had died by 5-year follow-up and a further 18% (n=28) were transplanted.

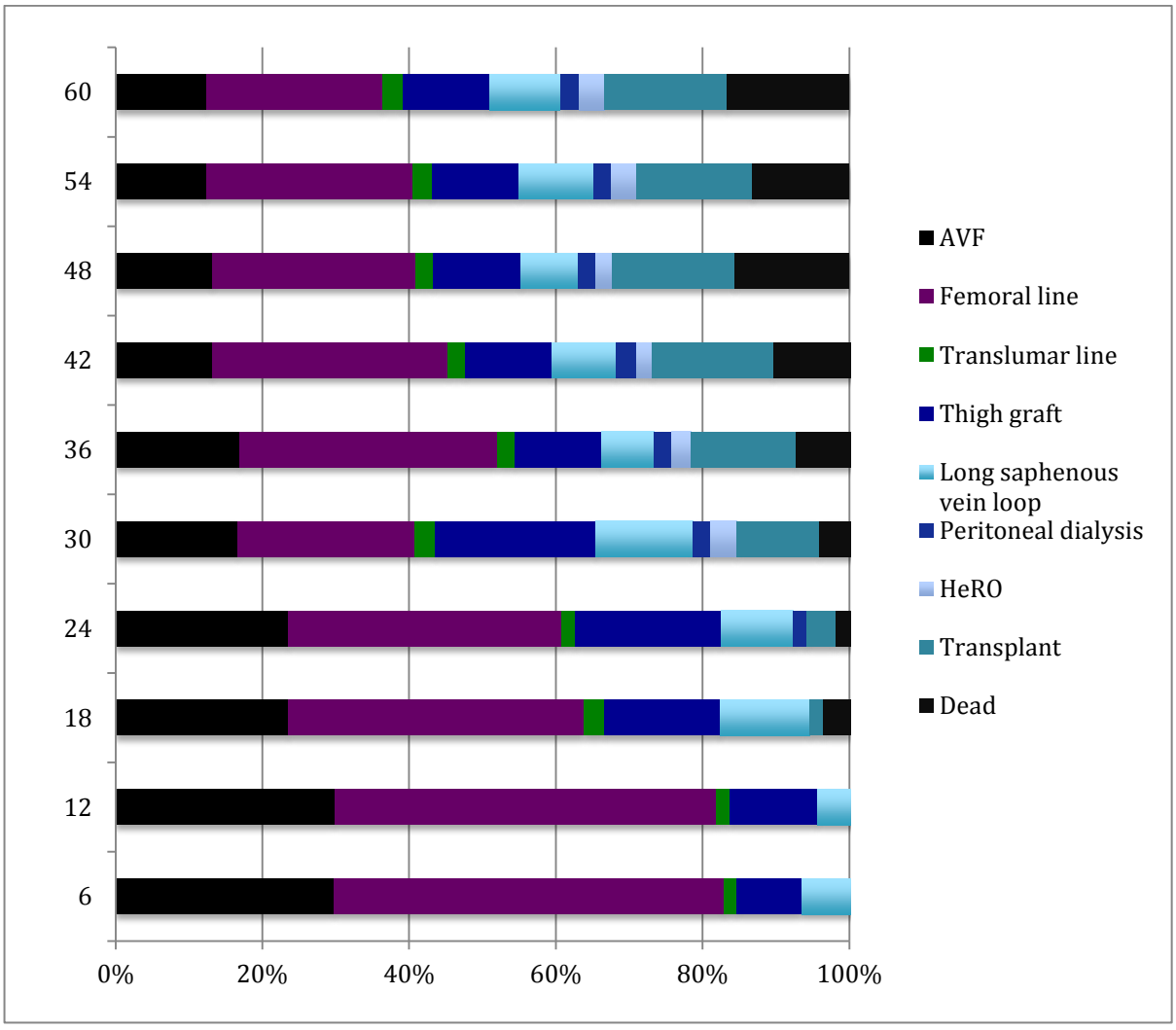


Figure 3.1: Vascular access/ RRT modality utilised by patients with CVS at 6 monthly intervals following diagnosis.

3.3.4. Economic cost of central vein stenosis

The crude costs for managing patients with CVS are outlined in Table 3.4. The average annual cost/ patient to treat CVS in this cohort was £27 000 in year 3 of diagnosis. Bilateral CVS incurs significant more annual cost than unilateral stenosis, escalating on an

annual basis as maintaining vascular access becomes more problematic (£22 500, £24 000 and £28 000 for bilateral in year 1, 2 and 3 respectively compared to £17 500, £8 000 and £15 500 for unilateral).

3.3.5. Personal cost of central vein stenosis

Quality of life data was collected on 120 patients with CVS (77.4%). 1 year follow-up data was collected on all patients who completed initial EQ-5D questionnaires.

Median EQ-5D quality of life scores at baseline were as follows: mobility 2 (IQR 2,4), self-care 2 (IQR 1,3), usual activities 2 (IQR 2,4), anxiety/ depression 2 (IQR 2,4), pain 3 (IQR 2,5). There was a significant increase in two domains of the EQ-5D score at 1 year: anxiety/ depression 4 (IQR 3,5) ($P<0.01$) and usual activities 3 (IQR 3,4) ($P<0.01$). There was no significant difference in the other three domains of the EQ-5D score after 1 year.

For ease of analysis, the EQ-5D score was also used to calculate a mean QoL score at 0, 6 and 12 months. These were 0.557, 0.484 and 0.448 respectively. (By comparison, patients established on haemodialysis generally have EQ5D/L scores between 0.6 and 0.7 in the first year of diagnosis (Manns et al. 2003))

The cost-per-QALY of maintaining vascular access in the first year of diagnosis of central vein stenosis equates to £42 308.

3.3.6. Outcomes in patients with bilateral central venous occlusion and end-stage vascular access

Sixty-two patients had evidence of bilateral CVS with loss of upper limb access at some point during the follow-up period. These patients were considered to have “end stage” vascular access and have been evaluated separately from the overall cohort. These patients reflect 40% of the overall CVS population and 5.2% of the entire dialysis population.

155 procedures for RRT access were performed on the 67 patients with ESVA during a four-year follow-up period, including 62 tunnelled femoral catheters in 36 patients and 25 prosthetic thigh grafts in 21 patients (Table 3.5). Table 3.6 outlines the basic demographics for each group. All but two of these patients had undergone previous attempts to salvage upper limb access with cutting balloon angioplasty ± stenting of the central veins.

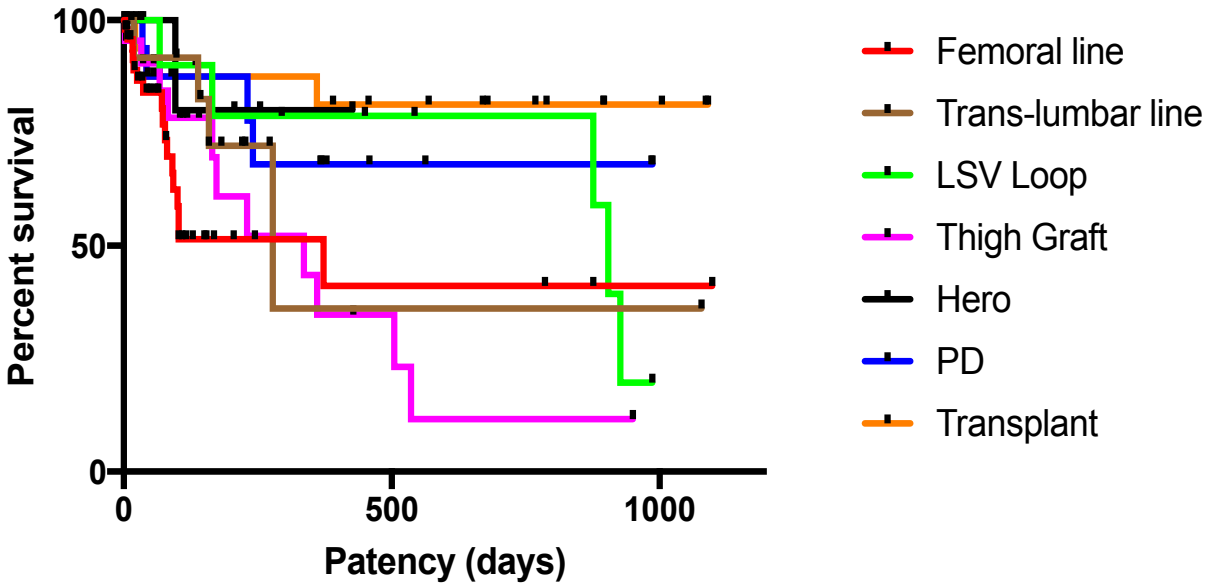
Access modality	Total number of procedures	Total number of patients receiving this access modality	Number of patients receiving access modality as first access	Number of patients receiving access modality as second access	Number of patients receiving access modality as third access	Number of patients receiving access modality as fourth access
Tunnelled femoral catheter	62	36	29	6	1	
Tunnelled translumbar catheter	25	23	14	9		
Long saphenous vein loop	15	13	9	3	1	
HeRO	6	6	0	2	4	0
Prosthetic thigh graft	25	21	10	6	2	4
Peritoneal dialysis	8	8	0	2	3	3
Renal transplant	18	18	0	5	8	5

Table 3.5: Numbers of procedures to achieve access for RRT performed on patients with end stage vascular access.

	Tunnelled femoral catheter (n=36)	Translumbar catheter (n=23)	Long saphenous vein loop (n=13)	HeRO (n=6)	Prosthetic thigh graft (n=21)	Peritoneal dialysis (n=8)	Renal transplant (n=18)	P-value
Age (years)	65.5 (6.5)	62.3 (6.3)	53.4 (7.9)	49.6 (6.5)	58.7 (8.7)	62.3 (6.7)	44.6 (9.3)	0.04
Sex (percentage male)	50%	52.2%	53.8%	50%	47.6%	50%	44.4%	0.87
Time on haemodialysis (years)	5.7 (3.1)	4.8 (3.2)	6.5 (4.6)	5.8 (6.8)	4.9 (2.8)	5.1 (3.2)	12.3 (5.6)	<0.01
Number of previous TCVCs (subclavian/ internal jugular)*	3 (1,8)	3 (1,6)	4 (2,7)	5 (3,7)	3 (2,5)	2 (1,4)	4 (2,10)	0.53
Number of previous upper limb AVF attempts*	2 (1,3)	2 (1,3)	3 (2,4)	3 (1,4)	3 (1,4)	3 (1,4)	3 (1,4)	0.65
Percentage of patients with at least 3 previous upper limb AVF attempts	16.7%	17.4%	23.1%	45.3%	28.1%	25%	36.3%	<0.01
Number of previous attempts at complex procedures for end-stage vascular access**	2 (1,5)	3 (1,5)	3 (1,6)	2 (1,4)	2 (1,4)	3 (1,6)	3 (2,6)	0.67

Table 3.6: Demographics of patients with end stage vascular access. Results presented as mean (SD) unless otherwise stated. * Number of previous upper limb AVF attempts and previous TCVCs is presented as median (IQR/ range); **Complex procedures for end-stage vascular access are those outlined in this paper (long saphenous vein loops, mid-thigh prosthetic grafts; femoral vein catheters; translumbar lines; HeRO).

The ultimate choice of access modality was made by the multidisciplinary vascular access team after discussion between patient, nephrologist, vascular access surgeon and interventional radiologist, taking into account patient choice, co-morbidities, and anatomical/ technical factors. Most patients tried more than one of the access modalities during the follow-up period (41 patients (67.2%) tried two and 10 patients (16.4%) tried three). 16 patients (26.2%) were unfit for thigh grafts and 42 patients (68.9%) were unfit for consideration of transplantation due to co-morbidities. 3 patients (4.9%) had contraindications to peritoneal dialysis (previous abdominal surgery or severe peritonitis). Mean follow-up time was 1,202 ±120 days per patient. Long-term secondary patency of each access/ RRT modality option is illustrated in Figure 3.2. Overall no access modality was superior to another (P=0.57) at 12 month follow-up, however the analysis is limited by lack of follow-up beyond two years for patients in the HeRO groups. Native long saphenous vein (LSV) loops had better secondary patency at 900 days (76.9%) than prosthetic thigh grafts (49.2%) or tunnelled femoral catheters (35.8%) ($p<0.01$), however there was a rapid decline in long saphenous vein loop patency beyond 900 days.



Number at risk	0 days	200 days	400 days	600 days	800 days	1000 days
Tunnelled femoral vein catheter	62	17	4	3	3	3
Tunnelled translumbar catheter	25	14	12	8	4	3
Prosthetic thigh graft	25	8	5	2	2	2
Native long saphenous vein loop	17	9	7	4	4	4
HeRO	6	4	4	0	0	0
Renal transplant	18	14	11	9	8	6
Peritoneal dialysis	8	7	6	4	4	2

Figure 3.2:Kaplan Meier survival curve outlining long-term patency/ durability of each of the access modalities. There was no difference in the long-term secondary patency with any of the access modalities (P=0.57).

Primary, primary-assisted and secondary patency rates at 3, 6 and 12 months for each of the modalities are shown in Table 3.7. Tunnelled catheters had acceptable 3 month primary and secondary patency rates, however this was poorer in the long-term. Whilst short-term primary patency rates of thigh grafts were poorer, secondary patency of both prosthetic thigh grafts and native long saphenous vein grafts were better (41.7% and 77.8% respectively). The HeRO device had a 1-year primary, primary assisted and secondary patency rate of 66%.

Infective complications are outlined in Table 3.8. Culture proven bacteraemia rate was highest in patients with tunnelled femoral catheters (1.8 per 1,000 catheter days) and peritoneal dialysis (2.0 per 1,000 dialysis days) in this patient population. There was no culture proven bacteraemia in patients with native long saphenous vein loops, however two patients did develop local infections at needling sites. Similarly the culture proven bacteraemia rate from prosthetic thigh loop grafts was 1.6 per 1,000 dialysis days, however 5 of 25 grafts (20%) also developed local infection without systemic sepsis.

Patients with femoral tunnelled central venous catheters (7.2 per patient/ year) and prosthetic thigh grafts (6.5 per patient/ year) required significantly more additional hospital days as a result of access (or transplant) related complications than the other access modalities ($P<0.05$). 12 patients died during the follow-up period, none as a result of loss of vascular access (3 cardiac events, 3 complications of peripheral vascular disease, 2 chest sepsis, 2 line sepsis, 1 diabetic hypoglycaemia, 1 pulmonary thromboembolism).

3.3.7. Expedited renal transplantation

24 of the 62 patients (38.7%) with ESVA were deemed to be eligible and fit for renal transplantation by their referring nephrologist. After discussion at the Renal Transplantation MDT meeting, 22 patients were deemed suitable for the “urgent” waiting list. 18 patients (81.8%) were transplanted during the follow-up period (9 patients (50%) via the “urgent” waiting list, 6 patients (33%) via the national waiting list and 3 patients (16.7%) received expedited live donor transplants). Two patients were removed from the waiting list as they became unfit for transplantation and two patients remain actively awaiting an “urgent” renal transplant (Figure 3.3).

	Tunnelled femoral catheter	Translumbar catheter	Long saphenous vein loop	Prosthetic thigh graft	HeRO	Peritoneal Dialysis	Renal transplant
Primary patency							
3 months	75.4%	88%	87.5%	64%	83.3%	62.5%	72.7%
6 months	48.1%	65%	60%	38%	66.6%	62.5%	72.7%
12 months	24%	50%	44.4%	23.5%	66.6%	50%	72.7%
Primary assisted patency							
3 months	75.4%	88%	87.5%	64%	83.3%	62.5%	72.7%
6 months	60%	65%	80%	38%	66.6%	62.5%	72.7%
12 months	28%	50%	56.5%	23.5%	66.6%	50%	72.7%
Secondary patency							
3 months	75.4%	88%	87.5%	72%	83.3%	62.5%	72.7%
6 months	60%	65%	80%	52.4%	66.6%	62.5%	72.7%
12 months	28%	50%	77.8%	41.7%	66.6%	50%	72.7%

Table 3.7: Primary, primary assisted and secondary patency of each of access modalities at 3, 6 and 12 months in patients with end-stage vascular access

	Tunnelled femoral catheter	Translumbar catheter	Long saphenous vein loop	Prosthetic thigh graft	HeRO	Peritoneal dialysis	Priority renal transplant	P-value
Culture proven bacteraemia rate (per 1,000 dialysis days)	1.8	0.6	0	1.6	0	2.0	0.1	<0.05
Additional bed days due to access related complications (per patient/year)	7.2	2.6	3.2	6.5	3.2	4.3	3.3	<0.05

Table 3.8: Access related complications in patients with end stage vascular access. Culture proven bacteraemia rate per 1,000 dialysis (or transplant) days and additional bed days (per patient/year) as a result of access related complications.

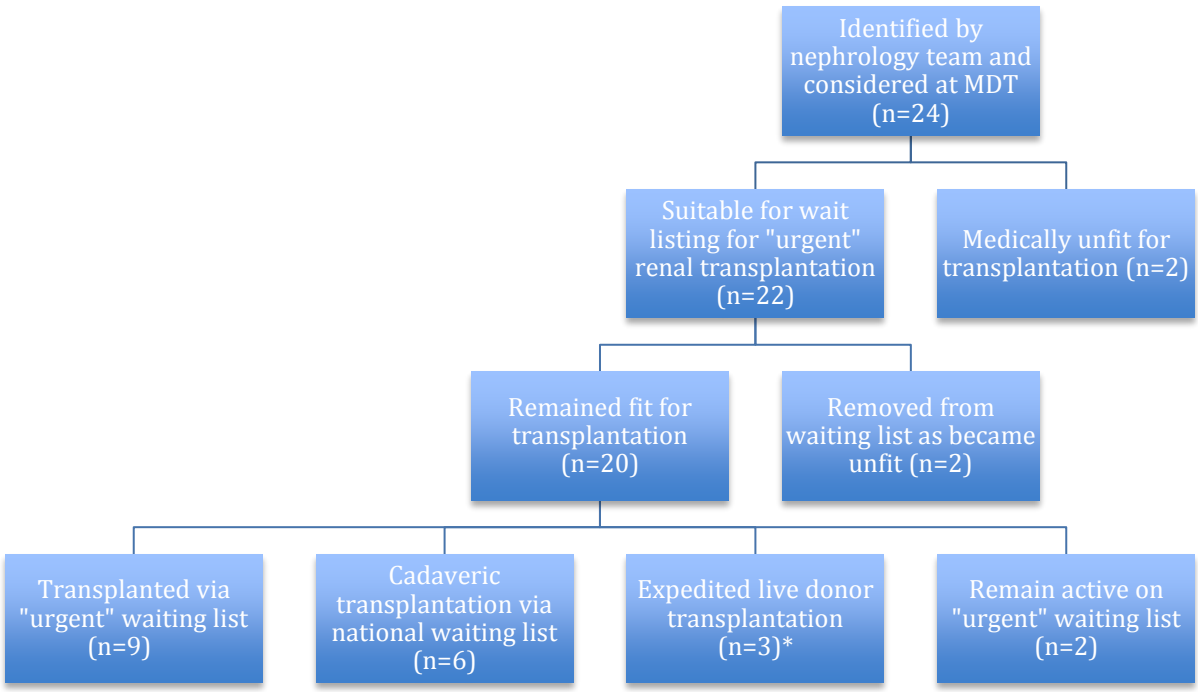


Figure 3.3: Flow diagram describing fate of patients considered for "urgent" renal transplant waiting list. 24 patients were considered and 22 deemed suitable for listing. 2 patients were subsequently removed from the waiting list as they became unfit. 18 patients were transplanted (9 via the "urgent" list, 6 via the national waiting list and 3 expedited live donor transplants (*one paired pool)). 2 patients remain active on the "urgent' renal transplant waiting list.

3.3.7.1. Demographics of ESVA patients considered for "urgent" transplantation

Table 3.9 outlines the characteristics of each patient with ESVA undergoing transplantation. Each patient was unique in the anatomical, technical and immunological challenges that they posed. These are described in the table.

EXPEDITED TRANSPLANTS												
Recipient age (years)	**Recipient sex**	**Current vascular access**	**Vascular access history**	**Donor type**	**Donor age (years)**	**Donor sex**	**cRF**	**Previous transplant**	**Additional immunological comments**	**Additional technical comments**	**eGFR at 1 year (ml/min/1.73m^2)**	**Complications**
37	Male	Femoral TCVC	4 upper limb AVF; 2 leg vein loops; 3 lower limb AVGs; failed PD; 25 TCVCs	DBD	64	Female	100%	1	Positive B-cell CDC crossmatch; DSA at time of transplant, cumulative MFI 28,000; ATG induction		13.3	Poor graft function; pulmonary thromboembolism and death 13 months post-transplant (unable to obtain any vascular access to permit thrombolysis)
45	Female	Femoral TCVC	3 upper limb AVF; 1 leg vein loop; 1 lower limb AVG; 14 TCVCs; unsuitable for PD	DCD	25	Male	95%	1	Weak DSA at time of transplant (MFI 1700); multiple mismatches with previous transplant; basiliximab induction	Donor AKI (creatinine approx. 300 at time of transplant)	47	
42	Female	Femoral TCVC	3 upper limb AVF; 6 TCVCs	DCD	41	Female	22%	2	Basiliximab induction	Long CIT (20 hours); poor perfusion; previously turned down by several other units	80.2	
54	Female	Thigh AVG with ruptured pseudo-aneurysm	2 upper limb AVF; failed PD; 8 TCVCs; 1 thigh AVG with ruptured pseudo-aneurysm on day of transplant	DCD	39	Female	48%	0	Basiliximab induction	Long CIT (16.5 hours)	71	
57	Male	Thigh AVG	18 TCVCs; 1 upper limb AVF; unsuitable for PD	DCD (dual)	66	Male	0%	0	Basiliximab induction	Donor hypertension (3 agents), diabetes and CKD; dual transplant	54	Transplant renal artery stenosis; thigh graft ligated post-transplant for steal.
46	Female	LSV loop	12 TCVCs, 3 upper limb AVF, 2 LSV loops, failed PD	DCD	50	Female	99%	1	Basiliximab induction	3 arteries	57.6	

62	Female	Thigh AVG	26 TCVCs, 3 upper limb AVF; APKD; unsuitable for PD	DCD	60	Male	58%	0	Weak DSA at time of transplant (MFI 1300). ATG induction		NA	Complicated by PRES and sepsis; CNI withdrawn, then got ABMR. Graft loss and death 5months post-transplant
30	Female	Thigh AVG (recently revised for pseudo-aneurysm)	6 TCVCs, no native upper limb options (1 failed AVF); 1 LSV loop; 1 thigh AVG (revised x2)	DCD	55	Female	97%	1	Multiple weak DSA at time of transplant (total MFI 8000). ATG induction		73.7	
44	Male	Thigh AVG (infected at time of transplant)	15 TCVCs, 4 upper limb AVF, Failed PD	DCD	62	Female	8%	0	Basiliximab induction		48.2	Infected thigh graft removed at time of transplant
END-STAGE VASCULAR ACCESS PATIENTS TRANSPLANTED VIA NATIONAL MATCHING ALGORITHM												
42	Male	Thigh AVG	16 TCVC, 3 upper limb AVF, LSV loop; thigh AVG; failed PD	DBD (dual)	3.5	Male	99%	1	No pre-formed DSA. ATG induction	En-bloc transplant of paediatric kidneys; donor IVC and aorta to recipient external iliac vessels	103.2	Thigh graft (ipsilateral) ligated intra-operatively to improve perfusion to transplant kidneys
46	Male	Subclavian TCVC (inserted after angioplasty)	25 TCVC, 5 upper limb AVF, PPM, failed PD	DBD	70	Female	91%	0 (previous heart transplant)	No pre-formed DSA. ATG induction		28	Re-explored x3 for post-op bleeding (heparinized)
54	Male	Temporary femoral line	3 upper limb AVF; 3 thigh AVGs, 32 TCVCs; failed PD	DBD	71	Female	96%	1	Multiple pre-formed weak DSA (cumulative MFI 10000); historic positive B-cell flow crossmatch; ATG induction	Iliac vessels completely occluded; donor renal artery and vein to recipient aorta and IVC	NA	Venous thrombosis; re-explored day 3; graft loss and graft nephrectomy day 7
40	Male	BCF draining to collaterals	2 upper limb AVF; thigh graft; subclavian to iliac graft	DBD	66	Female	98%	0	Multiple pre-formed DSA (cumulative MFI 7300). ATG induction		NA	Primary non-function; presumed ABMR; calciphylaxis and access loss; died 4 months post-transplant

44	Male	LSV loop	4 upper limb AVF; 24 TCVCs; 2 LSV loop; 2 thigh AVG	DBD	64	Male	100%	1	No pre-formed DSA. 000 mismatch. Basiliximab induction		24	
55	Female	Femoral TCVC	14 TCVCs, 2 upper limb AVF	DCD	67	Female	40%	0	Weak DSA (MFI 1000)		NA	Wound infection and breakdown; Gram negative sepsis; immunosuppression stopped; ABMR; persistent life-threatening sepsis; graft nephrectomy after 1 month; died from sepsis 2 months after transplant
ESVA PATIENTS HAVING LIVE DONOR TRANSPLANT												
25	Female	BCF draining via collaterals	2 upper limb AVF; failed PD	LD (related)	23	Male	98%	2	No pre-formed DSA. 000 mismatch. Basiliximab induction		125.6	
41	Female	Temporary femoral line	2 upper limb AVF; 2 thigh AVGs	LD (unrelated)	45	Male	0%	0	Basiliximab induction	Kidney transplanted onto iliac over femoral line as contralateral side not patent	19	Graft loss after 15 months; ABMR secondary to non-compliance
39	Femoral	Subclavian (post-angioplasty)	32 TCVCs; 4 upper limb AVF; failed PD	LD (paired pool)	52	Female	99%	1	No pre-formed DSA. Previous PTLD; basiliximab induction		36.7	

Table 3.9: Descriptive data summarising demographics and transplant details of all patients with ESVA. DBD= donation after brain death; DCD= donation after cardiac death; LD= live donor; PD= peritoneal dialysis; TCVC= tunnelled central venous catheter; AVF= arteriovenous fistula; AVG= arteriovenous graft; BCF=brachiocephalic fistula; LSV= long saphenous vein; IVC= inferior vena cava; PTLD= post-transplant lymphoproliferative disorder; PPM= permanent pacemaker; APKD= adult polycystic kidney disease; CKD= chronic kidney disease; ABMR= antibody mediated rejection; ATG= anti-thymocyte globulin; DSA= donor specific antibody; MFI= mean fluorescence intensity

The mean age of patients with ESVA undergoing renal transplantation was comparable to that of the general transplant population (44.6 ±9.3 years vs. 48.8 ±12.9 years; P=0.65). There was also no significant difference in wait time prior to transplantation between patients with ESVA and the overall transplant cohort (1305.4 ± 925.5 days vs. 1168.2 ±675.4 days; P=0.15) (Table 3.10). Immunologically patients with ESVA were also more complex to transplant than the overall transplant cohort. 11 patients (61.1%) with ESVA had a cRF (calculated reactive frequency) >90%. Mean cRF and match score in the ESVA cohort and overall transplant population were 96% (IQR; 40%, 99%) vs. 32% (IQR: 24%, 83%) and 12 (IQR 0,41) vs. 132 (IQR 67, 237); P<0.001 respectively. Patients with ESVA had been on dialysis for longer than the overall transplant cohort (12.3 ±5.6 vs. 3.7 ± 1.2 years; P<0.001). 11 of the 18 patients (61.1%) were receiving a second or subsequent transplant and most were dialysing via either a TCVC or AVG at the time of transplantation (Table 3.10).

Table 3.10: Basic demographics of patients with ESVA undergoing renal transplantation compared to a control group of all patients undergoing renal transplantation at our institution over the same time period. There was no significant difference in age or gender, however patients with ESVA were more likely to be dialysing via a TCVC or AVG rather than AVF and were also more highly sensitised and more difficult to transplant. Results are reported as either mean (SD) or median (IQR). AVF= arteriovenous fistula; AVG= arteriovenous graft; TCVC= tunnelled central venous catheter; cRF= calculated reaction frequency, match score= a hypothetical score calculated based on recipient HLA-type and blood group (it reflects the number of patients out of a standard cohort of 10,000 patients who are blood group identical, HLA-compatible and 000 of favourably [100, 010, 110] matched); match points= converts the match score into a points score for the matching algorithm based on ease of transplantation.

	Patients with ESVA undergoing renal transplant	**All renal transplants (n=452)**	**P-value**
Age (years)	44.6 (9.3)	48.8 (12.9)	N.S.
Sex (%age male)	44.4% (n=8)	47.1% (n=213)	0.13
Vascular access			
AVF	22.2% (n=4)	74.1% (n=335)	
AVG	38.9% (n=7)	1.1% (n=5)	
TCVC	33.3% (n=6)	24.8% (n=112)	
Temporary line	5.5% (n=1)	-	<0.01
cRF (%age)	96% (IQR 40%,99%)	32% (IQR 24%, 83%)	0.02
Waiting time (days)	1305.4 (925.5)	1168.2 (675.4)	0.15
Total time since first commencing dialysis (years)	12.3 (5.6)	3.7 (1.2)	<0.001
Match score	12 (IQR 0,41)	132 (IQR 67,237)	<0.001
Match points			
Easy (1-3)	22.2% (n=4)	39.8% (n=180)	
Moderate (4-7)	27.8% (n=5)	44.7% (n=202)	
Difficult (8-10)	50% (n=9)	15.5% (n=70)	<0.001

3.3.7.2. Outcomes of renal transplantation in patients with ESVA

Patients with ESVA were more likely to experience delayed graft function (DGF) post-transplant than the general population (44.4% vs. 24.7%; P<0.001). Primary non-function was also more common (11.1% vs. 1.1%; P<0.001) (Table 3.11). Not unsurprisingly, given the higher immunological risk that these patients pose, biopsy-proven acute rejection (BPAR) was also more common in the first year post-transplant (27.8% vs. 8.4%; P<0.001). Five patients with ESVA had BPAR on indication biopsy. One patient had been non-compliant with medication, three patients developed BPAR after immunosuppression was reduced or withdrawn as a result of other complications and one patient developed BPAR whilst on adequate immunosuppression (cell-mediated which responded well to intravenous methylprednisolone). One-year graft survival was lower in patients with ESVA (77.8% vs. 92.0%; P<0.001); however in those with a functioning graft at 1-year eGFR was comparable to that of the overall transplant population (62.0 ±13.4 vs. 58.4 ±20.9 ml/min/1.73m$^{2;}$ P=0.54) (Table 3.11). 1-year patient survival in the ESVA cohort undergoing transplantation was lower than in the overall transplant cohort (83.3% vs. 95.1%; p<0.001) however this was higher than in the cohort of ESVA patients (n=45) during the same time period that did not get transplanted (P<0.01). In this cohort, one-year survival (from time of identification as having ESVA) was 68.9%, with one dying as a result of loss of access and inability to dialyse and the others dying from co-morbidities and complications of end-stage renal disease.

Table 3.11: Outcomes of transplantation in patients with ESVA compared to the overall transplant cohort demonstrating higher rates of DGF, BPAR and primary non-function amongst patients with ESVA. One-year graft and patient survival was also lower, however in those patients with ESVA who had a functioning graft at 1 year, the eGFR was comparable to that of the overall transplant population.

	Patients with ESVA undergoing renal transplant	**All renal transplants**	**P-value**
DGF (%age)	44.4% (n=8)	24.7% (n=112)	<0.001
BPAR in first year post-transplant (%age)	27.8% (n=5)	8.4% (n=38)	<0.001
Primary non-function (%age)	11.1% (n=2)	1.1% (n=5)	0.01
eGFR at 6 months (ml/min/1.73m^2)	63.4 (14.5)	61.2 (15.4)	N.S.
eGFR at 12 months (ml/min/1.73m^2)	62.0 (13.4)	58.4 (20.9)	N.S.
1 year graft survival (%age)	77.8% (n=14)	92.0% (n=416)	<0.001
1 year patient survival (%age)	83.3% (n=15)	95.1% (n=430)	<0.001

3.3.7.3. Characteristics and outcomes of patients with ESVA receiving an expedited cadaveric renal transplant

There was no significant difference in donor or recipient age between patients with ESVA receiving a transplant via the expedited list or national matching algorithm (46.3 ± 10.0 vs. 46.8 ± 6.3 years; P=0.54 and 51.3 ± 14.2 vs. 56.9 ± 26.3; P=0.11 respectively) (Table 3.12). All kidneys came from extended criteria donors in both cohorts. 88.9% (n=8) of the expedited transplants came from donation after cardiac death (DCD) donors, whilst most of those allocated from the national matching algorithm were donation after brain death (DBD) donors (83.3% [n=5]). There was also no significant difference in waiting time between patients with ESVA transplanted via the expedited list and national matching algorithm (1254.3 ±754.8 vs. 1403.4 ±403.4 days; P=0.26).

There was no significant difference in the eGFR obtained at 12 months from kidneys allocated via the expedited list and those allocated via the national algorithm to patients with ESVA (65.8 ±23.2 vs. 56.9 ±26.3 ml/min/1.73m^2; P=0.16). DGF was less common in patients transplanted via the expedited list (33% [n=3] vs. 100% [n=6]; P<0.001). There was no significant difference in 1-year patient survival (88.9% [n=8] vs. 66.7% [n=4]; P=0.09), however 1-year graft survival was better in the expedited transplant cohort than those transplanted via the national algorithm (88.9% [n=8] vs. 50% [n=3]; P=0.04) (Table 3.12).

3.3.7.4. Impact of transplantation of patients with ESVA on resource utilisation

Table 3.13 compares the number of hospital admissions, bed days and interventions performed in patients with ESVA during the year prior to a following renal transplantation. Overall there were fewer hospital admissions following transplantation (6.5 ±1.6 vs. 2.4 ±2.7 days/ patient/ year; P<0.01) and patients spent less time hospitalised in the year after transplant than in the year before (21.3 ±12.3 vs. 11.6 ± 0.7 days/patient/year; P=0.02). This latter observation would be even more marked were it not heavily influenced by three patients who had very complicated and torrid post-operative courses with in-patient stays >3 months. Notably the mean length of hospital stay for the entire transplant population was 11.2 ± 3.2days/ patient in the first year post-transplant (P=0.72).

Table 3.12: Comparison of transplants carried out in patients with ESVA (expedited cadaveric; those allocated via national matching algorithm; and live donor). Recipient characteristics were comparable. Graft outcomes are at least comparable and may be better in the expedited cadaveric cohort than in those transplanted via the national matching algorithm. Results are reported as either mean (SD) or median (IQR). DBD= donation after brain death; DCD= donation after cardiac death; cRF= calculated reaction frequency, match score= a hypothetical score calculated based on recipient HLA-type and blood group (it reflects the number of patients out of a standard cohort of 10,000 patients who are blood group identical, HLA-compatible and 000 of favourably [100, 010, 110] matched); match points= converts the match score into a points score for the matching algorithm based on ease of transplantation. The level of match reflects the HLA-mismatch (Level 1: 000, Level 210, 010, 110, 200 or 210; Level 3: 020, 120, 220, 001, 201, 011, 111 or 211; Level 4: 021, 121, 002, 102, 202, 012, 112, 212, 022, 122 or 222). DGF= delayed graft function; eGFR= estimated glomerular filtration rate.

	Patients with ESVA undergoing expedited renal transplant (n=9)	**Patients with ESVA receiving cadaveric transplant via national matching algorithm (n=6)**	**Patients with ESVA having live donor transplant (n=3)**	**P-value***
Recipient Age (years)	46.3 (10.0)	46.8 (6.3)	35 (8.7)	N.S.
cRF (%age)	58% (IQR 22%,99%)	97% (IQR 91%,99%)	90% (IQR 0%,99%)	N.S.
Waiting time (days)	1254.3 (754.8)	1403.4(634.6)	342.6 (267.5)	N.S
Match score	0 (IQR 10,33)	12 (IQR 2,16)	266 (IQR 1,320)	N.S.
Level of mismatch Level 1 Level 2 Level 3 Level 4	 11.1% - 66.7% 22.2%	 33.3% - 33.3% 33.3%	 33.3% - 66.7% -	 N.S
Donor age (years)	51.3 (14.2)	56.9 (26.3)	40 (15.1)	0.11
Type of donor (%age) DBD DCD	 11.1% (n=1) 88.9% (n=8)	 83.3% (n=5) 16.7% (n=1)	 NA	 <0.001
Extended criteria donor (%age)	100% (n=9)	100% (n=6)	NA	N.S.
DGF (%age)	33.3% (n=3)	100% (n=6)	33% (n=1)	<0.001
eGFR at 12 months (ml/min/1.73m^2)	65.8 (23.2)	56.9 (26.3)	58.5 (47.3)	0.16
1 year graft survival (%age)	88.9% (n=8)	50% (n=3)	100% (n=3)	0.05
1 year patient survival (%age)	88.9% (n=8)	66.7% (n=4)	100% (n=3)	0.09

Table 3.13: A comparison between the number of bed days and hospital admissions in patients with ESVA in the year prior to and the year following transplantation.
Results are presented as mean (SD) and are expressed per patient per year.* Interventions include any surgical procedure e.g. transplant or vascular access procedure, interventional radiology procedure e.g. angiography or nephrostomy or other invasive procedure e.g. line insertion performed on the patient.

	In the year prior to transplantation	**In the year following transplantation**	**P-value**
Number of hospital admissions (per patient/yr)	6.5 (1.6)	2.4 (3.7)	<0.01
Number of unplanned hospital admissions (per patient/yr)	4.9 (1.9)	1.4 (3.2)	<0.01
Number of bed days (per patient/yr)	21.3 (12.3)	11.6 (13.6)	0.02
Number of interventions* (per patient/ yr)	5.4 (4.3)	1.6 (0.7)	<0.01

Fewer interventional procedures were also performed in the year post transplantation (5.4 ± 4.3 vs. 1.6 ± 0.7 procedures per patient/ year). Pre-transplant the procedures primarily related to vascular access including 37 TCVCs, 52 angioplasties or declotting procedures and 32 access creations. Post-transplant procedures also primarily related to complications of vascular access including ligation/ removal of access for infection, steal or rupture (n=7), TCVC insertion (n=4) and also one patient who required nephrostomy insertion.

A total of 39 cross-match tests have been performed to permit 9 expedited transplants (4.33 cross matches per transplant).

3.3.7.5. Chance of transplant in patients with end-stage vascular access

Compared to an age and sex matched cohort (n=18), patients with ESVA had a higher cRF, poorer match score, longer wait time and more previous transplants (Table 3.14). As a result, their chance of transplantation is significantly lower. The age and sex-matched cohort has a 50% chance of transplant after 3.7 years according to the NHS Blood and Transplant Chance of Transplant Calculator (NHS Blood and Transplant, 2014), whilst 12 of the 18 patients (66.7%) in the ESVA had a 50% chance of transplant >5 years. The ESVA cohort had a 4%, 10%, 20%, 32% and 43% chance of transplant at 1, 2, 3, 4 and 5 years respectively (Figure 3.4).

Table 3.14: Comparison of patients with ESVA undergoing renal transplantation (n=18) and an age and sex-matched cohort of other patients undergoing renal transplantation (n=18). Patients with ESVA had a higher cRF, longer wait time and poorer match score. Results are presented as a mean (SD), median (IQR) or percentage of total. cRF= calculated reaction frequency, match score= a hypothetical score calculated based on recipient HLA-type and blood group (it reflects the number of patients out of a standard cohort of 10,000 patients who are blood group identical, HLA-compatible and 000 of favourably [100, 010, 110] matched); match points= converts the match score into a points score for the matching algorithm based on ease of transplantation.

	Patients with ESVA undergoing renal transplant (n=18)	**Age and sex matched cohort (n=18)**	**P-value**
cRF (%age)	96% (IQR 40%,99%)	21% (IQR 12%, 85%)	<0.01
Waiting time (days)	1305.4 (925.5)	1032.4 (457.4)	<0.01
Total time since first commencing dialysis (years)	12.3 (5.6)	3.2 (1.3)	<0.001
Match score	12 (IQR 0,41)	167 (IQR 79,312)	<0.001
Number of previous transplants 0 1 2 3	 38.9% (n=7) 50% (n=9) 5.6% (n=1) 5.6% (n=1)	 94.4% (n=17) 5.6% (n=1)	 <0.01

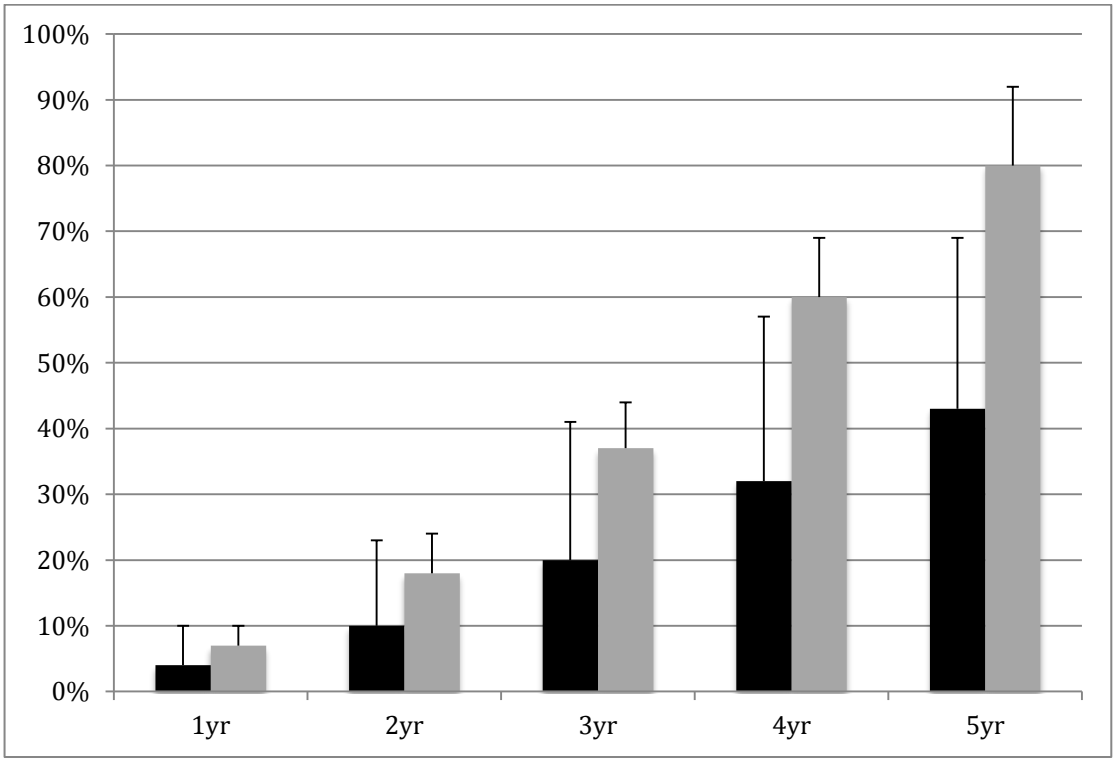


Figure 3.4: Chance of transplant at 1, 2, 3. 4 and 5 years post wait-listing in patients with ESVA (black) compared to an age and sex-matched cohort (gray). Error bars show 1 SD

3.3.7.6. Patients with ESVA still untransplanted despite expedited transplant list

After 5 years of the expedited transplant list, two patients remain untransplanted. Both have been on the expedited waiting list for the entire 5 years with total waiting times of 3657 and 1954 days respectively. Both patients have a cRF of 100% (even after removing weak unacceptable [MFI<3000]) and match scores of 1. Each has been considered for over 20 potential "priority" blood group compatible kidneys but no cross-match performed due to high levels of unacceptable antibodies. Figure 3.5 outlines the antibody profile of one of these two patients, highlighting the difficulties of transplantation in this cohort.

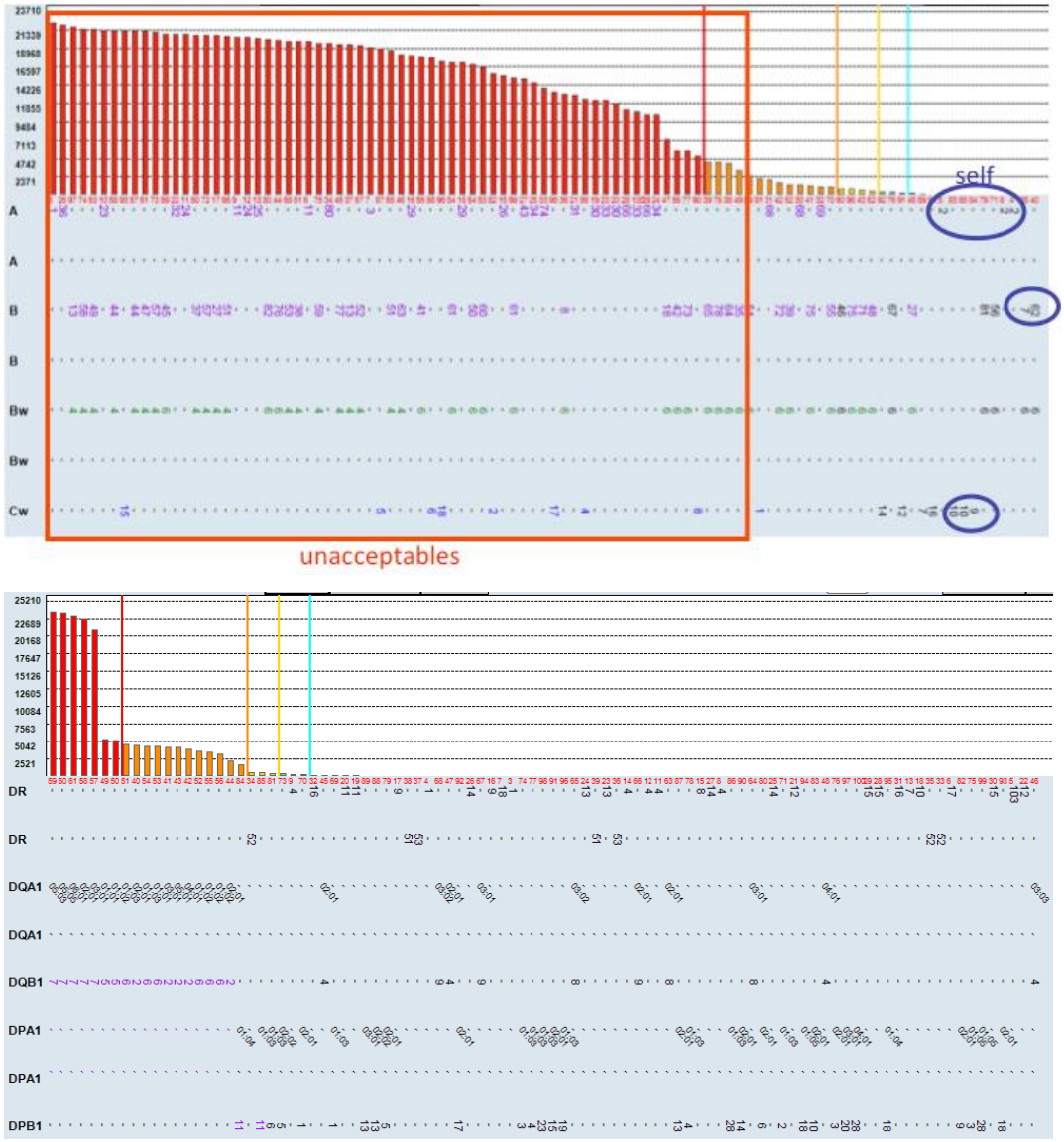


Figure 3.5: Antibody profile of one of the two patients with ESVA in whom it has not been possible to find a kidney for transplantation via the expedited waiting list. Even after removing all acceptable mismatches (MFI <3000), he still has a cRF of 100% and match score of 1. He has high levels of pre-formed antibodies to most HLA class I (top) and almost all HLA class II except self (-DR4, -DQ4, -DP3, -DP4) (bottom). With thanks to Dr Ann-Margaret Little.

3.3.7.7. Impact of the expedited list on the rest of the transplant population

All patients who were ranked top of the local matching algorithm on the day that the kidney was allocated to an ESVA patient via the expedited waiting list were transplanted within one year and all bar one were transplanted within 6 months. The mean waiting time from the day of the potential offer to transplantation was 128.2 ± 97.5 days. During this time one patient had an arteriovenous fistula that failed and required admission for TCVC and new AVF creation. Otherwise no patient suffered any obvious adverse consequence of additional waiting time and no additional hospital admissions were incurred.

3.4. DISCUSSION

3.4.1. The burden of central vein stenosis

Although central vein stenosis is a well recognised phenomenon in individual patients, the collective extent and impact on the overall patient cohort and the subsequent healthcare costs has been underappreciated. This study has utilised a comprehensive electronic database of all procedures and complications to allow, for the first time, the true impact of CVS on the RRT population to be analysed. We have shown that CVS is common, costly and has a dramatic adverse impact on quality of life (QoL). These data, in addition to the widely recognised risks of infection, allow a risk to be estimated from the consequences of using TCVC in both the short and long-term.

There is a clear causative relationship between central vein stenosis and TCVC use in both this study and others (Lumsden et al. 1997) supported by histopathological evidence demonstrating stenosis formation after even short periods of central venous catheterisation (Agarwal, 2013).

In this cohort of patients, the prevalance of clinically significant CVS was 13%. Other studies that report a higher prevalence included patients with incidental findings on angiography (Agarwal et al. 2007; Suroweic et al. 2004). A critical new observation in this patient cohort is the description that the principal presenting complaint in CVS is vascular access dysfunction rather than isolated limb or facial swelling. Preservation of the original vascular access was just 16% by 3 years, highlighting that the fate of dysfunctional access should be a key primary outcome when reporting on intervention for CVS.

CVS patients demonstrated objective evidence of deterioration in QoL. The quality of life outcome is limited by incomplete data collection. Only three-quarters of the cohort completed QoL questionnaires. The demographics of this subgroup were, however, similar to the overall CVS cohort. This is the first published QoL data for patients with CVS. Previous studies have shown that quality of life on HD with a functioning fistula is comparable to with TCVC (Manns et al. 2003). Although direct comparisons cannot be drawn, this reinforces the assertion that the psychosocial impact of CVS carries negative effects for the patient beyond the frequency of procedures and hospitalisation.

CVS also carries a significant economic and financial burden. The healthcare costs of repeated and frequent intervention rapidly accumulates. This does not appear to be as a result of the failure of any one of our treatment strategies. Angioplasty (Dammers et al. 2003a; Kovalik et al. 1994), TCVC (Agarwal, 2013) and AVG (Harish & Allon, 2011) outcomes were largely in keeping with those published in specific series. Clinical performance met accepted standards. The crude cost of looking after 97 patients in the first year of diagnosis was £2.1 million. This equated to a cost per QALY of £42 307.69. In the UK, the National Institute of Clinical Excellence (NICE), generally only consider funding treatments with a cost per QALY of less than £20 000, extended to £30 000 under certain circumstances (NICE, 2014). While this costing does not represent one specific treatment, it does represent a treatment philosophy that is representative of that which is provided by most clinicians managing patients with CVS. As a total cost to the NHS, if a prevalence of 13% nationwide is assumed amongst the 20 000 patients on HD in the UK, nationally this could amount to a spend of £57 million per annum. This reflects the delayed price that both patients and healthcare systems are paying for the early convenience of commencing dialysis with a line. Better systems of planning and initiating dialysis at diagnosis of end stage renal failure are required to protect patients from this significant delayed complication.

CVS presents two major challenges: prevention and “cure”. This study demonstrates the burden of care incurred in the pursuit of a “cure” for CVS and indirectly highlights the importance of prevention. Contemporary practice has inherited a generation of HD patients who have been exposed to a practice whereby central vein catheterisation was performed more liberally than it is today, following the drive for “Fistula First” and timely creation of autologous access (Vassalotti et al. 2012). Prevention of CVS should be considered a clinical priority. Timely referral, education and an integrated structure for referral and access creation is essential to optimise the rates of autologous vascular access in incident

HD patients (Hughes et al. 2013). Emergency peritoneal dialysis is an under-explored potential alternative (Ilbaca-Avendano et al. 2008) . The development of prosthetic early cannulation arteriovenous grafts (ecAVGs), which can be used within 24 hours of insertion, may provide a viable alternative to TCVCs in patients who need to commence HD but who do not yet have a functioning vascular access (Tozzi et al. 2014b). Perhaps even revisiting old technologies such as the Scribner shunt (Quinton et al. 1962) for emergency dialysis may allow for safe anaesthesia prior to insertion of a more durable access.

3.4.2. End stage vascular access: outcomes of differing treatment modalities

Contrary to other published series, we report good short and longer term patencies of native long saphenous vein loop grafts in patients with bilateral central venous occlusion .The 900 day primary assisted patency rate of 76.9% is favourable compared to 66% at 2 years and 40% at 3 years presented by other institutions (May et al. 1980), however long-term patency is unlikely to rival that of femoral vein transposition (56% at 9 years) obtained by some authors (Hazinedaroğlu et al. 2004) . We believe that this is a result of careful patient selection, pre-operative ultrasound imaging to confirm suitability of the vessels and aggressive surgical and radiological re-intervention for stenotic and thrombotic complications. We advocate that long saphenous vein loops be considered as an excellent lower limb autologous option for all end-stage access patients who are fit enough and are likely to require vascular access for haemodialysis for more than 6 months.

Lower limb prosthetic thigh grafts have been used with variable success in patients with ESVA. Both primary and secondary patency rates were lower than native long saphenous vein loops and comparable to other published series. Cull et al. (2004) report 2-year primary and secondary functional patency rates for prosthetic lower limb grafts of 19% and 54% respectively. There was a high culture-proven bacteraemia rate from prosthetic thigh grafts in the high-risk patient group with bilateral central vein stenosis, which was comparable to that of TCVCs (Harish & Allon, 2011). Furthermore, infected haematomas proved problematic in many cases (Aitken et al. 2014a). Nevertheless, novel ecAVGs may be beneficial in patients who require immediate vascular access for haemodialysis and cannot wait for a native vein loop to mature, with superior patency rates than tunnelled femoral catheters.

Bacteramia rates associated with tunnelled catheters were relatively low in the end-stage access cohort (1.8 per 1,000 catheter days and 0.6 per 1,000 catheter days for tunnelled femoral and translumbar catheters respectively) compared to standard rates for all-comers on HD. Local culture-proven bacteraemia rate of tunnelled central venous catheters is 1.6 per 1,000 catheter days for all patients on haemodialysis (Thomson et al. 2010). Power and colleagues (2010) report exit site infection rates of 2.02 per 1,000 catheter days and culture proven bacteraemia rates of 0.8 per 1,000 catheter days for translumbar catheters. For tunnelled femoral lines, Falk (2007) quotes a bacteraemia rate of 6.3 per 1,000 catheter days. We postulate that the low infection rates seen in our cohort, even with higher risk femoral catheters, may be due to heightened vigilance for infection control procedures in patients deemed to have precarious vascular access with protection of the "last access option".

There were a small number of patients (n=6) who had a HeRO in this cohort. All had a Gore®ACUSEAL graft (W.L. Gore Associates, Flagstaff, AZ, USA) attached to permit immediate cannulation. Follow-up in this patient cohort is limited, as the device only became available in the UK in 2013, however primary, primary assisted and secondary patency at 12 months was 66%. Unlike other modalities in this series, multiple interventions within the first year were not required to maintain patency of the HeRO device. Our results are at least comparable with those observed in other series. Nassar and colleagues (2014) report 1-year primary and secondary patency rates of 34.8% and 67.6% respectively. Similarly, Katzman et al. (2009) report a secondary patency rate of 72.2% at mean follow-up 8.6 months.

No patient died as a result of loss of vascular access and there was no requirement of exotic, "last resort" procedures within this patient group. This highlights that it is possible to maintain the majority of patients with bilateral central venous occlusion and ESVA on RRT with a relatively limited number of secondary vascular access procedures and renal transplantation where appropriate. Most patients needed to utilise more than one access modality, illustrating the burden of bilateral central vein stenosis on both the patient and healthcare services. Additionally, this demonstrates the importance of individualised vascular access care, which needs regular review and revision.

This study is limited by its retrospective, observational nature and relatively short follow-up. The choice of access procedure performed in each patient often reflects clinician preference and, as such introduces an inherent and indefinable selection bias. It therefore

cannot be used to determine the superiority of any treatment option for bilateral central venous occlusion .Nevertheless, intervention outcomes appeared 'satisfactory' in all modalities for providing dialysis. Furthermore, large randomised studies in this population would be very difficult to conduct due to the relative rarity of the condition and very heterogeneous population. Observational data perhaps better reflects the complexities that these patients face in the real world, switching between treatment modalities to achieve a "personal solution".

As the life-expectancy of patients on haemodialysis improves (Scottish Renal Registry, 2015), the number of patients with complex vascular access needs will increase. This study demonstrates that it is possible to maintain patients with ESVA on RRT, often via a combination of modalities including renal transplantation, however the morbidity associated with bilateral central vein stenosis is considerable. Prevention of central venous stenosis by catheter avoidance is essential to minimise the number of patients with complex vascular access needs in the future.

3.4.3. Expedited renal transplantation in patients with failing vascular access

Almost every clinician involved in the care of patients with ESRD will recall a handful of patients who have died as a result of vascular access loss. Despite this, there are virtually no reports in the academic literature of the phenomenon and there is no consensus agreement about how best to manage patients with failing vascular access. Many countries' transplant allocation algorithms pay lip service to "medically urgent" patients (Canadian Council of Organ Donation and Transplantation, 2007), however these strategies are often ad hoc and the number of patients who benefit (or who might be eligible to benefit but have not been considered) is unknown. To our knowledge, this is the first description of outcomes from renal transplantation in a system based on clinical need. We describe acceptable outcomes from transplantation in this cohort, with comparable 1-year post-transplant eGFR in patients with failing vascular access, those with failing access who were prioritised for transplantation and. the overall transplant cohort at our centre. We also demonstrate a reduction in morbidity following transplantation in patients with failing vascular access (fewer hospital admissions and fewer bed days), with minimal negative impact on our global transplant population.

As we have already described, patients with ESVA consume a vast amount of healthcare resources. On average, in the year prior to transplantation they had 6.5 ± 1.6 hospital

admissions and utilised 21.3 ± 12.3 bed days per patient, almost solely as a result of access-related complications. Repeated interventions to preserve or restore vascular access were shown to cost £27 000 per patient/ year, often with more than one access modality required to provide ongoing vascular access. 12-month primary patency of most access modalities was less than 50% in this patient cohort. Additionally, the plethora of vascular access complications result in considerable morbidity and have a negative impact on QoL Expedited transplantation appears to offer an escape from this cycle of problematic and failing vascular access.

Transplantation can prove challenging, both anatomically and immunologically in patients with failing vascular access. The median cRF in this patient cohort was 96%. Patients were often receiving a second or subsequent transplant. Nearly half the patients had pre-formed DSAs and one-third required ATG induction therapy. Not unsurprisingly therefore, rates of BPAR were higher in this patient cohort. Additionally, these patients proved technically complex to transplant. A number had been anuric for many years, with mean time on dialysis prior to transplantation approximately 12 years. As a result, the bladder was often chronically shrunken and atrophic and arteries heavily calcified. Often the venous anatomy was even more challenging. Several patients had occluded iliac veins, necessitating transplantation onto the inferior vena cava. In one case, the only vascular access was an ipsilateral femoral line, which remained positioned in the iliac veins while the transplant was performed. Another patient with an ipsilateral thigh graft had it ligated in the early post-operative period in an attempt to improve graft perfusion. The intricacies of transplantation in this difficult patient group require an intimate knowledge of both donor and recipient to ensure that the right kidney is given to the right patient at the right time e.g. the 57 year-old Asian gentleman dialysing via a rather precarious thigh graft, in whom a decision was made to perform a dual-kidney transplant from a 67 year old, hypertensive, diabetic donor with CKD 3 and proteinuria (kidneys which had previously been rejected by several other transplant centres due to concerns regarding primary non-function) because it was felt that the chances of him receiving a better offer prior to his vascular access failing was slim. Additionally, given these complexities, a recognition and acceptance of a possible stormy perioperative period is required and allowances should be made for potentially longer hospital stays and higher readmission rates than the over transplant cohort (though still substantially lower than within the same cohort on dialysis).

The concept of medical urgency is inherent in most countries' renal transplant matching algorithms (Canadian Council for Organ Donation and Transplantation, 2007; Baran,

2006) however only the EuroTransplant zone has an explicit "high urgent" list within their Kidney Allocation System (ET-KAS) (Eurotransplant, 2014) The exact criteria for listing as "high urgent" differ between the Netherlands and Germany, however both countries will list "medically urgent" patients for priority organ allocation above all other adult recipients. In South Africa, patients get allocated additional "points" within the standard matching algorithm for conditions such as failing vascular access necessitating accelerated transplantation (Muller, 2013). Other countries, including Australia and New Zealand, the United States and Canada (The Transplantation Society of Australia & Zealand, 2014; Organ Procurement and Transplantation Network, 2015) have no such formalised policy. This was also the case in the United Kingdom until last year, when the Kidney Advisory Group produced a policy advocating prioritisation for patients 'whose vascular access has "run out"'(Kidney Advisory Group, 2014b, pp.1). Patients can now be referred to a National Appeals Panel and, if deemed appropriate, will be placed top of the national matching run. A priori requirements for consideration are failed peritoneal dialysis and consideration at a vascular access multidisciplinary meeting. The exact criteria for vascular access failure however are poorly defined. A number of suggestions are provided within the document ranging from failed internal jugular catheterisation to dialysis via a transhepatic line. No consideration is given within the guidelines for more aggressive and novel attempts to salvage autologous or definitive access such as the HeRO (Katzman et al. 2009; Shakarchi et al. 2015c) or lower limb access (Antoniou et al. 2009), despite patients using such forms of vascular access often being in similarly dire need of transplantation to those using tunnelled lines. In our cohort of patients only one-third was actually dialysing via a TCVC despite the clinical team considering them to be at imminent risk of access loss. This is likely the result of an aggressive vascular access service (Aitken & Kingsmore, 2012a; Aitken et al. 2014a) at our centre, and does not reflect the fact that these patients are at any lesser need of transplantation than those dialysing via a transhepatic line. We fully recognise and understand the difficulties faced by the authors of the Kidney Advisory Group (KAG) guidelines (2014b) in defining the patient cohort with "failing vascular access". Even locally, within our cohort of patients, there is great heterogeneity and it is problematic outlining the exact patient population who should be considered for such an intervention. However we would argue that, particularly given the uniqueness and individual idiosyncrasies of these patients, a national strategy for their management cannot best serve their needs. Unlike the prioritisation for liver transplantation, where it is possible to clearly define indications for "super-urgent" transplantation based on clinical need (Liver Advisory Group, 2014) e.g. fulminant liver failure due to paracetamol poisoning with coagulopathy or refractory acidosis,

characterising access failure and predicting the trajectory or mortality risk in a meaningful way is very difficult. We would advocate that a local approach to organ allocation for these patients permits the complexities of each case to be considered on their own merits and allows flexibility to be built into the system. Our local criteria to consider a patient with failing access were intentionally loose to allow adaptation to facilitate transplantation of patients who were considered to be in desperate need of a transplant. Our selection criteria included patients with bilateral central venous stenosis and loss of upper limb access, however the role of a multidisciplinary team who knew the patient intimately cannot be over-emphasised. Additionally, as highlighted in the KAG policy document (Kidney Advisory Group, 2014b), different units have different strategies to vascular access provision. In order to ensure equity, it is essential that priority transplantation does not serve as a solution to poor access planning or management. Local allocation would prevent unit differences in access provision affecting this. Furthermore, the loose definitions and soft symptoms of access failure could lead to exaggeration of a patient's condition in an attempt to allow them to be listed for "urgent" transplantation. Again, local allocation of organs to patients known personally to those deciding on listing would prevent any "gaming" either intentional or otherwise.

Transplantation is a specialty founded on ethical principles. Currently matching algorithms attempt to ensure distributive justice of a limited resource (Paul et al. 2004), and any proposed change in organ allocation must be transparent and maintain equity of allocation and access. The concept of equity is not always synonymous to equality (Davis, 2006). We believe that our strategy of prioritising based on clinical need maintains distributive justice, whilst facilitating a life-saving intervention in those who require it urgently without negatively impacting on the rest of the transplant population. Furthermore, given that in the majority of cases, patients with failing access are young and (apart from their failing vascular access) often don't have the significant co-morbidities of many other patients with ESRD, a functioning graft is likely to be sustained for many years. We have demonstrated good graft outcomes in this patient cohort with similar 1-year eGFR to the overall transplant cohort, and would argue that this strategy also ensures best use of the organs and fulfills the principle of utility (Davis, 2006).

This study involves only a small cohort of patients who were transplanted and, like the description of other RRT/ access modalities, is limited by short-term follow-up only. However for most patients with failing vascular access, one-year post-transplant survival seems an appropriate end-point as, without transplantation, many will not survive even this

short time. It has proven difficult to quantify the true success or failure of our strategy of expedited renal transplantation as an appropriate comparator group is difficult to define. The overall transplant population is an inappropriate comparator as the intended outcomes, goals and aims of transplantation in this cohort are principally in optimising graft and patient survival and longevity, where as in patients with failing access, the priority and objective of transplantation is primary function and short-term survival. Conversely, comparing patients with failing access who received an expedited transplant to those with failing access who were not transplanted (only 31% of the patients with ESVA were eligible for transplantation) is also inappropriate, because often there was another reason e.g. comorbidity why these patients were not transplanted, which could confound results. For this reason, wherever possible (and despite small numbers) we have attempted to compare patients with failing access transplanted via the expedited list to those patients with failing access transplanted via the National Matching algorithm, because we believe that this is the most representative comparator group.

The current study is UK centric and its direct generalisability beyond patients transplanted via the NHS-BT Deceased Donor Organ Allocation Policy (Kidney Advisory Group, 2016) is difficult to quantify. Furthermore, the implications and impact of the new Kidney Advisory Group recommendations for regional sharing of DCD kidneys (Kidney Advisory Group 2014a) (rather than the local sharing of DCD kidneys within Scotland between the transplant centres in Glasgow and Edinburgh, which permitted early crossmatching and short cold ischaemic times) on our system remain to be elucidated. Our study does however highlight the problems faced by patients with failing access in a quantifiable manner and, for the first time, describes an attempt at a "real-world" clinical solution to this difficult issue. We believe that the numbers and problems described in this patient group are representative of those seen to transplant centres elsewhere in the UK and that this "hard data", lacking in many other descriptions of failing vascular access, could be instrumental in informing national policy.

In summary, we have described a unique local strategy for managing patients with failing vascular access by renal transplantation within the constraints of a national matching algorithm that doesn't account for clinical need. The medical urgency of transplantation and high mortality without transplantation in patients with ESVA has been highlighted. We believe our strategy, working within the NHS-BT Deceased Donor Organ Allocation policy but allowing local discretion of organ allocation for certain higher risk kidneys to specific recipients in dire clinical need, provides the best option for management of these

complex patients. We welcome the Kidney Advisory Group's appeals policy for priority kidney allocation due to shortage of vascular access (Kidney Advisory Group, 2014b) in highlighting the plight of these patients, but would caution against a national "urgent" waiting list for kidneys. A national list fails to consider the individuality that each unique patient with failing access has within a very heterogeneous patient cohort. The personal complexities (anatomical, immunological and psychosocial) can only be fully understood by the group of clinicians directly involved in the patient's care. For this reason, we advocate local discretion in organ allocation for the management of these rare patients. Our results have demonstrated that it is possible to achieve this in an equitable fashion within the constraints of the current utilitarian national allocation policy without adversely impacting on the rest of the transplant waiting list.

3.4.4. Summary

This chapter highlights the significant personal and economic burden of central vein stenosis. Effective treatment options are limited and associated with considerable morbidty. Ultimately, without an "exit strategy", complete vascular access failure with an inability to dialyse may occur. It is clearly evident that prevention is very much preferred over attempts at cure. Improving autologous vascular access rates and minimising TCVC use in incident haemodialysis patients is therefore vital.

The legacy of bad vascular access decision-making in the early period remains with the patient throughout their life on dialysis. CVS may occur with only 12 days exposure to CVC. Similarly, catheter-related bacteraemia is highest in the early days after commencing on dialysis with a median time from TCVC insertion to first bacteraemic episode only 54 days (Thomson et al. 2010). Only 11% of patients commencing dialysis via a TCVC are using an AVF after 3 months (UK Renal Registry, 2014), and more than 60% of "crashlanders" still have their TCVC after 6 months (National Kidney Care Vascular Access Report, 2012). Given that prolonged catheter dependence is associated with increased long-term complications including bacteraemia and CVS, the work presented in this chapter clearly demonstrates the importance of getting it right from the outset. Starting HD via a TCVC should be considered a treatment failure, with CVS perhaps the strongest argument for the "Fistula First, Line Last" mantra.

PREDICTING FISTULA MATURATION IN INCIDENT DIALYSIS PATIENTS: THE INFLUENCE OF URAEMIA

4.1. INTRODUCTION

Arteriovenous fistulae (AVF) are the dialysis access modality of choice for patients with end stage renal disease (ESRD) (UK Renal Registry, 2016; NKF-KDOQI, 2010). They are associated with lower risks of systemic sepsis, infective and all-cause mortality (Thomson et al. 2007; Bray et al. 2012). For this reason both the UK Renal Association and the Fistula First Initiative in the United States have set targets that two-thirds of incident haemodialysis patients should commence dialysis via an AVF (Renal Association, 2011; Massoud et al. 2006).

There is little evidence however regarding the optimal timing of vascular access creation in incident HD patients. Broad consensus exists that timely surgical referral for access creation is important, however clinical practice guidelines are largely opinion-based and vary widely. Furthermore, the exact timing of dialysis initiation for an individual patient can be unpredictable (O'Hare et al. 2007). The UK Renal Association (2011) advocates that referral for vascular access should occur when the patient enters CKD stage 4 taking into account co-morbidities, rate of decline in renal function and the surgical pathway. Similarly, the Canadian Society of Nephrology guidelines recommend that a patient be referred with 'creatinine clearance <15-20ml/min or serum creatinine 3.4-5.6mg/dl (300-500μmol/l) depending on the size and weight of the patient' (Jindal et al. 2006, pp.S7). In contrast, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (2006, pp.S260) provide a timeframe for referral 'at least six months before the anticipated need for dialysis'.

One of the major problems in vascular access planning is the unpredictability of successful maturation. Initial patency rates vary from 60-80% (Lazarides et al. 2007; Dixon et al. 2002) and one recent multicentre study found that 60% of AVFs were not suitable for cannulation 4-5 months after creation (Dember et al. 2008). Various risk factors for early AVF failure have been identified including advancing age (Feldman et al. 2003), female gender (Lok et al. 2006) and diabetes (Huijbregts et al. 2008).

Several authors have speculated that the timing of access creation itself may influence AVF outcome. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicates that patients are less likely to start HD via an AVF if there was a longer time from referral to surgical evaluation or longer time from creation to first cannulation (Ethier et al. 2008). The presence of a central venous catheter at the time of commencing dialysis has also been shown to be associated with poor AVF maturation (Brunori et al. 2005). Similarly, Weber and colleagues (2009) demonstrated a trend towards improved patency in AVF created when the patient was pre-dialysis, but the study was underpowered to formally assess this secondary outcome measure.

Associations between the uraemia which occurs in CKD, altered immune response (Vaziri et al. 2012) and deranged vascular biology (Juncos et al. 2011; Croatt et al. 2011) are well recognised. It may be, therefore, that the uraemic state of patients with ESRD influences AVF outcomes. In a rat model of AVF maturation, Langer and colleagues (2011) found inferior vessel dilatation and an exacerbation of neointimal hyperplasia in uraemic animals. These factors may need to be taken into account when planning and timing AVF creation.

The aim of this study was to evaluate the hypothesis that uraemia drives vascular smooth muscle (VSM) cell proliferation and impairs AVF maturation. Early fistula failure rates (6 weeks) were compared between pre-dialysis patients and those already on haemodialysis for different eGFR and serum urea at time of AVF creation and (in those patients who had already commenced HD) between patients who dialysed on the same day as surgery and those who dialysed on the day prior to surgery.

4.2. METHODOLOGY

4.2.1. Study design and participants

Retrospective analysis of a prospectively collected database of all simple arteriovenous fistulae created in our tertiary referral vascular access centre during a three-year period (January 2010-December 2012) was performed. The database was derived from the Scottish Electronic Renal Patient Record. Patients were excluded if they were switching from peritoneal dialysis to HD or if they had a failing transplant. Patients undergoing brachiobasilic AVF creation were also excluded, so the study population only included brachiocephalic (BCF) and radiocephalic (RCF) fistulae.

Approval was obtained from the West of Scotland Research Ethics Committee Number 1. Research was conducted in accordance with the Declaration of Helsinki. Written informed consent was not required unless additional blood samples were taken for a sub-study (not presented).

4.2.2. Data collection

Demographic details (age, sex, number of previous fistulae), operative details (site of AVF, type of anaesthetic) and details regarding dialysis status and renal function (dialysis modality, estimated glomerular filtration rate (eGFR) and serum urea in patients who were pre-dialysis (Pre-D) at the time of AVF creation and whether or not the patient had pre-operative haemodialysis on the day of surgery in patients who were already dialysis dependant (HD) were recorded. A measurement of serum urea and eGFR were obtained within 2 weeks prior to surgery. eGFR was calculated using the Modification of Diet in Renal Disease 4-variable (MDRD-4) formula.

4.2.3. Outcome measures

The primary outcome variable was clinical patency at 6 weeks. Clinical patency was defined as an AVF with thrill and bruit and adequate maturation to permit needle cannulation if required as assessed by Vascular Access Specialist Nurses. Secondary outcomes were functional patency (defined as the ability of the AVF to sustain six consecutive dialysis sessions with two needles in those patients who required haemodialysis), clinical patency at time of hospital discharge (defined as the presence of thrill or bruit) and date of loss of clinical patency.

4.2.4. Statistical analysis

Statistical analysis was performed using the SPSS Statistics for Windows Version 19.0 (IBM Corp., Armonk, NY, USA). Patients were stratified according to site of AVF. Dialysis status (HD or pre-D), eGFR, serum urea and whether or not the patient dialysed pre-operatively were evaluated to determine if they affected early AVF failure. Results are presented as a mean ± SEM or percentage of the total population. Continuous data were compared using a Mann Whitney U-test and categorical data compared using chi-squared test. Kaplan Meier survival curves were used to assess long-term patency. These were compared using a log-rank method. $P<0.05$ is considered significant.

4.3. RESULTS

A total of 705 AVF were created during the three-year period. 12 (1.7%) were excluded as the patient had a failing transplant and 23 (3.3%) were excluded as the patient was on peritoneal dialysis at the time of AVF creation. 102 patients undergoing BBF formation were also excluded, leaving 569 AVF for analysis (287 RCF, 282 BCF). Of these, 216 (38.0%) were created in patients already on haemodialysis and 353 (62.0%) were created in pre-D patients. Table 4.1 outlines the patient demographics and operative details.

Table 4.1: Basic demographics of the 705 patients undergoing AVF creation. Results are presented as mean ± SEM or percentage of total for the entire population and by dialysis status at the time of AVF creation. *P-values compare pre-D and HD populations.

	Total population	**Pre-D (n=353)**	**HD (n=216)**	**P-value***
Age (years)	60.5±0.9	62.3±1.2	59.1±1.9	<0.05
Sex (%age male)	56.2% (n=320)	52.4% (n=185)	62.5% (n=135)	<0.001
Previous attempted AVF?	31.8% (n=181)	17.8% (n=63)	54.6% (n=118)	<0.001
Anaesthesia Local Regional General	 24.1% (n=137) 50.3% (n=286) 25.7% (n=146)	 30.0% (n=106) 49.0% (n=173) 21.0% (n=74)	 14.4% (n=31) 52.3% (n=113) 33.3% (n=72)	 <0.001
Site of AVF RCF BCF	 50.4% (n=287) 49.6% (n=282)	 53.3% (n=188) 46.7% (n=165)	 45.8% (n=99) 54.2% (n=117)	 N.S.

There was no significant difference in the primary outcome (loss of clinical patency at 6 weeks) of either RCF or BCF depending on dialysis status (pre-D RCF 31.4% (n=188) vs. HD RCF 29.3% (n=99), P=0.34; pre-D BCF 22.4% (n=165) vs. HD BCF 25.9% (n=116), P=0.43). There was no significant difference in either patency on discharge or functional patency between pre-D and HD groups (Table 4.2).

There was no difference in mean eGFR between those patients with early AVF failure (loss of clinical patency at 6 weeks) and those without (11.2 ± 0.2ml/min/1.73m^2 vs. 11.6 ± 0.4 ml/min/1.73m^2 ; P=0.47). Uraemia was strongly associated with loss of clinical patency at 6 weeks. Mean serum urea in pre-D patients with early AVF failure was 35.0 ± 0.7mg/dl compared to 26.6 ± 0.3mg/dl in those with patent AVF at 6 weeks (P<0.001). Similarly, in patients already established on HD, loss of clinical patency at 6 weeks was

more likely to occur in patients who dialysed the day prior to surgery for AVF creation compared to those who dialysed on the same day as AVF creation (32.9% vs. 17.7%; P=0.005) (Table 4.3).

Table 4.2: Comparison of AVF outcomes of RCF and BCF created in patients who were pre-D and those on HD at the time of AVF creation. *Functional patency was defined as the ability of an AVF to sustain HD for 6 consecutive sessions with two needles at any time during the follow-up period. AVF that failed to achieve initial patency on discharge and AVF that never required needling (i.e. the patient remained pre-D or was transplanted prior to ever using the AVF) were excluded from this analysis.

	Radiocephalic		P-value	Brachiocephalic		P-value
	Pre-D	HD		Pre-D	HD	
Primary outcome Clinical patency at 6 weeks	69.6% (n=130)	71.7% (n=71)	0.34	77.6% (n=128)	74.1% (n=86)	0.43
Secondary outcomes Patency on discharge	90.4% (n=170)	91.9% (n=91)	0.76	89.1% (n=147)	90.5% (n=105)	0.72
Functional patency*	80.3% (n=98)	80.2% (n=65)	0.87	84.1% (n=122)	81.7% (n=85)	0.79

Table 4.3: Effect of eGFR, uraemia, and pre-operative haemodialysis on early AVF failure (loss of clinical patency at 6 weeks). *For patients who are pre-D; **For patients who are already dialysis dependant at time of AVF creation.

	Clinical patency at 6 weeks	Failure to achieve clinical patency at 6 weeks	P-value
eGFR (ml/min/1.73m^2)*	11.6±0.4	11.2±0.2	0.47
Serum urea (mg/dl)*	26.6±0.3	35.0±0.7	<0.001
Pre-operative HD** Percentage of patients having pre-operative HD	82.3%	17.7%	0.005
Percentage of patients not having pre-operative HD	67.1%	32.9%	

Long-term clinical patency of RCF was better in patients with lower serum urea when the AVF was created (P=0.01; Figure 4.1b). This association between uraemia and AVF failure was not seen in BCF (P=0.78; Figure 4.1d). Similarly there was no association between eGFR and long term RCF (P=0.38; Figure 4.1a) and BCF (P=0.61; Figure 4.1c) patency.

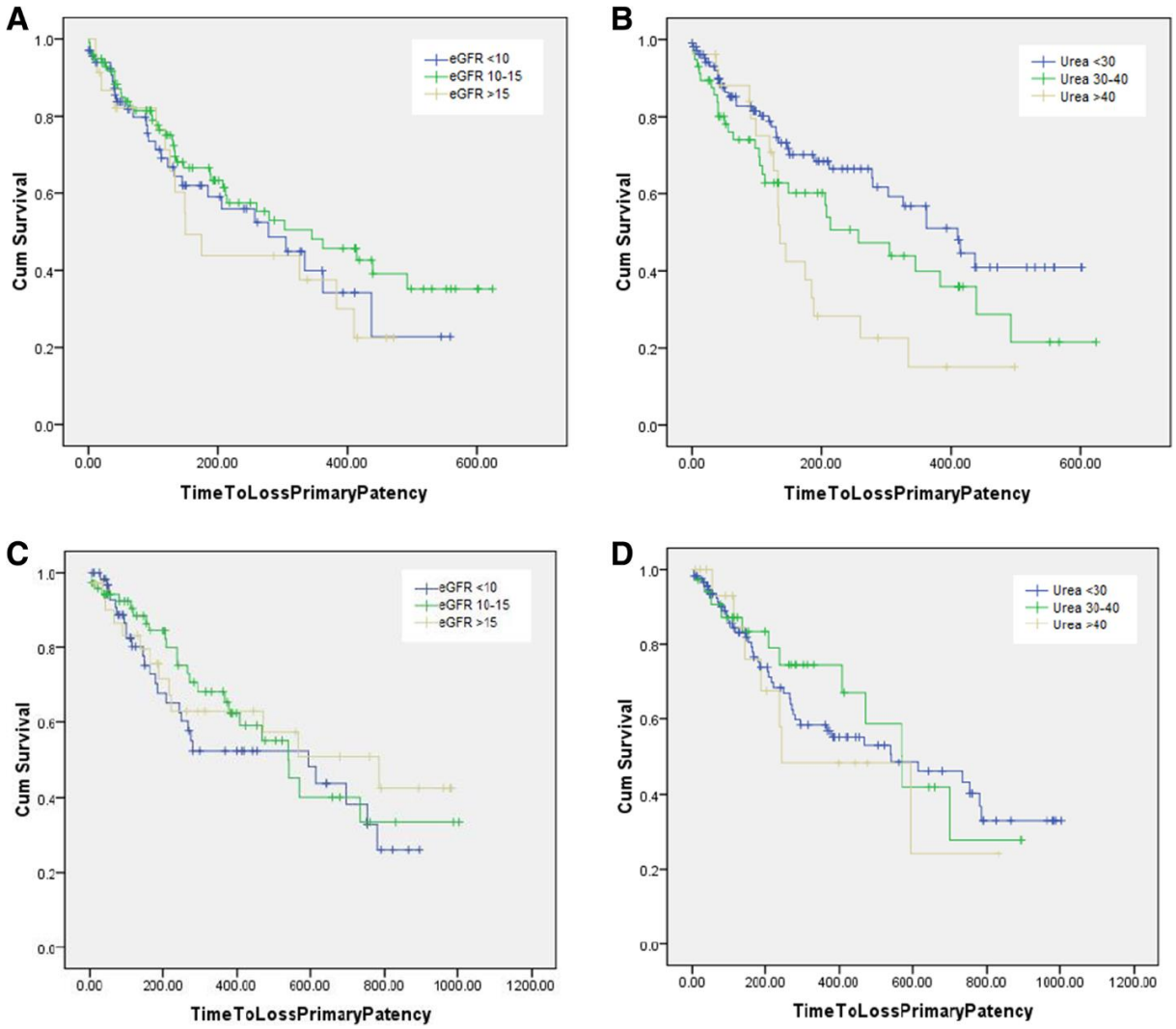


Figure 4.1: Kaplan Meier survival curves comparing long term AVF clinical patency stratified by eGFR(<10 ml/min/1.73m^2; 10-15 ml/min/1.73m^2; >15 ml/min/1.73m^2) and serum urea (<30mg/dl; 30-40mg/dl; >40mg/dl) in patients who were pre-D at the time of AVF creation. A. There was no difference in long-term RCF patency with different eGFR (P=0.38). B. Long-term patency of RCF was better in patients with lower serum urea at the time of AVF creation (P=0.01). C. There was no difference in long-term BCF patency with different eGFR (P=0.61). D. There was no difference in long-term BCF patency depending on serum urea at time of AVF creation (P=0.79).

4.4. DISCUSSION

No difference was found in the primary outcome, patency at 6 weeks, between pre-D and HD patients for either BCF or RCF. This novel finding is in conflict with the results of Rayner and colleagues (2003), who concluded that dialysis via a TCVC at the time of access creation was associated with early access failure. Similarly, Weber and colleagues (2009) achieved excellent "real world" outcomes in their cohort of patients who had AVF created prior to starting HD compared their cohort of patients who had AVF creation delayed until after commencing HD, with 81% vs. 44% of patients using an AVF at 6

months. It should be noted however that the criteria for referral for access creation in this study was an eGFR ≤25ml/min, whilst the mean eGFR at time of AVF creation in our study was 11ml/min.

This is the first clinical study to evaluate the relationship between renal function and AVF outcome. We found no association between eGFR at the time of access creation and either short or long-term patency. However increasing serum urea was associated with worse clinical patency at 6 weeks and poorer long-term outcomes from RCF. Similarly, in those patients who had already commenced HD at the time of access creation, dialysis on the same day as surgery was associated with better early patency rates. These findings are consistent with our cell signalling experiments. It is hypothesied that the VSM cell proliferation and neointimal hyperplasia which occur at the site of endothelial injury and surgical trauma when the AVF is created are exacerbated by the pro-mitogenic effect of uraemic serum and are deleterious to early fistula maturation (Aitken et al. 2014d; MacCaskill et al. 2015).

The factors affecting AVF maturation are multifactorial including vascular anatomy (Papachristou & Vazquez-Padron, 2012) and haemodynamics (Krishnamoothy et al. 2008; Krishnamoothy et al. 2012), vessel quality (Konner et al. 2013) and immune and biochemical properties (Juncos et al. 2011; Croatt et al. 2010). Fistulae require adequate arterial inflow and venous outflow to permit maturation. Inflow may be compromised by technical failure at the anastomosis or a poor quality arterial tree. Outflow may be impaired by anatomical or technical "kinking" of the vessels or altered vascular biology leading to VSM cell proliferation, neointimal hyperplasia and venous outflow stenosis. Uraemia alters vascular biology, physiology and biochemistry (Vazari et al. 2012; Juncos et al. 2011; Croatt et al. 2010) and may contribute to both inflow and outflow difficulties.

Both arterial stiffness and vascular calcification are increased in uraemic patients. In particular, calcification of the media is unique to ESRD and may impair AVF maturation by limiting arterial inflow (O'Neill & Lomashvili, 2010). Atherosclerosis is accelerated in patients with CKD with increased cardiovascular mortality (Linder et al. 1974) and increased intima-medial thickness in both coronary and carotid arteries (Schwarz et al. 2000; Ojo et al. 2002). An increased intima-medial thickness is seen in the radial artery of uraemic patients and is associated with poor arterial inflow and failure of maturation in RCF (Ku et al. 2006). Most studies of CKD-mediated vasculopathy focus on the arterial system, however it's likely that the detrimental effects of uraemia also affect the venous

system in a similar manner (Rothuizen et al. 2013). Arterial calcification is well known to impair an artery's ability to distend upon high flow stimulation (Guerin et al. 2000). Lee and colleagues (2012) have recently demonstrated extensive calcification within the intima and media of venous segments harvested at the time of vascular access surgery which, similar to in the arterial setting, may result in reduced venous compliance and inhibition of the outward remodelling of the venous outflow required for AVF maturation.

VSM cell proliferation and neointimal hyperplasia occur at the sites of vessel injury, for example the surgical anastomosis, leading to perianastomotic stenosis (Roy-Chaudhury et al. 2007). Uraemia has previously been shown to promote neointimal hyperplasia, inhibit vascular repair and promote stenosis in a rodent fistula model (Langer et al. 2011). Additionally endothelial progenitor cells (EPCs), which contribute to vessel repair and neovascularisation, have reduced ability to migrate in uraemic serum (Herbig, 2004). Work conducted at our institution has isolated human VSM cells and exposed them to hyperuraemic serum and compared proliferation and the associated pro-mitogenic signalling (MacCaskill et al. 2015). Our observations support the notion that hyperuraemic serum contains pro-growth factors which upregulate VSM cell proliferation and neointimal hyperplasia leading to early AVF failure. This process may occur de novo at the site of surgical injury or may be an exacerbation of existing neointimal hyperplasia of the outflow vein, which is known to predate AVF creation in patients with CKD (Moist et al. 2012). The clinical consequences are likely to be most marked in small vessels, as evidenced by the poorer long-term outcomes of RCF and not BCF created in uraemic patients.

As with many in ESRD, this study is limited by a heterogeneous patient population. Multiple potential confounding variables exist. In particular, our assertion that the improved AVF outcomes in patients who dialyse on the same day as AVF creation reflects reduction in serum urea may be erroneous. There are many potential confounding variables, including the administration of systemic heparin and optimisation of cardiovascular function, which could improve AVF outcomes in patients having HD on the same day as surgery. Secondly, our primary endpoint of clinical patency at six weeks is vulnerable to observer bias with different clinicians interpreting patency differently. We chose this pragmatic endpoint which does not include cannulation in an attempt to permit comparison between pre-D and HD patients. By using experienced Vascular Access Nurse Specialists to assess patency we have attempted to maintain standardisation and perform a clinically relevant assessment of outcome.

Our results indicate that uraemia (independent of dialysis status or eGFR) is a risk factor for early AVF failure. This has significant clinical implications regarding the timing of referral for AVF creation. Whilst most authors favour early referral (Jindal et al. 2006; Hiremath et al. 2011), a recent sensitivity analysis actually suggests comparable life expectancy and improved quality of life for patients with CKD stage 4 when a watchful waiting approach to access creation is adopted (Wasse et al, 2012). We would support creation of AVF in all incident patients prior to starting HD. Our results indicate that, in order to optimise maturation rates, even earlier referral prior to development of significant uraemic symptoms may be required. Secondly, for a number of years it had been local practice to expedite access creation in patients with rapidly declining renal function and progression to end-stage disease (Aitken et al, 2012a). The results of this study have prompted a change in that practice, given the poor AVF outcomes in uraemic patients. It may be that there is a subset of patients who are imminently requiring haemodialysis who would benefit for commencement of HD via a TCVC, physiological and biochemical optimisation and then AVF creation. Finally, the beneficial effect of same day haemodialysis has significant service provision and logistical implications if it is to be implemented for every patient.

A RANDOMISED CONTROLLED TRIAL OF INTERRUPTED VERSUS CONTINUOUS SUTURING TECHNIQUES FOR RADIOCEPHALIC FISTULAE

5.1. INTRODUCTION

As previously discussed, AVF are the haemodialysis access modality of choice for patients with ESRD (Vascular Access Working Group, 2006; National Kidney Care Vascular Access Report, 2012.). However, the Achilles' heel of native fistulae is poor early patency (Riella & Roy-Chaudhury, 2013). This limits greatly the universal use of AVF. Until recently few interventions have been proposed to help improve early patency. The next two chapters will focus on this issue: one looking at operative technique and one examining anaesthetic technique in an attempt to improve early fistula outcomes.

Approximately one-third of AVF fail at an early stage (Golledge et al. 1999; Nguyen et al. 2007). Early failures of RCF, made from the small, distal vessels at the wrist, are particularly common. Primary patency for RCF remains between 50-65% (Nguyen et al. 2007; Rooijens et al. 2004; Golledge et al. 1999). Numerous reasons for early failure and "failure to mature" have been postulated, including abnormal anastomotic haemodynamics, venous diameter, intimal hyperplasia and scarring/stenosis and inadequate arterial inflow (Lin et al. 2005; Hofstra et al. 1995). Technical factors will also invariably affect early AVF patency rates (Konner, 2002). The influence of operative technique is likely to be most marked for the challenging small wrist vessels and microsurgical anastomoses using magnification with operating loupes required for RCF (Lin et al. 2005; Konner, 2002; Mozaffar et al. 2013).

A number of different operative modifications, including side-to-side anastomoses (Hong et al. 2013; Moini et al. 2009), vein cuffs (Lemson et al. 2000) and variations in the anastomotic angle (Rajabi Jagahrgh et al. 2013), have been proposed in an attempt to improve flow dynamics and minimise early AVF failure. All use conventional continuous suturing techniques and none have proven particularly successful. Other clinical fields, including free-flap transfer (Griffin & Thornton, 2005), coronary artery bypass grafts (Gerdisch et al. 2003) and hepatic artery reconstruction (Starzl et al. 1985; Tzeng et al. 2010), and small animal models (Schlechter & Guyuron, 1994; Chen et al. 2001) utilise interrupted suturing techniques (or modifications of interrupted suturing techniques with

interrupted sutures for at least part of the anastomosis) for microsurgical anastomoses (with either operating microscope or surgical loupes) with excellent results. Theoretical benefits include improved anastomotic compliance and reduced puckering and luminal narrowing (Lin et al. 2005; Griffin & Thornton, 2005) .

In this study it was hypothesised that, akin to other microsurgical anastomoses, the small vessels of radiocephalic fistulae may benefit from interrupted suturing techniques. Our aim was to compare early patency rates of RCF created with interrupted versus continuous suturing techniques.

5.2. METHODOLOGY

5.2.1. Study design and participants

Patients were recruited from the regional Vascular Access Centre at the Western Infirmary, Glasgow between August 2012 and January 2014. All adults patients (over the age of 18 years) who were having RCF created were eligible to participate. Patients were excluded if they were unable or unwilling to provide consent; if they had previous ipsilateral attempts at AVF creation; if the radial artery was <1.8mm or cephalic vein at the wrist <2mm on pre-operative ultrasound (without tourniquet).

Ethical approval for this trial was granted by the West of Scotland Research Ethics Committee Number 4 and research has been carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent. The trial was registered prospectively with the ClinicalTrials.gov database (NCT01704313).

5.2.2. Randomisation

Patients were randomised in a 1:1 fashion to either interrupted or continuous suturing technique. The randomisation sequence was generated using a web-based random sequence generator and sequentially numbered, opaque, sealed envelopes were produced by a colleague independent of the research team.

5.2.3. Recruitment

Patients were approached pre-operatively by a member of the research team. If willing to participate, they were assigned a study number and sealed envelope. The sealed envelope was opened by the operating surgeon in theatre immediately pre-operatively. The operating surgeons were independent of the research team.

Both patient and research team were blinded to the allocation. Concealment was maintained until all patients had reached the primary end point.

5.2.4. Operative technique

The procedures were performed by a total of eight experienced consultant vascular access surgeons (or senior trainees under consultant supervision). All surgeons had experience of performing anastomoses with both interrupted and continuous suturing techniques however, prior to the study, all but one would routinely use a continuous suturing technique for creation of RCF.

Anaesthetic was provided with either supraclavicular block or local injection. All surgeons used operating loupes with x8 magnification. Standard approach to the vessels and arteriotomy was performed. The anastomoses were performed with 6.0 or 7.0 Prolene® (Ethicon, Sommerville, NJ, USA) as was surgeon preference. For the continuous suturing technique, a stay suture was inserted at the toe of the vein and then a single suture run around the entirety of the anastomosis starting from the heel (Figure 5.1). The interrupted suturing technique also required a stay suture. Then three single interrupted sutures were placed at the heel of the anastomosis and tied before a continuous suture used to complete the remainder of the anastomosis (Figure 5.1 and 5.2).

5.2.5. Outcome measures

The primary end point was primary patency at 6 weeks (assessed by a blinded observer for the presence of thrill and bruit). Secondary end points were immediate patency, functional patency (assessed clinically and by ultrasound) at six-weeks, patency at time of discharge from hospital and presence of anastomotic stenosis.

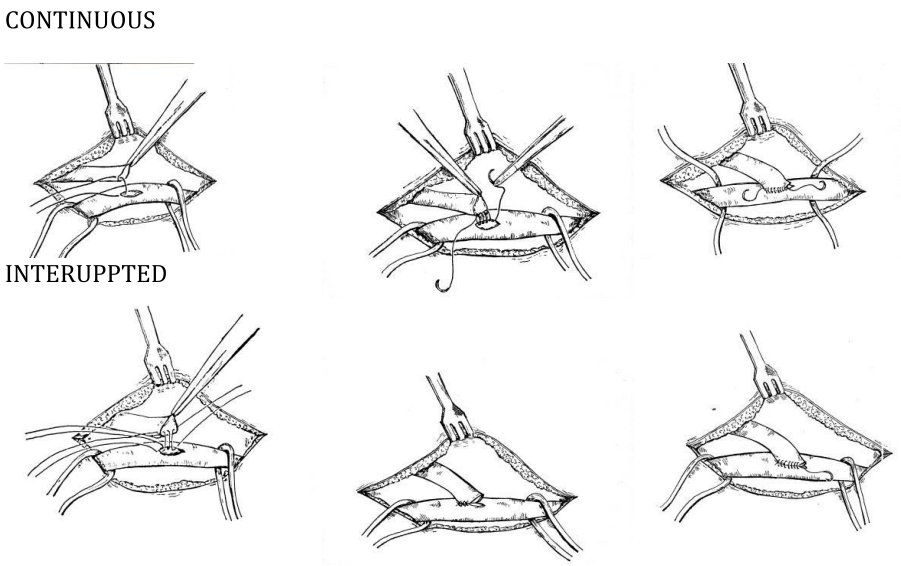


Figure 5.1: Illustration of continuous and interrupted suturing techniques. Continuous suturing technique (top): a single suture length is used to perform the entire anastomosis. Interrupted suturing technique (bottom): the interrupted sutures were inserted first into the heel of the anastomosis (bottom left). These were then tied down (bottom middle) before another suture was used to run around the rest of the anastomosis (bottom right). Diagram courtesy of Jessica Thompson, Dundee University Medical School.

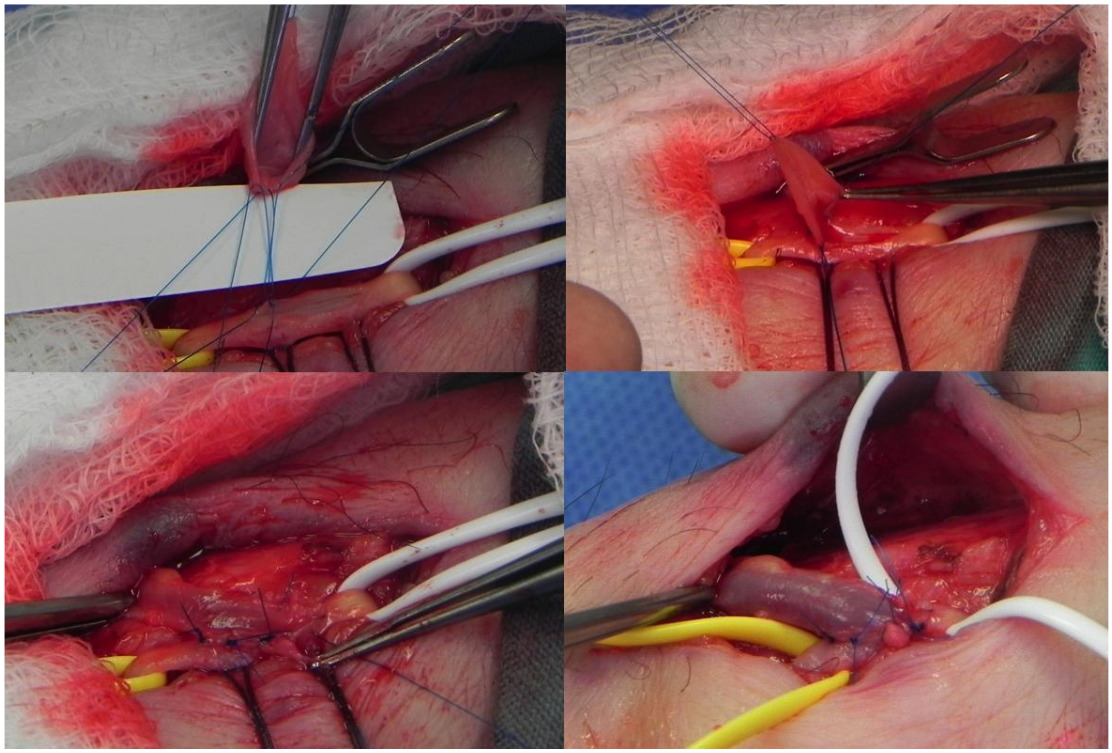


Figure 5.2: Photographs of the interrupted suturing technique. Top left: interrupted sutures at the heel of the anastomosis. Top right: Interrupted sutures at the heel of the anastomosis tied down. Bottom left: Continuous sutures were used to complete the anastomosis. Bottom right: Blood flow restored with dilatation of the anastomosis.

Primary patency at 6 weeks was assessed by blinded members of the research team. This was defined clinically as the presence of thrill and bruit confirmed by two members of the research team. Immediate patency and patency at time of discharge were also assessed clinically (presence of thrill and bruit) by the research team. Functional patency at six weeks was assessed by the research team both clinically (deemed suitable for cannulation by experienced dialysis nurse) and by ultrasound (>6mm diameter, <6mm from skin surface, flow rate >600ml/min) (Vascular Access Working Group, 2006; Tessitore et al. 2011) . All ultrasound measurements were obtained in triplicate by a single skilled-operator and an average obtained. Anastomotic stenosis was defined as a clinically relevant ultrasound-detected stenosis with access flow (Qa) <650ml/min (Tessitore et al. 2011) or peak systolic velocity ratio (SVR) ≥ 3:1 (Grogan et al. 2005) and failure to mature. Complications including need for re-exploration, bleeding and wound infection were also recorded.

5.2.6. Sample size calculation

A priori power calculation determined that a total of 78 patients (39 in each arm) would be required to detect an improvement in primary patency at 6 weeks from 50% to 80% with 80% power and significance 0.05. Due to the short follow-up period, it was not anticipated that there would be any drop-outs. However, due to organisational issues, concerns that patients may be randomised and then surgery not proceed were overcome by replacing any subject withdrawn from the study following randomisation with another subject.

5.2.7. Statistical analysis

Results were analysed using GraphPad Prism™ 6 (San Diego, CA, USA). Data were tested for normality. Assuming normal distribution, a student's t-test (2-tailed) was used to compare continuous data and Fischer's exact test used to compare categorical data. $P<0.05$ was significant. Results are presented as mean (SD) and median (IQR) if not normally distributed or as a percentage of the total population.

5.3. RESULTS

93 patients were considered for participation in the study. 3 were excluded (1 unable to provide informed consent; 2 declined participation). 90 patients were randomised. 78 patients completed the study protocol (36 continuous sutures; 42 interrupted sutures). 8

patients had surgery cancelled due to organisational issues and 3 for medical reasons (1 developed chest pain and 2 had uncontrolled hypertension) after randomisation and 1 patient had a protocol breach with the surgeon deciding to create a brachiocephalic fistula despite meeting the criteria for radiocephalic fistula and having been randomised. All 78 patients completed the study and follow-up period. The CONSORT diagram (Schulz et al. 2010) is shown in Figure 5.3.

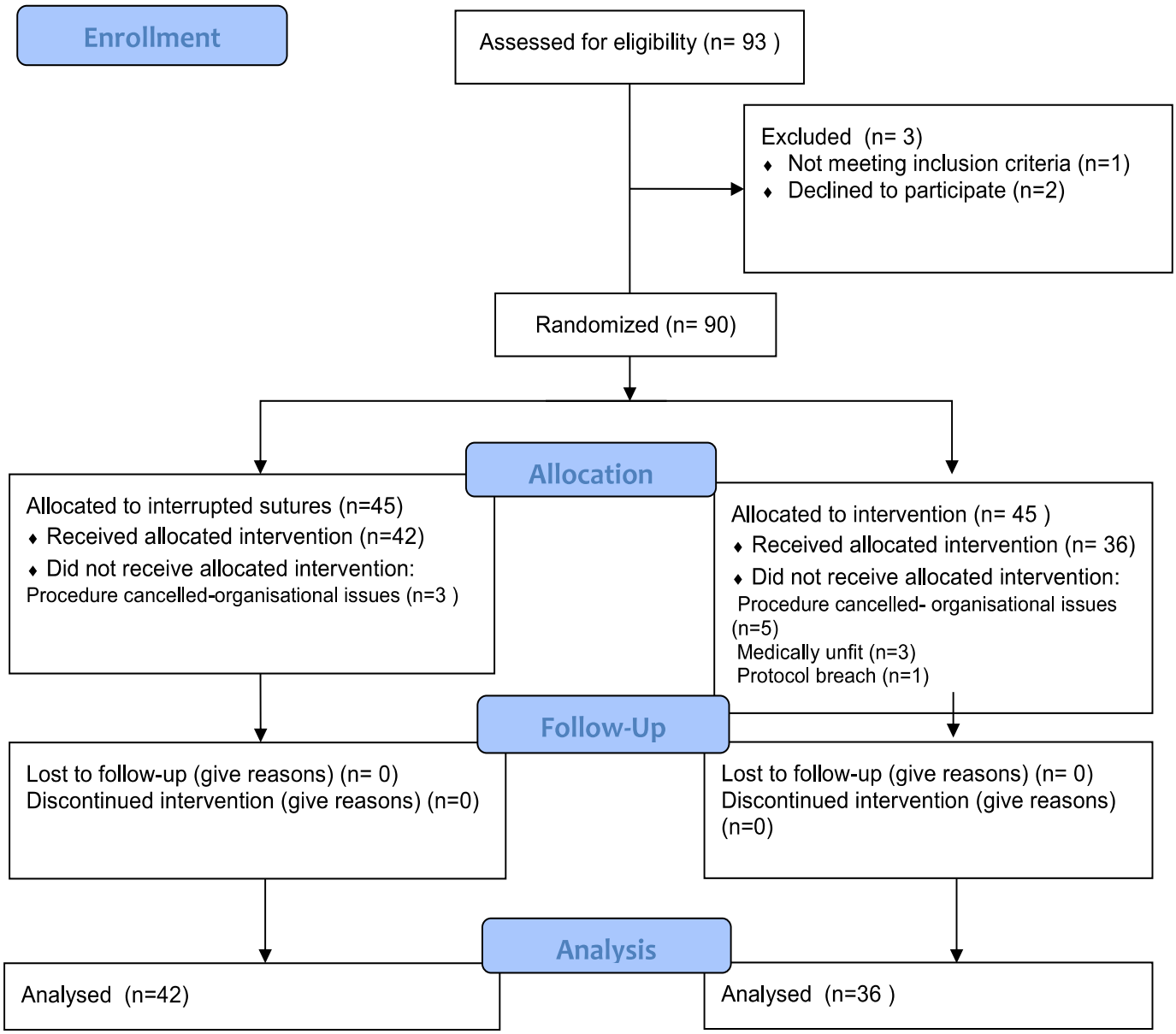


Figure 5.3: Trial flow and CONSORT diagram of assignment to interrupted or continuous suturing technique.

Mean patient age was 58.9 (13.3) years; 67.9% (n=53) male. Table 5.1 outlines basic patient demographics, co-morbidities and medications at the time of fistula creation. Generally the groups were comparable for age and sex. More patients in the interrupted cohort had peripheral vascular disease and atrial fibrillation, while more patients in the continuous cohort had adult polycystic kidney disease (APKD) as their cause of renal failure. There was no significant difference between the groups with regards dialysis status, anaesthetic technique or operating surgeon.

Table 5.1: Baseline characteristics of patients in the BPB and LA cohorts. Results are presented as mean (SD) or as a percentage of the total unless otherwise stated. * Median (IQR).

	Continuous	**Interrupted**
Age (years)	57.7 (15.2)	60.0 (12.9)
Sex (%age male)	69% (n=25)	67% (n=28)
Cause of renal failure		
Diabetic nephropathy	25% (n=9)	21% (n=9)
APKD	22% (n=8)	2% (n=1)
Glomerulonephritis	6% (n=2)	14% (n=6)
Reflux nephropathy	8% (n=3)	4% (n=2)
Hypertensive nephropathy	3% (n=1)	7% (n=3)
IgA nephropathy	3% (n=1)	19% (n=8)
Other	14% (n=5)	24% (n=10)
Unknown	19% (n=7)	7% (n=3)
Comorbidities		
Diabetes	36% (n=13)	31% (n=13)
Hypertension	28% (n=10)	43% (n=18)
Atrial fibrillation	14% (n=5)	5% (n=2)
PVD	0% (n=0)	9% (n=4)
IHD	17% (n=6)	19% (n=8)
Medications		
Antihypertensives (number)*	2(1,3)	2(1,4)
Beta-blocker	53% (n=19)	57% (n=24)
Aspirin	28% (n=10)	17% (n=7)
Clopidogrel	14% (n=5)	12% (n=5)
Warfarin	3% (n=1)	12% (n=5)
Statin	39% (n=14)	43% (n=18)
Dialysis status		
Pre-dialysis	53% (n=19)	57% (n=24)
Haemodialysis	44% (n=16)	38% (n=16)
Peritoneal dialysis		2% (n=1)
Failing transplant	3% (n=1)	2% (n=1)
Surgeon		
1	14% (n=5)	31% (n=13)
2	19% (n=7)	19% (n=8)
3	6% (n=2)	7% (n=3)
4	8% (n=3)	9% (n=4)
5	17% (n=6)	5% (n=2)
6	11% (n=4)	7% (n=3)
Others	25% (n=9)	21% (n=9)
Anaesthetic technique		
Local anaesthetic	56% (n=20)	52% (n=22)
Supraclavicular block	41% (n=15)	36% (n=15)
General anaesthetic	3% (n=1)	12% (n=5)

Pre-operative vessel diameters and radial artery blood flow were comparable between the two cohorts with mean radial artery diameter 2.16 (0.27) mm in the continuous cohort and 2.14 (0.24) mm in the interrupted cohort (P=0.71) and mean cephalic vein diameters 2.59 (0.61) mm in the continuous cohort and 2.41 (0.43) mm in the interrupted cohort (P=0.14) (Table 5.2). Mean pre-operative radial artery blood flow was also comparable between the two cohorts (44.3 (13.2) vs. 43.7 (12.9) ml/min; P=0.76) (Table 5.2).

Table 5.2: Pre-operative mean radial artery and cephalic vein diameters and radial artery blood flow. Results are presented as mean (SD).

	Continuous	**Interrupted**	**P-value**
Radial artery (mm)	2.16 (0.27)	2.14 (0.24)	0.71
Cephalic vein (mm)	2.59 (0.61)	2.31 (0.430	0.14
Blood flow in radial artery (mL/min)	44.3 (13.2)	43.7 (12.9)	0.76

Primary patency at 6 weeks was higher in the interrupted suturing technique group (71.4% vs. 47.2%; P=0.01). Immediate patency was also higher in the interrupted suturing technique group (92.9% vs. 66.6%; P<0.001). There was no significant difference in functional patency at 6 weeks (52.4% vs. 36.1%; P=0.18) (Table 5.3).

Table 5.3: Comparison of patency rates between RCF created with interrupted and continuous suturing techniques. Results are presented as a percentage of the total (n).

	Continuous	**Interrupted**	**P-value**
Patency at 6 weeks	47% (n=17)	71% (n=32)	0.01
Functional patency at 6 weeks	36% (n=13)	52% (n=22)	0.18
Immediate patency	67% (n=24)	93% (n=39)	<0.01
Thrill on discharge	53% (n=19)	83% (n=35)	<0.01
Bruit on discharge	56% (n=20)	88% (n=37)	<0.01

Three patients developed an anastomotic stenosis. All were in the interrupted suturing technique group. One patient in the continuous suturing cohort developed evidence of a venous outflow stenosis (5cm above the anastomosis) during the follow-up period. One patient from the interrupted suturing technique cohort required re-exploration and ligation for bleeding from the suture line day 3 post-operatively. 3 patients in the continuous suturing technique arm were re-explored immediately due to absence of thrill and bruit.

Patency was restored in one of the three. 8 patients required surgical revision after assessment at 6 weeks due to inadequate maturation and lack of functional patency (3 anastomotic stenosis (all in the interrupted arm); 2 superficialisation; 3 ligation of collaterals). The venous outflow stenosis was successfully treated with angioplasty.

5.4. DISCUSSION

These results demonstrate superiority of an interrupted suturing technique for the creation of radiocephalic fistulae with improved early (6 week) primary patency rates compared to continuous techniques (71.4% vs. 47.2%; P=0.01). There was no significant difference in functional patency at 6 weeks (52.4% vs. 36.1%; P=0.18). This is the first clinical study to demonstrate benefit of a specific suturing technique in arteriovenous fistulae creation.

Latterly there has been increasing interest in involved and technically advanced vascular access procedures for patients with complex vascular access needs e.g. central venous stenosis (Agarwal et al. 2007) . Such procedures are time consuming, costly, associated with significant morbidity and generally have poor outcomes (Bakken et al. 2007). Similarly many targets and tariffs focus on optimising prevalent vascular access in long-term haemodialysis patients (Lok, 2007). Conversely, optimising native AVF usage in incident patients, new to haemodialysis is simpler, more cost-effective and may prevent to complex “end-stage” vascular access cases for the future. Local root cause analysis (presented in Chapter 2) has determined that one of the principal reasons for incident patients commencing haemodialysis via a TCVC is failure of the initial AVF to mature (Aitken et al. 2014a). Patients who start haemodialysis via a TCVC are more likely to continue with a long-term TCVC (with patient choice and loss of future access options being sited as potential causes) (Hughes et al. 2013), therefore optimising early AVF patency and incident vascular access is essential to minimise TCVC usage. This study has demonstrated that simple modifications to the anastomotic suturing technique can improve early patency.

Interrupted suturing techniques are well-established and used routinely in clinical practice for many microsurgical anastomoses in plastic surgery and maxillofacial surgery (Griffin & Thornton, 2005) . However much of the evidence derives from small animal models. Schelchter and Guyuron (1994) demonstrated a reduced rate of anastomotic stenosis with interrupted suturing techniques in their rabbit femoral artery model. Similarly, Tozzi and colleagues (2002) demonstrated increased anastomotic luminal diameter with interrupted

suturing in their bovine model of internal mammary artery grafting and Gerdisch et al. (2003) showed improved anastomotic compliance, reduced pulsatility indices and increased diastolic and peak flow through the vessels in their porcine model of coronary artery bypass grafting. The ability of the anastomosis to expand between the interrupted sutures (rather than tightening and puckering as occurs with continuous techniques) permits distension of the anastomosis (Lin et al. 2005).This is particularly important in the vessels of RCF, which are often sub-2mm (Konner, 2002; Laskar et al. 1988). Additionally, improved anastomotic compliance and reduced compliance mismatch have been found by other authors to improve haemodynamics and are believed to reduce perianastomotic neointimal hyperplasia (Lin et al. 2005; Clark et al. 1976; Smith et al. 2012). Notably however, Joos and colleagues (1990) failed to demonstrate any histological differences at the anastomosis of rodent femoral vein 3 weeks following anastomosis with interrupted and continuous microsuturing techniques. Ongoing work at an English university evaluating the relationship between anastomotic compliance and histological changes at AVF anastomoses in humans, may better clarify this in the future (Smith et al. 2012).

Several clinical studies have demonstrated benefit of interrupted suturing techniques (or modifications of the interrupted suturing technique) for hepatic artery reconstruction in liver transplantation (Starzl et al. 1985) and coronary artery bypass grafting (Loop et al. 2009). Other authors have shown no difference in patency in animal models (Chen et al. 2001; Lee et al. 1982). The sole previous clinical study of suturing technique for RCF, showed no benefit of interrupted over continuous suturing technique (Laskar et al. 1988). Their patient numbers however were small (only 20 patients in each arm) and follow-up was over 3 years, potentially missing the important differences in early patency related to the anastomotic technique and risking confounding factors, not least neointimal hyperplasia and venous outflow stenosis at sites of needle injury (Roy-Chaudhury et al. 2003). Studies of side-to side anastomoses in both RCF and BCF are small and retrospective. Nevertheless they have indicated that, despite the obvious improved flow volume across the anastomosis, AVF patency is not improved compared to simple end-to-side anastomoses (Hong et al. 2013; Moini et al. 2009). Zeebregts and colleagues (2004) demonstrated improved patency and fewer anastomotic stenoses in AVF created with interrupted titanium clips over continuous sutures. They cite superior haemodynamics and improved healing pattern with the interrupted clipping technique as an explanation. In our cohort, the incidence of anastomotic stenosis was actually higher in the interrupted technique arm. Three patients in the interrupted suturing technique arm had an anastomotic

stenosis. All three went on the have successful surgical revision of the AVF, ultimately resulting in functionally patent AVF. It is hypothesised that the patients in the interrupted technique arm of the study who developed an anastomotic stenosis may be akin those in the continuous technique arm who had an early thrombosis, but they retained patency (albeit with an anastomotic stenosis) perhaps due to improved haemodynamic properties of the anastomosis.

One of the criticisms of the interrupted suturing technique is that it is more time consuming (Chen et al. 2001) . Our interrupted technique is similar to the "combined interrupted-continuous" technique described by Lykoudis and colleagues (2008), utilising interrupted sutures around the heel of the anastomosis and then continuous sutures for the rest. Other authors who report an "interrupted" suture technique commonly use modifications of this with partial interrupted and partial continuous sutures (Starzl et al. 1985; Tzeng et al. 2010). In this way, it takes no longer than a standard continuous anastomosis to perform.

Additionally, there is a theoretical risk that interrupted sutures could bleed more from the gaps between suture lines. Chen and colleagues (2001) found a significantly increased bleeding time and blood loss from interrupted suture lines in their rabbit femoral artery model. Alternatively it could be argued that the improved anastomotic compliance of the interrupted anastomosis actually improves contraction and may reduce the risk of bleeding((Lin et al. 2005). In our cohort, the single bleeding complication was in the interrupted suturing technique arm. Bleeding from the anastomosis was identified when the patient underwent re-exploration 3 days post-operatively and the fistula required ligated. The exact bleeding point could not be identified. It is postulated that this bleed was a sporadic event, however no clear conclusions can be drawn from this as the study was inadequately powered to detect complications.

The primary end point for this study was primary patency at 6 weeks as assessed by two independent blinded members of the research team (an experienced clinician and a senior dialysis nurse). An early end point was chosen to minimise the multiple confounding factors (e.g. cannulation technique, outflow stenosis etc.) that are inherent to evaluating vascular access. A clinically relevant end point for the study was essential. Ideally primary functional patency evaluated by ability to sustain dialysis would have been chosen as the end point. However, due to the large number of patients who were pre-dialysis at the time of AVF creation, this was not feasible. It is acknowledged that clinician assessment could be open to observer bias, however both observers were blinded and there was 100%

agreement between independent assessors for both patency and functional patency, indicating good validity and reproducibility. Furthermore, confirmation of patency by defined ultrasonographic criteria provides a second quantitative measurement of functionality.

As with any operative technique, both the interrupted and continuous suturing techniques in this study are susceptible to surgeon bias. Nearly half of the AVF created in this study were formed by only two surgeons. One routinely performed RCF using interrupted technique, the other routinely used a continuous technique. There was no significant difference in the relative proportions of interrupted and continuous technique AVF created by any surgeon and the study was underpowered to evaluate outcomes by individual surgeon. However it is recognised that the technical abilities and preferences of individual surgeons could skew results.

In conclusion, this is a single-centre randomised controlled trial comparing interrupted to continuous suturing techniques for creation of the radiocephalic AVF anastomosis. Superiority of the interrupted suturing technique with improvement in the primary outcome (patency at six weeks) has been demonstrated. On this basis, it is advocated that an interrupted suturing technique be adopted for all radiocephalic fistulae.

A RANDOMISED CONTROLLED TRIAL COMPARING LOCAL VERSUS REGIONAL ANAESTHESIA IN ARTERIOVENOUS FISTULA CREATION

6.1. INTRODUCTION

As discussed in the previous chapter, one of the major shortcomings of autologous AVF is their high early failure rate.

Different anaesthetic techniques can influence both pre-operative arterial and venous diameters and early blood flow within the fistula, factors which are known to affect AVF maturation (Dember et al. 2008; Lin et al. 2005; Hofstra et al. 1995). Regional anaesthetic techniques can directly influence venous diameter as well as intra- and post-operative blood flow (Wong et al. 2011). However, there is no conclusive evidence that any particular anaesthetic technique can significantly influence either early patency or long-term AVF outcome.

General anaesthesia, regional anaesthesia and local anaesthetic (LA) infiltration are all acceptable anaesthetic techniques for AVF creation. Whilst general anaesthesia increases intra-operative vasodilatation, it is associated with increased cardiorespiratory complications in ESRD patients (Howell et al. 1998). Regional anaesthesia, such as a brachial plexus block (BPB), involves targetted injection of LA to specifically "block" the motor and sensory nerves that supply the operative site, avoiding the need for general anaesthesia. Both local and regional anaesthesia avoid the risks associated with general anaesthesia, but only regional anaesthesia produces an associated sympathetic nerve block. This sympathetic blockade increases venous diameter and arterial flow both intra-operatively and in the early post-operative period (Shemesh et al. 2006; Mouquet et al. 1989). Maintenance of adequate blood flow through the fistula in the perioperative period may prevent thrombosis and early fistula failure and can assist in maturation (Mouquet et al. 1989). Additionally, arterial and venous spasm has been demonstrated to be more common with local infiltration than regional (or general) anaesthesia (Konner, 1999).

Several small, single-centre observational cohort studies have previously demonstrated that, compared to local infiltration, a BPB results in better immediate AVF patency rates (Shemesh et al. 2006; Zaliunate et al. 2011) and also improved surgical ability to identify

the optimal site for intervention (Glover et al. 2007). To date however there is no evidence that any short-term benefits of regional anaesthesia can influence medium- or long-term AVF patency. There are only two small, randomised trials in the literature comparing BPB and LA. One detected increased AVF flow rates for up to 8 weeks in patients who received a BPB compared to local infiltration, but with no difference in primary patency (Laskowski et al. 2007). The other demonstrated increased vessel diameters in the BPB cohort (Renaud et al. 2015).

It was hypothesised that immediate and medium-term AVF patency could be improved by using regional anaesthesia (BPB) compared to local anaesthesia. We aimed to conduct a randomised controlled trial to answer the question: Does regional anaesthesia, compared to local infiltration, improve medium-term AVF patency (3 months)?

6.2. METHODOLOGY

6.2.1. Study design and participants

This prospective randomised controlled trial recruited patients from three University teaching hospitals in Glasgow (Stobhill Ambulatory Care Hospital, Western Infirmary and Queen Elizabeth University Hospital) between February 2013 and October 2015. All adults patients (over the age of 18 years) who were having primary RCF or BCF fistulae created were eligible to participate. Patients were excluded if they were unable or unwilling to provide consent, if they had previous ipsilateral attempts at AVF creation, if the radial or brachial artery was <1.8mm or cephalic vein was <2mm at the wrist or <3mm at the elbow on pre-operative ultrasound (without tourniquet). Patients with allergy to local anaesthesia, coagulopathy, infection at anaesthetic or surgical site, significant peripheral neuropathy or neurological disorder affecting the upper limb or known ipsilateral central vein stenosis (even if treated) were also excluded.

Ethical approval for this trial was granted by the West of Scotland Research Ethics Committee 5 (12/WS/0199) and research was carried out in accordance with the Declaration of Helsinki and adhered to the standards of ICH Good Clinical Practice. All participants provided written, informed consent. The protocol was published prior to the initiation of recruitment (Macfarlane et al. 2013).

6.2.2. Randomisation

Patients were randomised in a 1:1 fashion to either BPB or LA anaesthetic technique. The randomisation sequence (in blocks of 8) was generated using a web-based computer random sequence generator. Sequentially numbered, opaque, sealed envelopes were produced by a colleague independent of the research team.

6.2.3. Recruitment

Patients were approached pre-operatively by a member of the research team. Pre-operative ultrasound was performed to ensure suitable vessels for AVF creation. If suitable and willing to participate, they were assigned a study number and sealed envelope. The sealed envelope was opened by the anaesthetist immediately pre-operatively. Due to the nature of the intervention, it was not possible to blind, patient, surgeon, anaesthetist or study team involved at the time of surgery, however the Vascular Access Nurse Specialist who assessed the primary end point was independent and blinded to the randomisation.

6.2.4. Operative technique

The procedures were performed by a total of nine experienced consultant vascular access surgeons (or senior trainees under consultant supervision). No formal operative technique was stipulated within the study protocol in order to permit individual surgeons to react to variations in anatomy that might be encountered intra-operatively. Nevertheless, surgeons largely followed a standard operating technique. All surgeons used operating loupes with x8 magnification and microinstruments. A standard approach to the vessels was performed with transverse incision at, or just below, the elbow crease for BCF and longitudinal incision at the wrist for RCF. The cephalic vein (or median cubital vein if suitable at the elbow) were dissected and skeletalised for a short length proximally. Visible branches were ligated and divided. The vein was then divided, spatulated and flushed with heparinised saline. The artery was then dissected and controlled with bulldog clamps. At the elbow, a true BCF was created in every case rather than proximal RCF. The decision to utilise median cubital, perforating branch or true outflow cephalic vein was left to the surgeon's discretion. Similarly the surgeon's discretion was utilised to determine the size of the arteriotomy performed based on risks and benefits for the individual patient (e.g. vessel quality, risk of steal etc.) Generally arteriotomies on the brachial artery were between 3-5mm in length with radial artery arteriotomies made slightly larger (7-10mm).

An end-to-side anastomosis of vein to artery was then performed with continuous 6.0 (elbow) or 7.0 (wrist) Prolene® (Ethicon, Sommerville, NJ, USA). Most procedures were performed as day case surgery.

6.2.5. Anaesthetic techniques

Two consultant anaesthetists skilled in BPB (or senior trainees under consultant supervision) performed all of the BPBs in this study. Patients in the BPB group all received an ultrasound guided BPB. The supraclavicular approach was chosen unless there was a contraindication, in which case an axillary block was undertaken. A 1:1 mixture of 0.5% L-bupivacaine and 1.5% lignocaine with epinephrine (1 in 200,000) was injected up to a maximum volume of 40 mL (Soares et al. 2007). Maximum dose limits of 2 mg/kg for bupivacaine and 7 mg/kg for lignocaine with epinephrine were observed. The time taken to perform the block and any technical problems during block insertion (intravascular puncture, paraesthesia) were recorded. Measurements of the sensory block of the musculocutaneous, median, radial and ulnar nerves were recorded every five minutes by a non-blinded observer using a previously validated 3-point scale using a cold test: 0 = no block, 1 = analgesia (can feel touch but not cold) and 2 = anaesthesia (patient cannot feel touch). Motor block of the musculocutaneous, median, radial and ulnar nerves was graded as either 0 = no block, 1 = paresis, 2 = paralysis (Rodriguez et al. 2004). Measurements were continued until either the sensory block was adequate in the operative area distribution or a maximum of 20 minutes had elapsed at which point the block was supplemented by targetted axillary or midhumeral supplementation as appropriate using ultrasound. If a BPB block failed despite supplementation, LA infiltration was used. This was recorded as a failed block. If additional analgesia or conversion to general anaesthesia was required, this was regarded as a failed block.

Patients in the LA infiltration group received infiltration of local anaesthetic into the surgical site by the operating surgeon under sterile conditions using a combination of 0.5% L-bupivacaine and 1% lignocaine injected subcutaneously immediately prior to the commencement of surgery. Maximum dose limits of 2 mg/kg for bupivacaine and 3 mg/kg for lignocaine were observed, recognising that these are additive.

6.2.6. Duplex ultrasound

Pre-operative vein mapping and Doppler ultrasound assessment of the upper limb arterial tree was performed on all patients prior to the administration of anaesthesia by a member of the study team experienced in ultrasound assessment of peripheral vessels. Measurement of the cephalic vein diameter 2cm above the wrist and at the elbow and of the basilic vein of the elbow were recorded in triplicate. Radial and brachial artery diameters and brachial artery blood flow was also recorded in triplicate. Similar assessment of the vasculature was performed following administration of anaesthesia, immediately pre-operatively and at 3-month follow-up. At the 3-month follow-up visit the diameter of the outflow cephalic vein was measured at 5, 10 and 15cm intervals above the anastomosis.

6.2.7. Outcome Measures

The primary end point was primary patency at 3 months. Secondary end points were immediate patency (at time of discharge from hospital), functional patency (assessed clinically and by ultrasound) at 3 months and the change in brachial artery blood flow and diameter and cephalic vein diameter immediately following administration of anaesthesia and after 3 months. Additionally the need for additional administration of local anaesthesia, pain scores and patient satisfaction scores were also evaluated. Operative and anaesthetic complications were recorded.

Primary patency at 3 months was assessed by a Vascular Access Nurse Specialist, blinded to the mode of anaesthesia. Primary patency was defined clinically as the presence of a thrill or bruit in the absence of any additional intervention to re-establish function. Immediate post-operative patency (patency at time of discharge from hospital) was also assessed clinically (presence of thrill and/or bruit) by the research team. Functional patency at 3 months was assessed by the research team both clinically (used for dialysis or, in pre-dialysis patients, deemed suitable for cannulation by the Vascular Access Nurse Specialist) and by ultrasound (>6mm diameter, <6mm from skin surface, flow rate >600ml/min) (NKF-KDOQI, 2006; Vascular Access Working Group, 2006). All ultrasound measurements were obtained in triplicate by a member of the research team pre-anaesthetic, immediately following anaesthesia and at 3 months follow-up as described previously. Pain scores were recorded on a Numeric Pain Rating Scale (0 (no pain) to 10 (worst pain ever)) immediately after and one hour following the procedure. Patient

satisfaction scores were recorded prior to discharge on a Numeric Pain Rating Scale (0 (very dissatisfied) to 10 (highly satisfied)).

6.2.8. Sample size calculation

A priori power calculation determined that a total of 126 patients (63 in each arm) would be required to detect an improvement in primary patency at 3 months from 65% to 85% in patients having AVF creation under BPB with 80% power and significance 0.05, allowing for 10% loss to follow-up or mortality. The 65% primary patency rate at 3 months is representative of maturation rates for AVF described elsewhere in the literature (Dember et al. 2008). We anticipated that an increase in primary patency at 3 months from 65 to 85% was a conservative estimate given local observational data had previously demonstrated AVF patency of 93% in patients having BPB compared to 52% in those having AVF creation under LA (Zaliunate et al. 2011).

6.2.9. Statistical analysis

Results were analysed using SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY). Data were tested for normality. Assuming normal distribution, a student's t-test (2-tailed) was used to compare continuous data and chi-squared or Fischer's exact test used to compare categorical data. Mann-Whitney U-tests were used for non-normally distributed data. $P<0.05$ was significant. Results are presented as mean (95% CI ±SD) or as median (IQR) if not normally distributed, or as a percentage of the total population and odds ratio (OR). Missing data was limited and assumed to be missing at random. If a data point was missing, this case was removed from analysis of the specific variable of interest. Data has been analysed on an intention-to-treat basis.

The trial was registered prospectively with the ClinicalTrials.gov database (NCT01706354).

6.3. RESULTS

163 patients were considered for participation. 37 were excluded and 126 patients were randomised. 125 patients completed the study protocol (63 LA; 62 BPB). 1 patient had a protocol breach having been randomised prior to vein mapping ultrasound at which point no suitable vessel was found for RCF/BCF creation. This patient was followed-up on an

intention-to-treat basis. All 126 patients completed the study and follow-up period. The CONSORT diagram is shown in Figure 6.1 (Schulz et al. 2010).

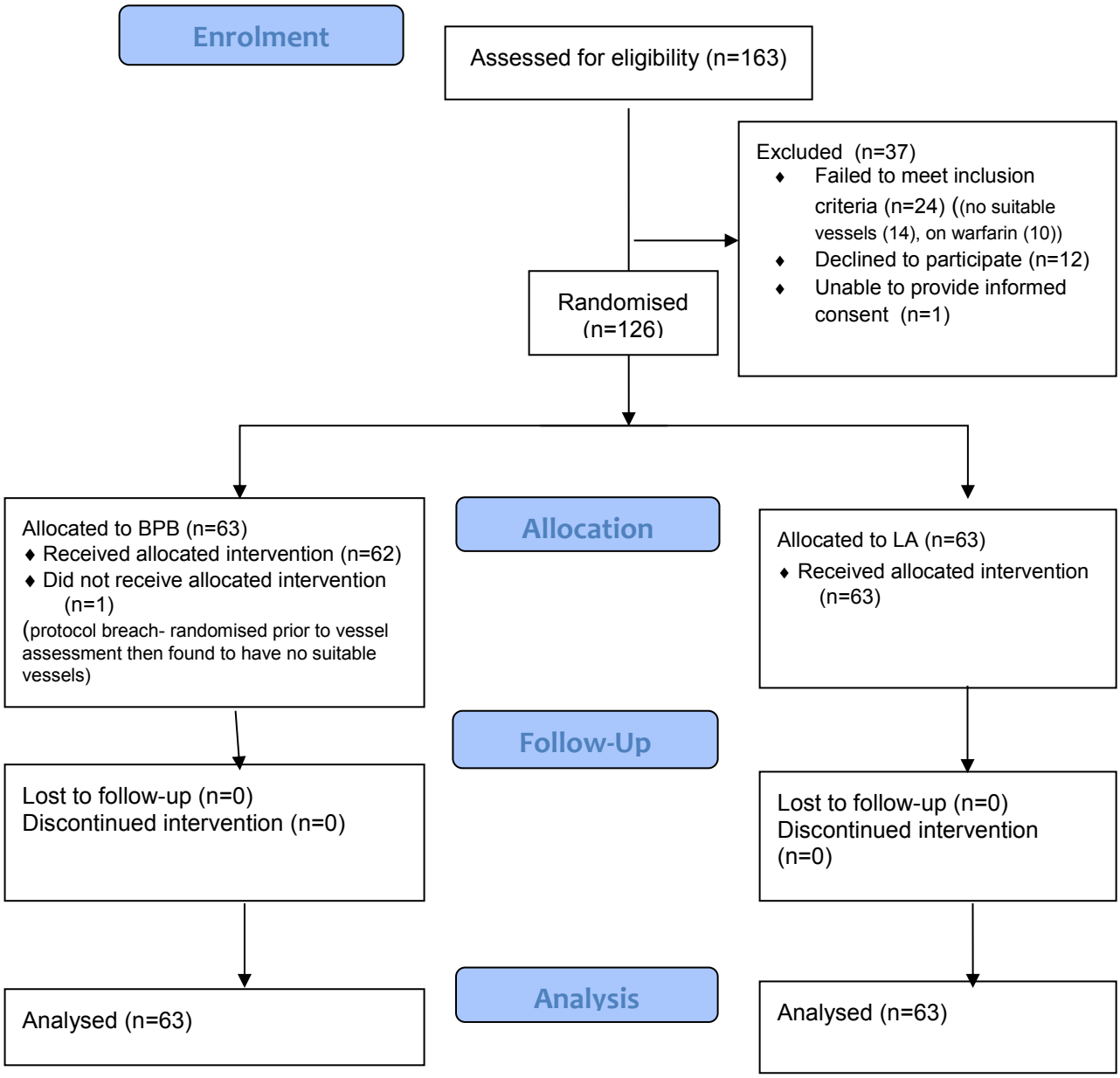


Figure 6.1: Trial flow and CONSORT diagram of assignment to local or regional anaesthesia.

The groups were comparable for age, sex, co-morbidities, medications and renal replacement modality (Table 6.1). There was no significant difference between the groups with regards operating surgeon or site of AVF.

Table 6.1: Baseline characteristics of patients in the BPB and LA cohorts. Data are presented as n (%) or mean ± SD unless otherwise stated. *median (IQR)

	Overall patient population (n=126)	**BPB (n=63)**	**LA (n=63)**
Age (years)	60.8+/-14.8	59.5+/-15.3	62.1+/-14.3
Sex (% male)	79 (62.7%)	40 (63.5%)	39 (61.9%)
Primary renal disease			
Diabetes	21 (16.7%)	10 (15.9%)	11 (17.5%)
Multisystem	16 (12.7%)	9 (14.3%)	7 (11.1%)
Interstitial	41 (32.5%)	16 (25.4%)	25 (39.7%)
Glomerulonephritis	24 (19.0%)	15 (23.8%)	9 (14.2%)
Unknown	24 (19.0%)	13 (20.6%)	11 (17.5%)
Co-morbidities			
Diabetes	34 (27.0%)	17 (27.0%)	17 (27.0%)
IHD	48 (38.1%)	22 (34.9%)	26 (41.2%)
CVA	9 (7.1%)	3 (4.8%)	6 (9.5%)
Hypertension	93 (73.8%)	40 (68.3%)	53 (84.1%)
Obesity (BMI <30)	41 (32.5%)	22 (34.9%)	19 (30.2%)
Medications			
Antihypertensives (number)*	2 (1,4)	2 (1,4)	2 (1,4)
Aspirin	85 (67.4%)	42 (66.7%)	43 (68.3%)
Clopidogrel	29 (23.0%)	13 (20.6%)	16 (25.4%)
Statin	73 (57.9%)	38 (60.3%)	35 (55.6%)
RRT modality at time of randomisation			
HD	63 (50%)	30 (47.6%)	33 (52.4%)
Pre-dialysis	63 (50%)	33 (52.4%)	30 (47.6%)
Site of AVF			
RCF	51 (40.5%)	26 (41.2%)	25 (39.7%)
BCF	75 (59.5%)	37 (58.7%)	38 (60.3%)
Surgeon			
1	35 (27.8%)	16 (25.4%)	19 (30.2%)
2	23 (18.3%)	13 (20.6%)	10 (15.9%)
3	16 (12.7%)	8 (12.7%)	8 (12.7%)
4	16 (12.7%)	8 (12.7%)	8 (12.7%)
5	14 (11.1%)	8 (12.7%)	6 (9.5%)
Others	22 (17.4%)	10 (15.9%)	12 (19.0%)
Anaesthetist			
1		36 (57.1%)	
2		27(42.9%)	

51 patients (40.5%) had RCF creation, with the remainder having BCF creation. Mean brachial artery flow was 30.7±13.1mL/min (95% CI: 28.4%, 33.0%) (n=124). There was no difference in pre-operative brachial artery blood flow in patients who had AVF creation under BPB compared to LA (31.3 ± 14.1mL/min (95% CI: 30.5, 35.1) vs. 30.1 ± 12.1mL/min (95% CI: 27.0, 31.4); P=0.61). In patients undergoing RCF creation, mean pre-operative radial artery diameter was 2.1 ± 0.29mm (95% CI: 1.99, 2.21) and cephalic vein (wrist) was 2.28 ± 0.49mm (95% CI: 2.15, 2.41). In BCF, mean brachial artery diameter was 3.05 ± 0.57mm (95% CI: 3.01, 3.09) and cephalic vein (elbow) was 3.23 ± 0.75mm (95% CI: 3.1, 3.35). There was no significant intraobserver variability in the measurement of brachial artery/ cephalic vein diameter or brachial artery blood flow

(Appendix 3). There were no significant differences in any of these parameters between BPB and LA cohorts (Table 6.2).

Table 6.2: Pre-operative vessel diameters and brachial artery blood flow. All measurements have been obtained in triplicate. Mean (95% CI) are presented.

	Overall patient population	**BPB**	**LA**	**P-value**
BA blood flow (mL/min) (n=124)	30.7 (28.4, 33.0)	31.3 (30.5, 35.1)	30.1 (27.0, 31.4)	0·61
RCF (n=51)				
Radial artery diameter (mm)	2.10 (1.99, 2.21)	2.11 (2.0, 2.21)	2.08 (1.99, 2.17)	0.79
Cephalic vein (wrist) diameter (mm)	2.28 (2.15, 2.41)	2.21 (2.13, 2.29)	2.32 (2.24, 2.4)	0.82
BCF (n=75)				
Brachial artery diameter (mm)	3.05 (3.01, 3.09)	3.09 (3.04, 3.14)	3.02 (3.0, 3.04)	0.75
Cephalic vein (elbow) diameter (mm)	3.23 (3.10, 3.33)	3.30 (3.12, 3.48)	3.16 (3.05, 3.25)	0.31

Primary patency at 3 months was higher in patients having their AVF created under BPB than LA (84.1% (73.0%, 91.3%) vs. 61.9% (49.5%, 72.3%); P=0.005; OR 2.1). This difference was observed for both RCF and BCF but the effect size appeared to be greater in RCF (76.9% (64.6%, 87.4%) vs. 48.0% (34.8%, 61.5%); P=0.03; OR 3.6). Immediate patency was also better in patients having BPB (92.6% (82.3%, 97.0%) vs. 73.0% (60.9%, 81.4%); P=0.005; OR 4.6). There was 100% concordance for functional patency at 3 months when assessed clinically and by ultrasound. There was no significant difference in functional patency at 3 months overall (41.3% (30.0%, 53.6%) vs. 27.0% (17.5%, 39.1%); P=0.09; OR 7.3), however a difference in favour of BPB was observed in RCF (73.1% (60.3%, 84.2%) vs. 40.0% (27.6%, 53.8%); P=0.02; OR 4.1) (Table 6.3).

Patients in the BPB group experienced significant increase in both arterial and venous diameters following administration of anaesthesia. A similar change was not observed in the LA patient cohort (Table 6.4). An increase in brachial artery blood flow was also observed in the BPB cohort that was not seen in the LA group, when comparing immediately prior to and immediately following administration of anaesthesia (+45mL/min (95% CI: 16, 74) vs. +1mL/min (95% CI: -6, 8)); P<0.001). At 3 months follow-up, there was no significant difference between the groups in the diameter of the outflow vein at 5, 10 or 15cm above the anastomosis in mature fistulae. There were more patients in the BPB cohort with brachial artery flows >250mL/min at 3 months follow-up (68.3% (56.0%, 78.5%) vs. 42.9% (31.4%, 55.1%); P=0.01; OR 2.9).

Table 6.3: Patency rates of AVF in BPB and LA cohorts (immediate*, 3-month primary and 3-month functional). Numbers presented are total number of patients (percentage [95% CI]).* Immediate patency is patency at time of discharge from hospital.

	Overall patient population (n=126)	BPB (n=63)	LA (n=63)	P-value
ALL AVF				
Immediate patency*	104 (82.5%) [74.9%, 88.2%]	58 (92.1%) [82.3%, 97.0%]	46 (73.0%) [46.2%, 64.9%]	0.005
Primary patency at 3 months	92 (73.0%) [64.6%, 80.3%]	53 (84.1%) [73.0%,91.3%]	39 (61.9%) [49.5%,72.3%]	0.005
Functional patency at 3 months	44 (34.9%) [27.1%, 43.6%]	26 (41.3%) [30.0%, 53.6%]	18 (28.6%) [18.8%, 40.7%]	0.15
RCF				
Immediate patency*	38 (74.5%) [62.5%, 85.8%]	23 (88.5%) [76.9%, 98.9%]	15 (60.0%) [40.7%, 77.6%]	0.02
Primary patency at 3 months	32 (62.7%) [50.1%, 75.9%]	20 (76.9%) [64.6%, 87.4%]	12 (48.0%) [34.8%, 61.5%]	0.03
Functional patency at 3 months	29 (56.9%) [44.2%,70.6%]	19 (73.1%) [56.2%, 88.8%]	10 (40.0%) [23.4%, 59.3%]	0.02
BCF				
Immediate patency*	66 (88.0%) [77.2%, 92.9%]	35 (94.6%) [78.5%,98.0%]	31 (81.5%) [66.2%, 91.1%]	0.08
Primary patency at 3 months	60 (80.0%) [66.4%,85.0%]	33 (89.1%) [72.2%,94.7%]	27 (62.7%) [55.1%, 73.2%]	0.05
Functional patency at 3 months	15 (20.0%) [11.9%, 29.5%]	7 (18.9%) [8.9%, 33.7%]	8 (21.1%) [10.8%, 36.6%]	0.95

Table 6.4: Change in vessel diameters before and immediately following administration of anaesthesia. Results are presented as median (95% CI). Δ change (post-anaeasthetic minus pre-anaesthetic).

	BPB	LA	P-value
Δ Cephalic vein (wrist) diameter (mm) (n=87)	0.1 (-0.03, 0.5)	-0.5 (-1.7, 3.2)	0.37
Δ Cephalic vein (elbow) diameter (mm) (n=124)	0.5 (0.2, 1.2)	0.1 (-0.1, 0.2)	0.006
Δ Basilic vein (elbow) diameter (mm) (n=121)	0.5 (0.2, 1.4)	0.1 (-0.4, 1.3)	0.09
Δ Radial artery diameter (mm) (n=124)	0.1 (0, 0.4)	0 (-2.4, 4.7)	0.01
Δ Brachial artery diameter (mm) (n=124)	1.6 (0.5, 2.6)	0.2 (-0.4, 0.3)	<0.0001
Δ Brachial artery blood flow (mL/min) (n=120)	45 (13,75)	1 (-10, 9)	<0.001

Patients in the BPB cohort had mean volume of 23.7±4.0mL of 0.5% L-bupivacaine + 1.5% lignocaine with adrenaline (1 in 200,000), whilst a mean volume of 14.7 ± 5.0mL of 0.5% L-bupivacaine + 1% lignocaine was infiltrated in the LA cohort. The time taken to administer anaesthesia was significantly longer in the BPB cohort (17.0±-5.7 (95% CI:

12.5, 21.5) vs. 3.4 ± 2.5min (95% CI: 2.3, 4.5) ; P<0.0001). No patient developed any anaesthetic complications. Both cohorts of patients achieved excellent anaesthesia, with all patients reporting pain scores of 0 both during and 1 hour following completion of surgery. Significantly fewer patients in the BPB cohort required additional local anaesthetic supplementation (3.2% (1.2%, 7.5%) vs. 14.3% (8.5%, 21.2%); P<0.001). For the two patients in the BPB who required additional anaesthesia, one responded to targetted supplementation with an axillary block and one had a failed block necessitating local anaesthetic field infiltration. No patient required conversion to general anaesthesia.

Four patients had a change in operative plan following administration of BPB. Initial decision to create a BCF was modified to RCF as the diameter of the cephalic vein at the wrist increased following BPB. There was no difference in the duration of surgery between BPB and LA cohorts (62.1 ± 11.8 (95% CI: 55.4, 68.8) vs. 62.8 ± 12.2min (95% CI: 57.5, 68.1); P=0.77). One patient in the BPB developed a superficial wound infection and three patients in the LA cohort developed clinically significant steal necessitating operative intervention. No patient in the BPB cohort developed steal. Patient satisfaction scores were higher in the BPB cohort (9.8 ± 0.6 (95% CI: 9.7, 9.9) vs. 9.4 ± 1.0 (95% CI: 9.2, 9.6); P=0.02).

6.4. DISCUSSION

These results demonstrate superiority of BPB for the creation of AVF, with improved early (3 month) primary patency rates compared to LA (84.1% (73.0%, 91.3%) vs. 61.9% (49.5%, 72.3%); P=0.005; OR 2.1). This difference was associated with immediate and significant increases in both vessel diameter and brachial artery blood flow following administration of BPB. Patient satisfaction was high in both groups, but superior in the BPB group. This is the first randomised controlled trial to demonstrate benefit of a BPB on medium-term AVF patency and one of the few studies in which anaesthetic technique influences surgical outcome.

These findings are consistent with other recent studies which demonstrate an improvement in arterial blood flow and vasodilatation with regional anaesthesia (Sahin et al. 2011; Meena et al. 2015; Howell et al. 1998; Lo et al. 2010). The effect size of this difference appeared to be greater in distal RCF with small vessels. The biological plausibility of these observations is supported by the observed changes in the haemodynamics of the vascular tree. Dilatation of both artery and vein makes the anastomosis technically less challenging

(particularly in very small vessels) whilst improved arterial inflow (Lin et al. 2005; Wong, 2006), increased venous compliance (Lin et al. 2005) and reduced pulsatility index (Hofstra et al. 1995) promote blood flow through the AVF immediately after creation and reduce early thrombosis within the first hours to days. Once laminar "fistula-type" blood flow has been established, the rate of thrombosis appears similar between the two cohorts. Like other authors who found improved blood flow at 8 weeks with BPB compared to LA (Sahin et al. 2011), we observed that more patients in the BPB cohort had good blood flow via the AVF at 3 months (brachial artery blood flow >250mL/min). This is perhaps simply as there were more patent AVF in the BPB group, rather than any lasting effect of the BPB per se.

The benefits of BPB compared to LA in promoting AVF maturation appeared to occur early, with the difference in patency between the two cohorts manifesting immediately (at time of hospital discharge) but persisting until at least 3 months. Similarly the benefits were more marked in achieving a patent fistula rather than in obtaining functional patency with a fistula capable of sustaining dialysis. This discrepancy was most marked in the BCF, which achieved 80% primary patency at 3 months but only 20% functional patency. These functional patency rates fall below those observed in other retrospective series (Wilmink et al. 2016). The explanation for this is likely to be multifactorial. Balloon assisted-maturation is not performed at our institution and none of the AVF in this study had received any procedure to promote functional maturation by 3 months follow-up. It is anticipated that with future interventions, subsequent functional patency rates will improve. Secondly, the it is well recognised that advancing age, coronary artery disease and peripheral vascular disease are associated with inadequate maturation (Lok et al. 2006; Masengu et al. 2015). The patients in this cohort had significant co-morbidities. Finally over one-third of patients had a BMI >30, which is likely to necessitate superficialisation to achieve functional patency.

A further benefit of regional anaesthesia is that, as demonstrated elsewhere, the operative plan in this study was modified in several cases due to the vasodilatation from BPB, and more distal AVF were created (Reynolds et al. 2011). Indeed, in one study of patients deemed not to have any suitable vessels for autologous access, one-third of patients listed for arteriovenous graft insertion successfully underwent AVF creation following BPB (Schenk, 2010).

The administration of the BPB is operator-dependent and it is well recognised that failure rate of BPB is higher if the operator is inexperienced (Sandhu et al. 2006). In this study, only two consultant anaesthetists, experienced in ultrasound-guided BPB, performed the procedure to minimise inter-operator variability. There were no complications and only one block failure which was a combination of poor ultrasound views and patient discomfort during the nerve block leading to a decision to change to LA which would be quicker for the patient. Complications of supraclavicular blocks such as pneumothorax can occur, and adequate training is necessary to undertake these blocks (Soares et al. 2007). Nevertheless with the advent of ultrasound guidance this block is now commonly used for upper limb surgery (Perlas et al. 2009). It may be that other approaches to the brachial plexus confer the same benefit as all approaches result in sympathetic blockade but this cannot be inferred with certainty from the data presented here.

BPB took significantly longer than LA to perform (17.0 vs. 3.4 minutes; $P<0.0001$) and necessitated the presence of a skilled anaesthetist, which is not the case for LA. Performing regional anaesthesia and surgery in parallel rather than sequentially can help improve efficiency and minimise operative delays between patients (Chiazapis et al. 2014). Whilst an analysis of cost was outwith the scope of this work, any additional costs associated with employing an anaesthetist to perform BPB could potentially be offset against the cost savings of improved AVF maturation, reduction in need for second and subsequent surgeries and the complications of TCVC use.

The high early thrombosis rate of AVF observed in recent randomised controlled trials (Dember et al. 2008; Irish et al. 2017) coupled with an increasingly elderly, co-morbid population, have seen a growing body of opinion advocating alternatives to autologous vascular access in recent years (Tozzi et al. 2014a; Glickman, 2016). Furthermore, political pressure (such as the tariff imposed by the government in England and Wales) focuses on optimising prevalent, rather than incident, vascular access (Lok, 2007). Many of these prevalent patients have complex vascular access needs such as multiple failed AVF, prolonged TCVC use and central venous stenosis (Agarwal et al. 2007). Obtaining vascular access in such patients is time consuming, costly, associated with significant morbidity and generally has poor outcomes (Bakken et al. 2007). Conversely, this study has focussed on simple RCF and BCF creation, principally in incident patients with no previous vascular access. We have demonstrated that in this patient group it is possible to achieve good outcomes from autologous vascular access and that a relatively simple

modification to the anaesthetic technique (BPB) can improve immediate and longer term patency.

In summary, this randomised controlled trial compared BPB to LA for AVF creation and demonstrated superiority of BPB, with significant improvement in the primary outcome of patency at 3 months. Based on these findings, consideration should be given to utilising BPB for all AVF creation.

EARLY CANNULATION GRAFTS: OUR EARLY EXPERIENCE WITH GORE® ACUSEAL AND MODIFICATION OF A TECHNIQUE

7.1. INTRODUCTION

The merits of a fistula primacy at all costs approach to vascular access have been challenged in recent years (Lok, 2007; Lok & Davidson, 2012; Allon & Robbin, 2002). Age, co-morbidity and likely survival time on dialysis need to be balanced against the likely success or failure of a vascular access in order to choose the optimal access for the individual patient. Suboptimal AVF maturation rates and changing demographics of the dialysis population (Rayner et al. 2003) have led to a swing from a "Fistula First" to "Catheter Last" approach to vascular access planning (Lok, 2007; Tonnessen & Money, 2005). As a result, arteriovenous grafts are again gaining popularity as a choice for vascular access.

Universal usage of autologous AVF is hindered by a 6-8 week maturation period from creation to first cannulation (Donnelly & Marticorena, 2012) and 30%-50% early failure rate (Saucy et al. 2010; Rodriguez et al. 2000; Dember et al. 2008). Unfortunately, due to a combination of late referral, primary access failure and acute presentation of renal failure, 40%-50% of incident patients do not have a functioning AVF when they commence HD (Scottish Renal Registry, 2015). Current practice necessitates TCVC for these patients until definitive vascular access can be secured. Given that patients who began HD via a TCVC are more likely to remain with TCVC (Hughes et al. 2013), optimising incident vascular access is vitally important.

Arteriovenous grafts (AVGs) provide an intermediate option between AVF and TCVC, permitting earlier cannulation than AVF but lower bacteraemia rates than TCVC (0.6 per 1,000 catheter days) (Taylor et al. 2002). The recent development of early cannulation arteriovenous grafts (ecAVG), which permit needling within 24 hours of insertion, now means that grafts may be considered as an alternative to TCVCs in patients requiring immediate access for haemodialysis, in addition to their role in patients with no native vessels.

The Gore®ACUSEAL vascular access graft is one such ecAVG. The tri-layer construction comprises of an inner layer of heparinsied expanded polytetrafluoroethylene (ePTFE), outer layer of standard ePTFE graft and a central elastomeric layer. This central layer gives the graft its unique "low bleed" properties and permits early cannulation, reducing the time

to achieve haemostasis significantly compared to standard PTFE (Glickman, 2016). Cannulation within 24 hours of insertion is possible.

To date, there is little published in the literature on the use of the Gore®ACUSEAL vascular access graft. Tozzi and colleagues (2014a) report 12-month primary patency rates of 68% in their case series. In their multicentre study published last year Glickman and colleagues (2015) found a 79% 1-year cumulative patency rate. They observed 15 infections in their series of 138 patients.

In this chapter the initial experience with the Gore®ACUSEAL early cannulation graft in our unit is described. The initial problems and complications are highlighted along with our attempts to modify practice and technique to improve outcomes. A descriptive commentary of our experiential learning is provided.

7.2. METHODOLOGY

7.2.1. Initial experience with Gore®ACUSEAL

A single-centre early experience of Gore®ACUSEAL at the Department of Renal Surgery, Western Infirmary, Glasgow is described. As previously described, this is a large-tertiary referral vascular access centre in the West of Scotland, serving approximately 700 prevalent haemodialysis patients. There are approximately 170 incident patients annually. Around 400 vascular access procedures are performed each year (including approximately 100 for complex access). AVG usage at initiation of this study was <1%. 40-50% of incident patients commenced HD via a TCVC/temporary catheter.

All adult patients who had Gore®ACUSEAL ecAVG inserted over a 3-year period (between July 2010 and July 2013) were included for analysis ('early' cohort). Data were prospectively collected on indications for ecAVG, timing and success of initial cannulation, complications (including culture-proven bacteremia, other graft infection, thrombosis, stenosis and haematoma) and patency rates. Both local and systemic infections were recorded. Stenosis was defined as a 50% reduction in luminal diameter on ultrasound or angiography in the presence of typical symptoms.

Additionally, there was interest in the concept of vascular access providing a "personal cure." For example, ecAVG may function as a 'bridge' to transplantation or AVF maturation in some patients, whilst in others they may provide a salvage procedure for

end-stage vascular access. Data on the ultimate intention of the ecAVG were also recorded to determine if the patients achieved their "personal vascular access solution."

Bacteremia rates are presented per 1,000 dialysis days. Primary and secondary patency rates were determined from life tables. Other complication rates are presented as a percentage of the total population.

7.2.2. Changing practice to improve outcomes

It was perceived that the 'early' patient cohort treated with Gore®ACUSEAL experienced a relatively high rate of complications (described below), which the clinical team was determined to address and minimise.

A number of modifications to both operative and perioperative care were made, along with development of a more structured service for the management of complications (particularly thrombosis). This experiential learning and the adaptations made to practice are described.

Like any other novel technique, education and dissemination of lessons learned is critical. Several education sessions for dialysis nurses and vascular access surgeons were run during the implementation phase for the ecAVG. The rationale for and execution of these courses is described along with an evaluation of the impact that they made, in line with Kirkpartick's model of change (Kirkpatrick, 1996) (Appendix 1).

7.2.3. Re-evaluation of Gore®ACUSEAL outcomes

Over the six-months subsequent to recruitment of the initial patient cohort (July-December 2013) modifications in operative technique and perioperative care were gradually implemented. An expansion of the ecAVG practice was also observed, with 49 patients having Gore®ACUSEAL inserted over this time period ('later' cohort). Data were prospectively collected on complications (including culture-proven bacteremia, local graft infection, thrombosis, venous stenosis, pseudoaneurysm, steal, wound complications and haematoma). Outcomes from this second cohort of patients were compared to the 'early' cohort.

7.3. RESULTS

7.3.1. 'Early' experience with Gore®ACUSEAL

A total of 37 Gore®ACUSEAL were placed in 37 patients. Median follow-up was 17 months. Table 7.1 outlines basic patient demographics of the 'early' cohort.

Table 7.1: Basic demographics of the 'early' patient cohort of Gore®ACUSEAL.
Results are presented as percentage of total population (n) unless otherwise stated.

Median age (years)	42 (range: 21-72)
Sex (percentage male)	54.1% (n=20)
Mean time on dialysis (years)	3.2 (range: 0-10.2)
Median number of previous autologous AVF attempts	2 (range: 0-6)
Ethnicity White British Chinese	 (94.6% (n=35) 5.4% (n=2)
Co-morbidities Hypertension Diabetes Coronary heart disease Cerebrovascular disease Peripheral vascular disease Smoking	 97.3% (n=36) 40.5% (n=15) 32.4% (n=12) 21.6% (n=8) 21.6% (n=8) 35.1% (n=13)
Mean BMI (kg/m^2)	31.2 (range: 22.3-42.5)

The indications for ecAVG were as follows: "crashlander" to HD 13.5% (n=5) (three to AVF maturation, one had no native options, one as a bridge to transplantation); revision of existing AVF to permit immediate use 8.1% (n=3); bridge to transplantation 21.6% (n=8) (in three cases the patient had recurrent line sepsis and the ecAVG provided a sepsis-free window for live donor transplantation); removal of infected line 24.3% (n=9); no native options 67.6% (n=25) (including 17 patients with bilateral central vein stenosis).
A total of 11 upper limb AVGs (2 forearm loops, 3 interposition grafts of existing AVF, 2 brachial artery to basilic vein, 6 brachial artery to axillary vein); 24 mid- thigh loop grafts and two complex procedures in patients with end-stage vascular access (axillary artery to common femoral vein and common iliac vein to contralateral femoral artery) were performed. All grafts were at least 25 cm in length. 36 AVGs (97.3%) were successfully cannulated. Mean time to first cannulation was 30.4 ± 23.4 hours (range: 2-192).

There was one perioperative death after thigh graft insertion (postoperative day 1) from

myocardial infarction in an elderly gentleman with a history of ischaemic heart disease. There was one postoperative haematoma, which did not require re-exploration and one significant wound infection and dehiscence following upper limb graft. Long-term complications are outlined in Table 7.2. Venous outflow stenosis was common (29.7%) particularly in upper limb grafts. All but two of the stenoses were initially treated with angioplasty with limited benefit; four subsequently went on to have surgical revision. A total of 4 of 15 cases (26.7%) of thrombosis were treated with percutaneous thrombectomy, the others (73.3%) underwent surgical thrombectomy. The systemic bacteremia rate was 0.2 per 1,000 access days. However, 16.2% (n=6) developed local infection around the AVG at the site of haematoma, necessitating AVG removal in four cases. Local haematomas and pseudoaneurysms often related to poor needling technique with inadequate needle site rotation (Figure 7.1).

Table 7.2: Complications of ecAVG in the 'early' cohort. Data are presented as n (%) or mean ± SD unless otherwise stated.

Complication	**Percentage affected**	**Percentage resulting in failure of AVG**
Stenosis Venous outflow Inflow	 14 (37.8%) 11 (29.7%)	 12 (32.4%) 10 (27.0%)
Thrombosis	15 (40.5%)	13 (35.1%)
Haematoma Uncomplicated Associated local infection	 2 (5.4%) 6 (16.2%)	 - 4 (10.8%)
Systemic bacteraemia	2 (5.4%)	2 (5.4%)
Pseudoaneurysm	3 (8.1%)	3 (8.3%)
Graft breakdown	1 (2.7%)	1 (2.7%)
Steal syndrome	1 (2.7%)	1 (2.7%)
Wound infection/ dehiscence	1 (2.7%)	-

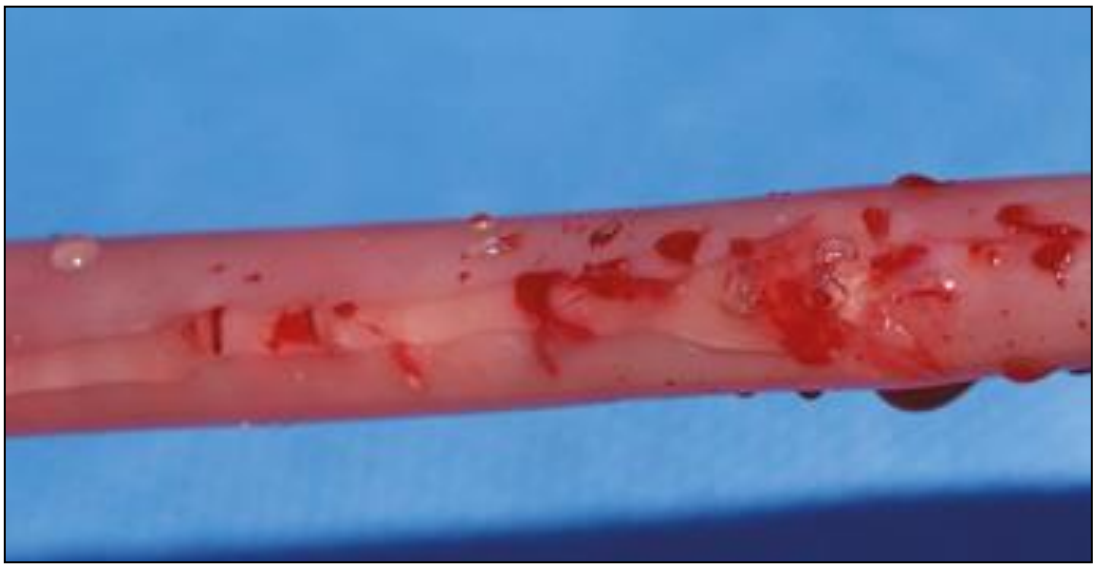


Figure 7.1: Explant ecAVG removed for extensive haematoma and bleeding. The front wall of the graft was found to have almost completely disintegrated from repeated area cannulation.

Primary and secondary patency rates at 3, 6 and 12 months were 64.9%, 48.6%, 32.4% and 70.2%, 59.4%, 40.5%, respectively (Table 7.3). These rates were comparable for upper arm grafts (72.7%, 45.5%, 27.2% and 72.7%, 55.5%, 45.5%) and lower limb grafts (58.3%, 50%, 37.5% and 66.6%, 58.3%, 33.3%).

Table 7.3: Primary and secondary patency rates of ecAVG in the 'early cohort' at 3, 6, 12 and 24 months

	Number at risk	Number failed	Timed out/ not yet reached follow-up	Effective sample size	Interval patency	Cumulative patency
Primary patency 3 months 6 months 12 months 24 months	32 20 10 2	8 6 4 2	4 4 4 0	30 18 8 2	75.0% 70.0% 60.0% 0%	64.9% 48.6% 32.4% 0%
Secondary patency 3 months 6 months 12 months 24 months	32 22 14 3	6 4 7 2	4 4 4 0	30 20 12 3	81.2% 81.8% 50.0% 33.3%	70.2% 59.4% 40.5% 35.7%

A total of 24 patients (64.9%) had prior TCVC. 17 patients (45.9%) had either TCVC or temporary line in situ at the time of ecAVG insertion. These were removed following first successful cannulation. All patients who had ecAVG inserted following an episode of line sepsis were 48 hours "plastic free" to ecAVG insertion. No patient with line sepsis went on to have infection of their graft.

In 26 of 37 patients (70.2%) the ecAVG provided a "personal vascular access solution" (Table 7.4); 35.1% of ecAVGs remain in use for HD (n=13), 1 patient died with a functioning ecAVG and 29.7% of patients successfully used their ecAVG as a bridge to either AVF maturation (n=3) or transplantation (n=8) with avoidance of TCVC.

Table 7.4: Ultimate intention of ecAVG highlighting the proportion of patients achieving a "personal vascular access solution"

Ultimate intention of ecAVG	Number of patients	Number achieving a "personal vascular access solution"
Permanent vascular access for HD (inc. patients with bilateral CVS)	25 (30)	15 (60%) (one death with functioning ecAVG)
Bridge to transplantation (inc. patients with bilateral CVS)	9 (7)	8 (86.9%)
Bridge to AVF maturation	3	3 (100%)

7.3.2. Changing operative technique to improve outcomes

7.3.2.1. Tunnelling

Many of the complications in the 'early' cohort of ecAVG related to difficulties with cannulation, in particular failure to adequately rotate needle sites, cluster/ area cannulation and "missed cannulations" leading to haematoma (21.8%) and pseudoaneurysm (8.1%) formation. Anecdotal evidence and verbal feedback from nursing staff was that the graft was often tunnelled too deep and that there was not enough length of superficial graft to permit adequate needle site rotation. The operative technique was subsequently modified in an attempt to provide a longer more superficial tunnel.

After exposure of the vessels the graft is tunnelled using a standard Kelly-Wick type curved tunneller. A long, looping tunnel has been adopted to assist in cannulation. For example, in an upper limb brachioaxillary graft, the tunnel will extend down the forearm in a loop before running back up the arm to drain into the axillary vein. This configuration has been found to provide the dialysis nurses with a long superficial segment of graft for

cannulation, permitting needle site rotation over a large area, thereby reducing the chance of "one site-itis" and pseudoaneurysm formation. Similarly in the leg, the mid-thigh loop of the 'early' cohort was modified to a D-shaped configuration with the arterial anastomosis to the common femoral artery at the groin and the venous anastomosis to the sub-sartorial femoral vein, leaving a long superficial segment of AVG suitable for cannulation on the lateral aspect of the thigh.

In the early cohort, wound breakdown commonly occurred at the site of tunnel relieving incisions, leading to areas of exposed graft (2.7%). The technique was adapted to off-set relieving incisions from the main tunnel to reduce the risk of infection and exposure of the graft (Figure 7.2).

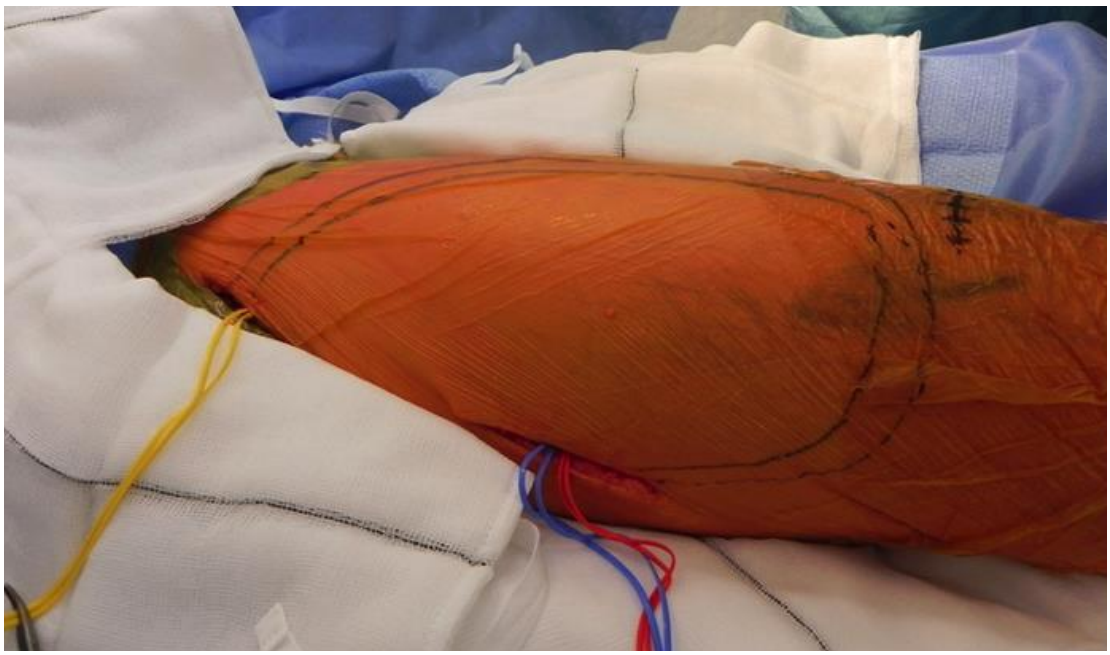


Figure 7.2: Photograph demonstrating the subcutaneous tunnel of a thigh graft. The tunnel extends out over the lateral aspect of the thigh to permit a long superficial segment of graft suitable for cannulation and relieving incision placed distant to the tunnel.

7.3.2.2. Arterial anastomosis

The Gore®ACUSEAL graft has a fixed 6mm internal diameter (Glickman, 2016), necessitating a 6mm arteriotomy (routinely made with an aortic punch) and end-to-side anastomosis of the graft onto the inflow artery is performed using 5.0 Prolene® (Ethicon, Sommerville, NJ, USA). A large arteriotomy predisposes to steal syndrome. In diabetics and women with small vessels who are at high-risk of steal, the technique has been modified to reduce the size of the anastomosis. Firstly the distal open end of the graft is

oversewn using 5.0 Prolene®. A small 3-4mm arteriotomy is then made in the side of the graft just proximal to the oversewn free end and a similar sized arteriotomy made in the native artery. A side-to-side (functional end-to side) anastomosis is then made of the graft onto the artery, again using 5.0 Prolene® (Figure 7.3). Alternatively, a long upper limb axillo-axillary loop may be performed to proximalise the graft inflow and avoid anastomosing onto a small brachial artery.

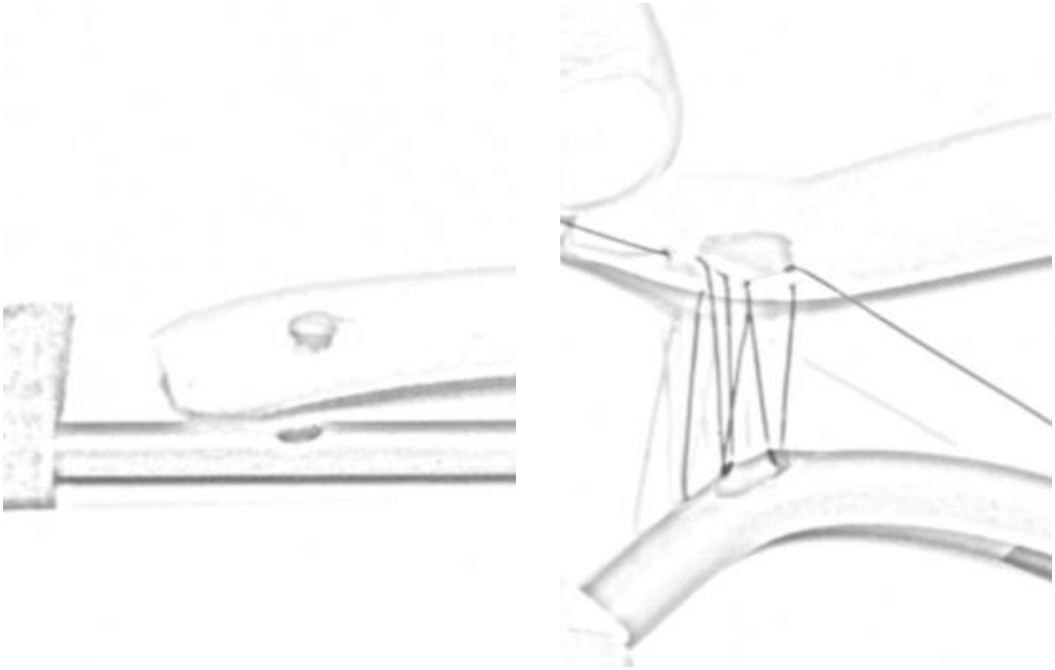


Figure 7.3: Diagrams illustrating the configuration of a small side-to-side arterial anastomosis to minimise steal. Left: The end of the graft was oversewn and a small (4mm) hole punched in the side of the graft to create the anastomosis. Right: Side-to-side anastomosis of graft (top) to artery (bottom).

7.3.2.3. Venous anastomosis

The early cohort of patients had a standard venous anastomosis where the graft was spatulated and then anastomosed end-to-side onto the venous outflow. Particularly in the upper limb, we observed high rates of venous stenosis and thrombosis. We have subsequently employed the technique described by Eric Chemla (St.George's Hospital, London) to perform the venous anastomosis (Chemla, 2014), with a reduction in venous outflow stenosis from 30% to 18% in the first 12 months after adoption.

A long 4cm venotomy is performed and the graft spatulated using sharp scissors to create a long 4cm "mouth" before performing the end-to-side venous anastomosis with 5.0 Prolene® (Figure 7.4). By lengthening the area of graft used for the anastomosis, the graft is "softened" and less distortion of the native vein is seen. It is hypothesised that the longer

anastomosis improves the flow dynamics of the graft outflow and stops the outflow vein being kinked and drawn up into the graft.

It was hypothesised that the high incidence of venous stenosis observed in the initial patient cohort may, in part, be due to initmal injury occurring when the outflow vein was clamped. Latterly, the technique of the Tozzi and colleagues (2014a) has been adopted, utilising a Foley catheter to control the venous outflow, with subsequent reduction in venous outflow stenosis.

7.3.2.4. Wound Closure

It is our opinion that meticulous wound closure is vital to reduce post-operative complications. Careful haemostasis is essential to avoid early post-operative haematoma which, in the initial cohort, subsequently became infected over two-thirds of cases. The gentamycin-impregnanted collagen, Colatamp™ (Tribute Pharmaceuticals, Milton, Ontario, Canada) is routinely placed around both anastomoses and in the subcutaneous tissue beneath the relieving incisions for the tunnel in an attempt to reduce early graft infection. The wound is then closed in layers with 2.0 Vicryl® (Ethicon, Sommerville, NJ, USA) for the subcutaneous tissue and 3.0 subcuticular Biosyn™ (Covidien, Dublin, Ireland) for the skin.

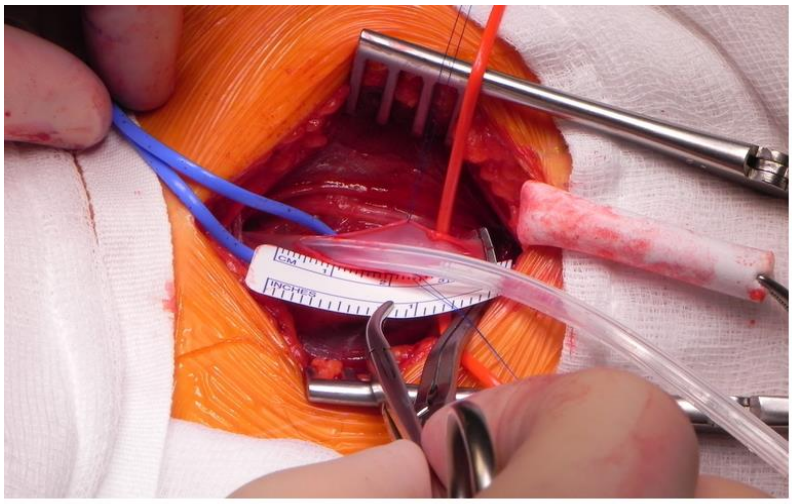
7.3.3. Optimising perioperative care to improve outcomes

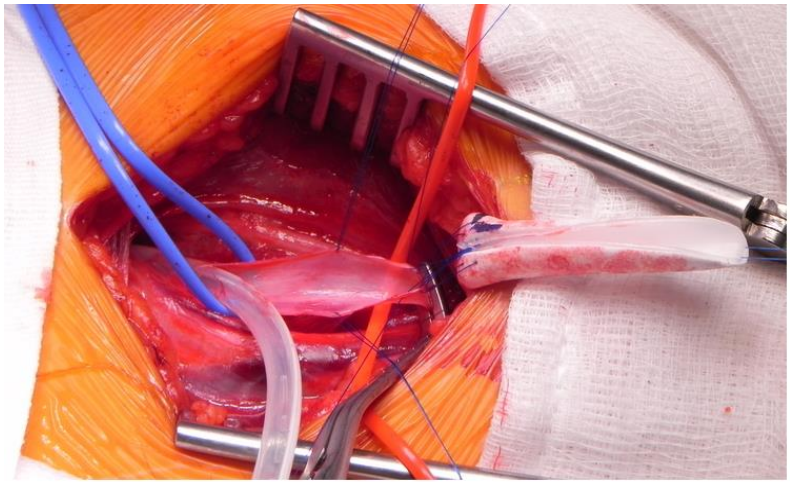
7.3.3.1. Prophylactic antibiotics and skin preparation

Local infection was one of the most common complications observed in the 'early' Gore®ACUSEAL cohort affecting 16.2% of patients. 5.4% developed systemic infection.

1g of intravenous vancomycin is administered at induction of anaesthesia as antibiotic prophylaxis for skin commensals. Pre-operatively the skin is prepared with chlorhexidine 2% and then covered using Ioban™ (3M Healthcare, Bracknell, UK) iodine-impregnated operative site dressing.

Prophylactic antibiotics are continued for 2 weeks following implantation of the Gore®ACUSEAL graft. 1g of vancomycin is administered intravenously three times per week on haemodialysis. If the patient is vancomycin allergic, intravenous teicoplanin is administered instead.





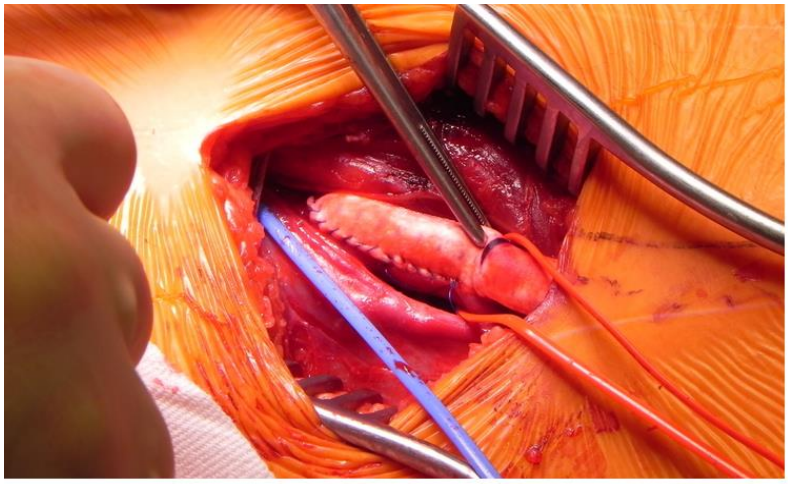


Figure 7.4: Creation of the venous anastomosis. Top The Foley catheter is placed proximally to provide control of the outflow. A 4cm venotomy is created. Middle. The end of the graft is spatulated and a parachute technique is used for the "heel" of the anastomosis using 5.0 Prolene®. Bottom: The completed anastomosis.

7.3.3.2. Anticoagulation

Over 40% of patients in the initial ecAVG cohort experienced thrombosis of their graft. The evidence for antiplatelets and anticoagulation to prevent graft thrombosis is limited, but the literature would suggest a moderate benefit in the use of an anti-platelet agent (Osborn et al. 2008).All patients are now commenced on oral clopidogrel 75mg o.d. for graft patency at the time of graft insertion. In the event of unexplained graft thrombosis (i.e. without underlying stenosis) full anticoagulation with warfarin (INR: 2-3) is employed after patency is restored. Latterly, in light of the findings of Lok and colleagues (2012), fish oil 1g QDS is also administered (although, given the findings of this trial were not published until after the protocol for our ecAVG RCT had been written, we did not implement this practice locally until 2016).

7.3.4. Modifying practice to treat complications

7.3.4.1. Stenosis, thrombosis and declotting the Gore®ACUSEAL graft

Venous stenosis occurred in between one-third and a half of all ecAVG in the early series, leading to thrombosis in the vast majority. A strategy for rapid thrombectomy is required to avoid TCVC insertion in such cases.

Our unit has developed a strategy of same day thrombectomy with simultaneous angioplasty of any outflow stenosis in the event of graft thrombosis. A combined procedure between the vascular surgeon and interventional radiologist is performed under local anesthetic. A small 2-3cm surgical incision is made over the graft and proximal and distal control obtained with sloops. A small transverse arteriotomy is made in the graft and the graft trawled proximally and distally with a 3 French Fogarty® catheter. The Gore®ACUSEAL graft is easy to declot in this fashion as the inner layer of PTFE is heparin bonded (Glickman, 2016). Upon restoration of flow, an angiogram is then performed and angioplasty ± stenting undertaken in the standard fashion. The arteriotomy in the graft is closed with 5.0 Prolene® at the end of the procedure and the patient systemically anticoagulated. The graft can be cannulated for dialysis immediately following the procedure, but care must be taken to needle distant from the arteriotomy site. By utilising an open thrombectomy technique, the declotting procedure takes only 5-10 minutes, whilst still allowing a subsequent radiological procedure to definitively treat the outflow stenosis at the same sitting. The entire procedure takes less than 30 minutes and has successfully restored patency in 92% of grafts.

7.3.4.2. Steal syndrome

The fixed outflow and high access flows (>600mL/min) occurring immediately after insertion of an arteriovenous graft mean that patients with AVGs are particularly at risk of steal syndrome and distal hypoperfusion (Al-Shakarchi & Inston, 2015a). Despite modifying the technique for the arterial anastomosis (as described above) to minimise the risk of steal, it still occurred in 10% of patients. In most cases it was mild and could be managed conservatively, however if severe, the graft can be occluded with simple firm digital pressure for 15-20 minutes to obstruct the flow of blood through the graft and cause it to clot. This has proven successful in three patients with symptoms of steal syndrome who no longer required their AVG. Firm external digital pressure alone was sufficient to occlude the graft permanently without complication and avoided the need for further surgery in these patients.

7.3.4.3. Exposed graft

A few cases skin breakdown leaving a short segment of exposed graft were observed in the early patient cohort. These patients were elderly or obese with fragile, vulnerable skin. The breakdown occurred at the site of the tunnel relieving incision (Figure 7.5). In each case, the graft continued to function without difficultly. We simply covered the area of exposed graft with a non-adherent Inadine® (Systagenics, Skipton, UK) dressing and continued to dialyse needling the graft distant to the exposed site. In all but one case the wounds closed by secondary intention after a few weeks.

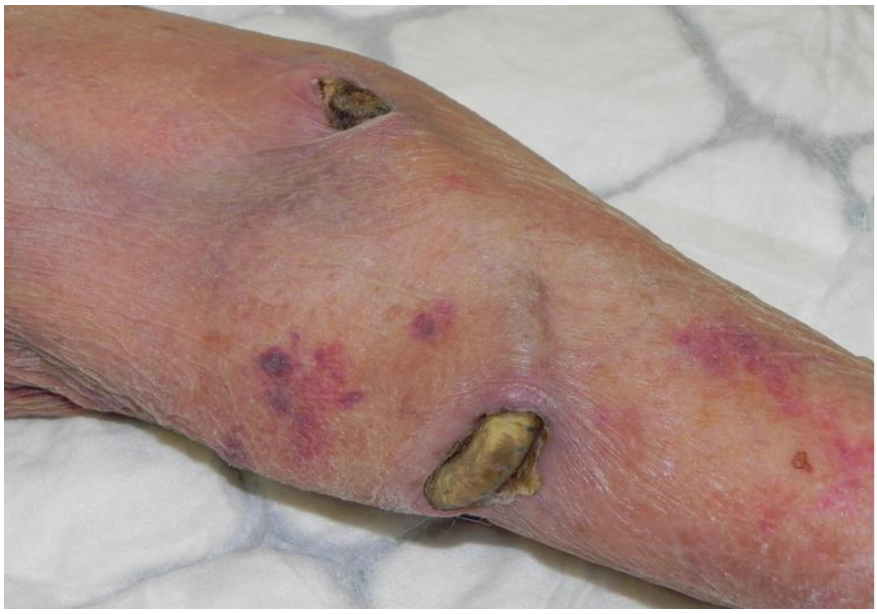


Figure 7.5: Exposed segment of graft at a relieving incision. This elderly lady had very thin, fragile skin.

7.3.4.4. Pseudoaneurysm and graft breakdown/ rupture

Pseudoaneurysms are a well-recognised complication of arteriovenous grafts (Sgroi et al. 2013). In the early cohort of Gore®ACUSEAL grafts, 3 of 37 patients (8%) developed a pseudoaneurysm. Repeated cannulation of the same area of graft ("one site-itis") damages the integrity of the wall of the graft and prevents it from self-sealing, leading to pseudoaneurysm formation. Explanted grafts from such patients were been found to have multiple puncture sites coalescing into larger holes in the graft (Figure 7.1). In the majority of cases pseudoaneurysm formation was attributed to poor needling technique. Dialysis nurse education sessions (outlined in detail below) focussed on the importance of needle site rotation and use of sharp, small gauge needles. In line with the manufacturer's guidance (W.L.Gore Associates, n.d.), cannulation with 17G sharp needles throughout the lifespan of the graft with needle site rotation of approximately 1cm with each cannulation was advocated. Firm pressure should be applied at needle sites for 10-15 minutes after removal of the needles to prevent local haematoma formation. Low flow rates of 200-250mL/min for the first two weeks after insertion to minimise damage to the venous anastomosis that may occur with higher flows is also advised. This cannulation technique was taught in the education sessions, following which no further complications with pseudoaneurysm formation were observed in the subsequent 49 graft implantations.

7.3.4.5. Graft infection

Despite preventative measures (meticulous haemostasis and antibiotic prophylaxis) graft infection still occurs. Like other authors (Harish & Allon, 2011), two peaks in the incidence of graft infection were observed in our cohort: early post-operatively and delayed (Figure 1.12). All but one (87.5%) of the infected haematomas occurred within two months of graft insertion and were either associated with post-operative haematoma (42.9%) or cannulation (57.1%). They all presented with erythema, pain and swelling at the graft site with minimal systemic upset. In the majority of cases, these were successfully managed conservatively with intravenous antibiotics without necessitating graft explant. Conversely, the graft infections that occurred later (>3months) were all associated with systemic signs of sepsis (pyrexia, tachycardia etc.) and normally demanded removal of the graft. It is believed that, at least in part, these later graft infections relate to poor cannulation technique, failure to adhere to strict aseptic technique and the introduction of skin commensals into the bloodstream resulting in systemic infection. Investment in education of dialysis nurses to re-itterate the importance of strict asepsis when cannulating

the graft and also the importance of pressure after removal of needles from the graft to minimise haematoma (that can then become secondarily infected), coincides with a significant reduction in the number of graft infections. Local infection rates fell following the education sessions from 22% to 4%. Whilst it is impossible to attribute the reduction in infection rates observed entirely to the education sessions and scrupulous cannulation technique, the temporal association implies a relationship. A coincidental reduction in haematoma associated with cannulation from 24% to 4% was also observed, adding plausibility to this assertion.

7.3.5. The ecAVG courses

Education sessions were originally instigated locally for dialysis nurses in response to a perceived need (high rate of cannulation-related complications). The initial intention had been to run a single course for a small core group of nursing staff (who could then disseminate the information back to individual dialysis units) in an attempt to optimise and standardise practice ahead of commencing the RCT (Chapter 9). However, the initial session was very well received and the course was expanded and developed allowing surgeons and dialysis nurses from around Europe to attend the latest iteration.

A two-day interactive, multi-disciplinary course was run at the Clinical Anatomy Skills Centre, University of Glasgow. The course was funded by industry (W.L. Gore Associates) but run by clinicians, with no industry involvement in the content. The focus was on discussing broad-themes of early cannulation grafts and strategies for line avoidance, rather than promotion of any particular graft. Multi-modal teaching methods were employed with hands-on small group sessions, in addition to more didactic lecturing styles and group discussion (Appendix 2). The emphasis was on strategies to solve "real-life" clinical problems. A faculty of five senior clinicians from various disciplines (vascular access surgeon, interventional radiologist, nephrologist, vascular access nurse) were supported by six "junior faculty" to assist in the running of the course. Parallel sessions were run for vascular access surgeons and dialysis nurses with cross-over and overlap as appropriate to permit multidisciplinary discussion between the different groups of professionals around common themes and how dialysis practice might affect surgical outcomes and vice versa (For example, the idea for a longer arm loop to facilitate better needle site rotation came from this forum). The second day of the course for the surgeons comprised of hands-on experience of insertion of early cannulation grafts using fresh-frozen cadavers. Delegates had the opportunity to perform upper limb (brachio-axillary

and forearm loop) and lower limb (femoro-femoral grafts). The session was supported by personalised advice and appraisal of surgical technique, along with tips and technical points from experienced vascular access surgeons. Following this dialysis nurses then had the opportunity to practice cannulating the newly inserted grafts in the cadavers.

30 surgeons, 3 nephrologists, 2 interventional radiologists and 56 vascular access nurses from around the UK attended the latter two courses. All participants reported that the course improved their knowledge and ability to think critically about the subject matter. Common themes identified in the post-course questionnaire (Appendix 1) were in support of the "multidisciplinary nature" of the course and the ethos of "team work" that it promoted.

Most of the nurses attending the course had a good knowledge of cannulation techniques and the particulars of graft cannulation prior to the course with 100% knowing of the need to apply pressure for 10-15 minutes after needle removal and 93% to use small gauge needles. This increased to 100% following the course. Fewer nurses were aware of the anatomy of grafts prior to the course, with only 45% understanding the configuration of a brachioaxillary graft and 78% being able to identify the venous outflow. At the end of the course, all nurses could accurately describe the anatomy of the graft and identify the venous outflow. Qualitative data from the free-text responses suggests that many nurses felt that a better understanding of the anatomy and operative procedure made them more confident in cannulation (Table 7.5).

Table 7.5: Responses of nursing staff in the post-course evaluation questionnaire.

"Cannulation will be much easier now that I can visualise the graft in 3D"
"It was great to see the DVD of how the graft is tunnelled. I now understand why the patients are sometimes bruised and sore."
"It was nice to see what the graft actually looked like because it will help with cannulation"
"I now know why I was having all the problems. My needle kept hitting the side of the graft. It was only once I could look at it in the cadaver that I could realise it"
"I'll be able to explain the procedure to my patients now"
"It's just given me better confidence in cannulation"

The course appeared to influence the subsequent behaviour and practice of participants. Prior to the course only 50% of nursing staff had any prior experience cannulating ecAVGs and 60% of surgeons had ever inserted one. Three months following the course

78% of nurses reported having cannulated an ecAVG, with 65% indicating they did so on a regular basis. 94% of surgeons inserted an ecAVG in the three months following the course, with a total of 35 successful graft procedures performed by course delegates.

With regards outcomes, it has already been highlighted that there was a significant reduction in cannulation related complications locally in the 6 months following the course (an observation which, at least in part, is likely attributable to the education of dialysis nursing staff). A five-fold reduction in cannulation-related haematoma and local infection was observed and no new pseudoaneurysms occurred in the six-months following the course.

7.3.6. Re-evaluation of Gore®ACUSEAL outcomes

A total of 49 Gore®ACUSEAL grafts were inserted locally in the six-months between July and December 2013 (following implementation of the modifications to technique and practice described above). A significant reduction in the incidence of local infection (4% vs. 22%; P=0.01) and haematoma (24% vs. 4%; P=0.01) was observed. There were no pseudoaneurysms in the latter cohort. Rates of thrombosis and venous stenosis were also lower, though this difference was not statistically significant (Table 7.6).

Figure 7.6: A comparison of the complications observed in the 'early' and 'later' cohorts of ecAVG.

	Graft outcomes in 'early' cohort (n=37)	**Graft outcomes in 'later' cohort (n=49)**	**P-value**
Thrombosis	41% (n=15)	31% (n=15)	0.23
Venous Stenosis	30% (n=11)	20% (n=10)	0.25
Systemic infection	5% (n=2)	-	0.09
Local infection	22% (n=8)	4% (n=2)	0.01
Haematoma	24% (n=9)	4% (n=2)	0.01
Pseudoaneurysm	8% (n=3)	-	0.02
Steal	3% (n=1)	10% (n=5)	0.14
Wound breakdown	3% (n=1)	4% (n=2)	N.S
Cardiovascular complications	3% (n=1)	4% (n=2)	N.S

7.4. DISCUSSION

Our early experience with Gore®ACUSEAL ecAVG was encouraging. The six-month secondary patency of 60% is comparable to other published series of standard PFTE (patency rates 40%-80% described) (Schild et al. 2007; Glickman et al. 2001). Perhaps of greater importance than long-term ecAVG patency was the provision of a "personal vascular access solution." Although the concept of "tailoring" vascular access to the individual is extensively described in the literature (Lok et al. 2005; Lok, 2007), this was the first study to highlight its practical application in clinical practice. In the early patient cohort, 26 of 37 patients (70.2%) achieved a "personal vascular access solution" from their ecAVG with the role of Gore®ACUSEAL in TCVC avoidance, as a bridge to transplant or alternative vascular access, clearly demonstrated.

Both primary and secondary patency rates at 12 months (32% and 40% respectively) in our early cohort of patients were lower then those described elsewhere in the literature on Gore®ACUSEAL. Tozzi and colleagues (2014a) report 12-month primary and secondary patencies of 68% and 93%. While, in their multicentre study, Glickman et al. (2015) report a secondary patency of 78% at 1-year. We believe that these discrepancies observed are the result of differences in case mix, with our early patient cohort reflecting the extremes of a dialysis population. Many of the patients treated with Gore®ACUSEAL in the 'early' cohort had been waiting for many years for a solution to their precarious vascular access. Nearly half had bilateral central vein stenosis and two-thirds of the procedures were lower limb grafts. Conversely, the grafts in the study of Glickman and colleagues provided 'upper limb vascular access in patients not suitable for arteriovenous fistulae' (2015, pp.465) and Tozzi et al. placed upper limb grafts in 90% of patients who were 'poor candidates for autologous access' (2014, pp.386).

The mean age of patients in our early cohort was 42 years. This is substantially younger than the average age of the dialysis population as a whole and also lower than in other published series of Gore®ACUSEAL (Maytham et al. 2015; Tozzi et al. 2014b; Glickman et al. 2015). This may potentially explain the low infection and complication rates observed. However, we believe that the relatively young chronological age of the patient cohort in this study does not reflect their biological age as they form some of the most complex, comorbid dialysis patients, having often accrued many years on HD resulting in end-stage vascular access.

Lower limb grafts are traditionally associated with high rates of infection (Harish & Allon,

2011). However, in our early cohort of patients, the systemic bacteremia rate of 0.2 per 1,000 dialysis days is lower than in other AVG studies and comparable to that of AVF, despite nearly two-thirds of patients having a lower limb graft placed (Taylor et al. 2002; Thomson et al. 2007). Local infection rates fell further following modification of operative technique and education of our dialysis nursing staff. We believe that careful patient selection, strict asepsis during surgery and cannulation, the use of Colatamp™, prophylactic antibiotics and the choice of mid-thigh loop grafts in the majority of patients explains this (Scott et al. 2006; Bagul et al. 2015).

This study and the subsequent modifications to technique that ensued highlight the importance of experiential learning. Despite the benefits of ecAVG observed in the initial cohort, it was perceived that outcomes were suboptimal and could be improved. The operative, perioperative and cannulation techniques evolved gradually, through trial and error in response to problems encountered. As such, no individual intervention can be credited with the improvements in graft outcome observed within the latter cohort.

Nevertheless, several of the practical lessons learned for our experiences warrant discussion. Firstly, patient selection is vitally important. Often patients requiring AVGs are frail with small vessels and have exhausted their alternative options. Many have been on HD for many years and have extensive vascular calcification. For these reasons careful assessment of cardiac fitness and the vascular tree is essential preoperatively to minimise ischaemic complications. Secondly good needling technique is vital. The haematomas and pseudoaneurysms observed in our 'early' cohort of patients are not unique. In fact, in almost every case series of ecAVG, the authors highlight the importance of cannulation technique and nursing education (Tozzi et al. 2014b; Berard et al. 2015; Al-Shakarchi & Inston, 2015b). Certainly the learning curve for ecAVGs applies equally to cannulation as operative technique.

The description of our graft course and its role as an intervention to improve outcome is the first such description of an educational intervention in vascular access. The success of the intervention was evaluated according the Kirkpartick's four-level model for learning evaluation (Kirkpatrick, 1996). To this end, we have demonstrated that the "reaction" to the courses was universally positive and that the nurses "knowledge" of the anatomy of AVGs improved significantly following the course. Both nurses and surgeons "behaviour" changed after the course with more nurses regularly cannulating grafts and all but one surgeon implementing their knowledge and inserting a graft in the three months following the course. Finally, whilst the improved graft "outcomes" and the lower complication rate

observed in the ‘later’ patient cohort cannot be directly attributed to attendance at the graft course, the temporal association makes a contributory influence likely.

In both patient cohorts, we describe a heterogeneous patient group with a variety of requirements from the ecAVG, including TCVC- free bridge to transplantation or AVF maturation and end-stage vascular access with no further autologous options. The variety of patients (and indications) that we have treated reflects the versatility of the Gore®ACUSEAL graft. It provides a useful option in a multifaceted approach to achieving a personal vascular access cure. Perhaps in the future, the traditional “Fistula First” idiom will require modification to “Line Last” in light of the unique role which ecAVGs can provide (Vassalotti et al. 2012). It may be that, temporally at least, a “Graft First” approach followed by AVF is favored for many patients.

In conclusion, our initial experience with the Gore®ACUSEAL graft proved encouraging with bacteremia rates comparable to native AVF. The fact that ecAVGs permitted cannulation within 24 hours of insertion meant that line avoidance was potentially achievable in the majority of patients. Nearly three-quarters of patients in the initial cohort achieved a definitive “personal vascular access solution”. With modification of technique and education it was possible to further reduce the rates of venous stenosis and local haematoma and pseudoaneurysm formation. We had taken ecAVGs from a novel concept utilised in a few selected patients to become a mainstream treatment option. The scene was set and the technique optimised to permit progress into further studies and ultimately a randomised controlled trial.

ARE EARLY CANNULATION ARTERIOVENOUS GRAFTS A VIABLE ALTERNATIVE TO TUNNELLED CENTRAL VENOUS CATHETERS: AN OBSERVATIONAL "VIRTUAL STUDY" AND BUDGET IMPACT ANALYSIS

8.1. INTRODUCTION

As previously discussed, AVF are the vascular access of choice for patients requiring haemodialysis. TCVCs are used only as an option of necessity (Fluck & Kumwenda, 2011). In practice however, AVF usage is limited by delays in operative planning, maturation time (necessitating AVF creation 3-4 months before the anticipated date of dialysis commencement) and a failure to mature rate approaching 60% in some randomised trials (Dember et al. 2008; Irish et al. 2017). If dialysis is required before the AVF is functionally mature, an alternative access modality (generally TCVC) is required (Rodriguez et al. 2000).

Dialysis via a TCVC confers significantly higher risk of infection, mortality and central venous stenosis than dialysis via an AVF. Recently, a Scottish study of 2666 patients revealed a 2-3 fold increased risk in all-cause mortality and a 7-fold increase in death from septicaemia with the use of TCVCs (Bray et al. 2012). The complications of vascular access are responsible for over 20% of hospitalisations in patients on HD and account for one third of all in-patient renal bed usage (Rayner et al. 2003; Thomson et al. 2010; Feldman et al. 1993). It therefore follows that a strategy of TCVC avoidance is likely to have significant benefits both for individual patients and healthcare providers.

Arteriovenous grafts (AVGs) provide an alternative means of vascular access. Traditionally AVGs have 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 TCVC in patients requiring vascular access imminently (Tozzi et al. 2014a; Aitken et al. 2014b). As previously discussed, 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 (Leermakers et al. 2013), but have rates of infection and complication rates lower than a TCVC (Thomson et al. 2007). Culture-proven bacteraemia rates for TCVCs are 1·77 per 1,000 catheter days compared to 0·6 per 1,000 dialysis days for an AVG and 0·3 per 1,000 dialysis days for an AVF (Taylor et al. 2002; Thomson et al. 2007). Primary patency rates

for AVGs range from 40-60% at 1 year (Fernstrom et al. 2007). However, with aggressive management of thrombosis, secondary patency rates of as high as 90% at 1 year can be achieved (Akoh, 2009).

30-35% of patients needing to start haemodialysis are referred for access creation less than 90 days prior to the date that they require to commence dialysis, leaving insufficient time for planning, surgery and maturation of an AVF (National Kidney Care Vascular Access Report, 2012.; Ethier et al. 2008). In the UK only 40% of patients commence haemodialysis via an AVF (UK Renal Registry, 2014). ecAVGs may have a role in these incident patients, in whom there has not been sufficient time to create and mature an AVF and avoid the need for TCVC in this population of "crashlanders" . (We do not advocate the long-term use of ecAVGs in patients in whom it would be possible to create an AVF, rather the ecAVG would provide temporary vascular access until the native option had matured adequately).

With this in mind, we proposed a "virtual study" to answer the question of whether (outwith the confines of an idealized, protected trial) ecAVGs could be a better real-world alternative to TCVC in patients requiring imminent haemodialysis. The study aimed to answer the following questions:

1. Is it an acceptable alternative for patients to have an ecAVG rather than a TCVC?
2. Are urgent ecAVGs a practical alternative in the population presenting with an immediate need for vascular access in a regional centre with limited resources?
3. What are the individual and service costs through the current pathways using TCVC and can these be reduced using ecAVGs?

We additionally estimated the potential budget impact to the centre of adopting ecAVGs for clinically suitable patients while they awaited a functioning AVF.

The "virtual study" is a novel concept not previously described in the literature, permitting a "real-world" observational study of current practice and comparing it to a hypothetical model of an alternative treatment strategy based on best available evidence and data collected "real-time" about the feasibility of any change in practice. It can be used to inform cost calculations, future research and the clinical implementation of any subsequent practice change. It may be useful in situations, such as the one proposed, where the implementation of any strategy involving ecAVGs as an alternative to TCVCs would necessitate a paradigm shift in nephrology thinking and service provision.

The results of our "virtual study" and the associated health economic cost-consequence analysis are presented.

8.2. METHODOLOGY

8.2.1. Study design and setting

A prospective observational cohort study of current standard practice (TCVCs) with a hypothetical comparator group (ecAVGs) and associated budget impact analysis was performed. Data was collected from the Department of Renal Surgery, Western Infirmary, Glasgow.

Formal approval from the Research Ethics Committee was not required for this observational study of standard practice. Approval for data collection was obtained from the hospital Clinical Effectiveness Department.

8.2.2. Recruitment and participants

This was an inclusive study. All patients having TCVC inserted over a 6-month period between December 2012 and June 2013 were included for analysis. It was anticipated that this time period would permit recruitment of a representative proportion of our dialysis population. All referrals for TCVC insertion were managed by a dedicated Vascular Access Coordinator who identified patients and highlighted them to the research team on the day of referral.

8.2.3. Data collection

Basic patient demographic data (including age, sex, cause of renal failure, duration on haemodialysis, indications for TCVC insertion) were obtained from the Scottish Electronic Renal Patient Record (SERPR). Prior to TCVC insertion all patients were approached by a member of the research team and the features of ecAVG explained. Patients were informed of the risks of infection and central vein stenosis of TCVC. ecAVG were proposed as an alternative with lower infection rates than TCVC. It was explained that ecAVG would necessitate an additional operative procedure with potential risks of steal and thrombosis described. It was explained to those patients for whom ecAVG was not intended to be the definitive management strategy, that further AVF creation was still needed. Their views and opinions regarding whether or not they would accept ecAVG in place of the TCVC, if the option were available to them, were explored. These same questions were asked to the

patients after 6 months follow-up also to assess if their opinion had changed. Ultrasound vein mapping was performed to determine the optimal placement of ecAVG and AVF. It was assumed that ultimate aim was to achieve autologous AVF wherever possible, with TCVC with and ecAVG used only as an interim measure. Patients were deemed anatomically suitable for ecAVG if they had an artery measuring >2.5mm diameter and suitable venous landing site. If no upper limb option was suitable, leg grafts were considered in patients fit for general anaesthesia. Patients who had previously had access ligated for steal or who had monophasic arterial flow were excluded from upper limb ecAVG. Finally the practicalities of ecAVG were considered: Was the patient fit for surgery? Did they have significant hyperkalaemia or pulmonary oedema necessitating temporary access for haemodialysis prior to ecAVG? Was there an operating theatre available that could be used to permit ecAVG insertion and AVF creation? What delays might be involved in this process? What was the patient's definitive vascular access and how might this be best expedited? Although no ecAVGs were implanted, the answers to these questions allowed us to assess patient suitability and waiting time in a hypothetical scenario.

8.2.4. Follow-up

All patients were followed-up for 6 months. Treatment delays and complications of TCVCs (wait time for TCVC insertion, bed days required as a result of vascular access complications, culture-proven bacteraemia, suspected bacteraemia, antibiotic usage, line thrombosis, urokinase infusions, new TCVCs/ temporary lines/ AVF other line complications) were recorded. Data were also recorded on AVF creation, maturation and suitability for cannulation for dialysis, along with what form of vascular access was used for haemodialysis at 6 month follow-up. Data was collected prospectively, so there were no missing data points and no patients were lost to follow-up. Patients who died had death recorded and data collated prior to death was retained for analysis.

8.2.5. Statistical analysis

Patient demographics and complication rates for patients having TCVC insertion are presented as mean ± SD or as a percentage of the total patient population (n=79). Data on the practicalities and acceptability of ecAVG are presented similarly.

This data was then used to create a model for "standard" practice of TCVC insertion, including treatment delays and complications. A similar model for ecAVGs was also

created using data obtained from the real-time study (acceptability derived from patient questionnaires, theatre availability and anatomically feasibility from clinical ultrasounds) and previously published rates of graft infection and thrombosis (Taylor et al. 2002; Akoh 2009). These models permitted a comparison of the "real-world" current practice of TCVC insertion until definitive autologous access could be created and a hypothetical model of ecAVGs used until the AVF was mature. It must be emphasised that the ultimate aim for every patients was to achieve autologous vascular access if possible. Both TCVCs and ecAVGs were considered a "bridge" to this definitive access wherever possible.

A budget impact model was used to estimate the total costs to the hospital of the two treatment strategies over a 6-month time period. These strategies are illustrated in Figure 8.1a and Figure 8.1b. Figure 8.1b reflects the current treatment pathway, where patients primarily use TCVCs as temporary vascular access while awaiting definitive AVF formation and maturation. Figure 8.1a represents the proposed strategy with ecAVGs replace TCVCs where possible. To reflect real-world practice, patient suitability and acceptability for ecAVG and AVF taken from the "virtual study" was incorporated into the analysis. Clinical inputs including referral delays for treatment, complications and repeat procedures were derived directly from the observational data, internal audits and published literature. We assumed that the re-intervention and infection rates of ecAVG were equivalent to conventional AVGs (58% secondary patency rate at 6 months (Schild et al. 2007; Akoh 2009)). Access-related bacteraemia rates for TCVCs were derived from the "virtual study" data and from the published literature for AVGs and AVFs (Taylor et al. 2002) (Table 8.1). The model includes costs for all initial procedures and re-interventions, in additional to treatment costs for complications including thrombosis and infection. The costs of individual procedures are listed in Table 8.2. Resource use was based on hospital practice and unit costs were taken from Personal Social Service Research Unit (PSSRU5) figures, NHS Reference Costs 2011-2012 and published literature (Curtis, 2012; Hockenhull et al. 2008; Department of Health, 2013). All costs are quoted in pounds Sterling (£). A sensitivity analysis was conducted to consider varying rates for TCVC bacteraemia, referral days for TCVC insertion, and the percentage of patients using the ecAVG as their definitive access option.

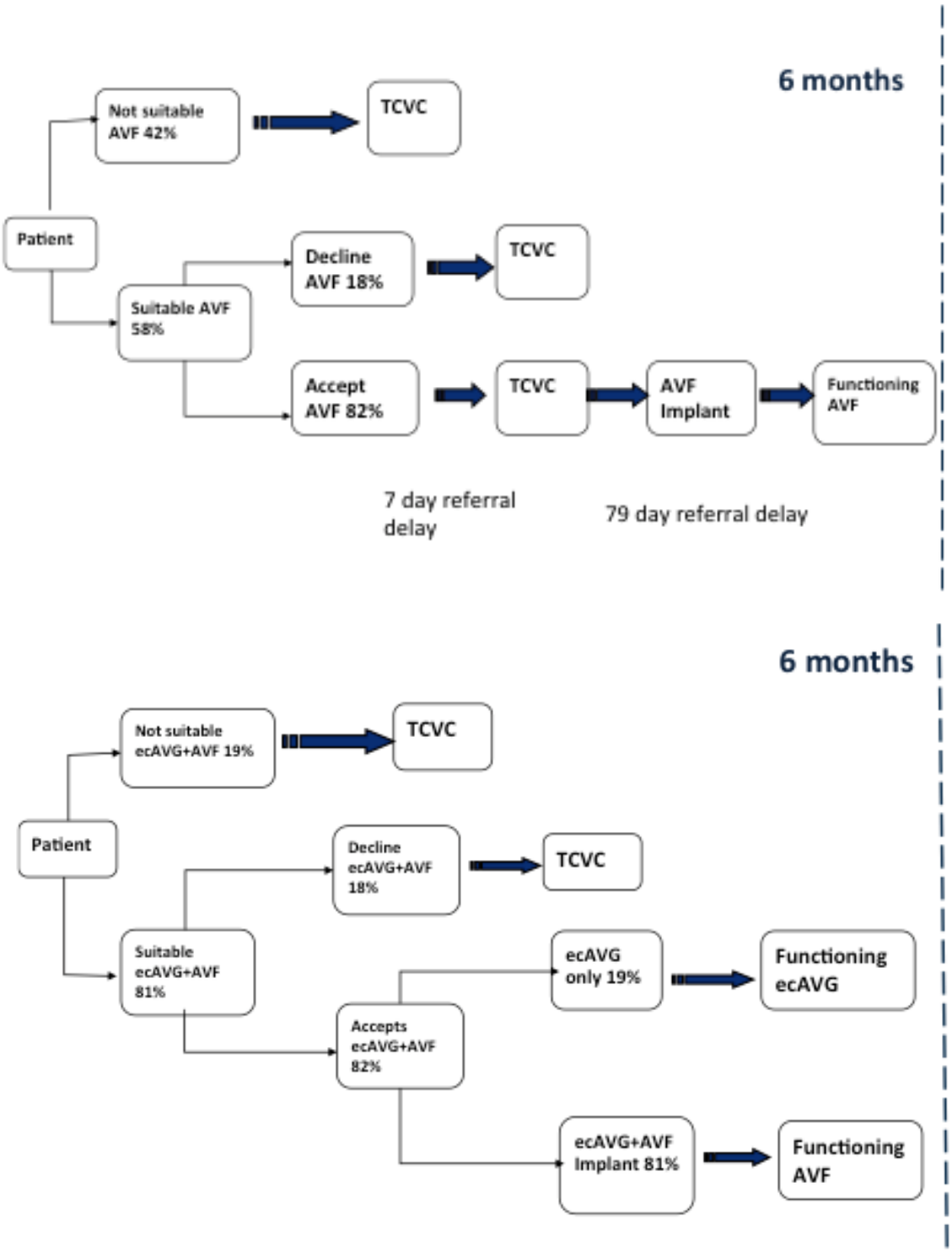


Figure 8.1a (above): Proposed novel treatment strategy for patients requiring urgent vascular access for haemodialysis (ecAVG). Figure 8.1b (below): Current treatment algorithm for patients requiring urgent vascular access for haemodialysis (TCVC).

Table 8.1: Vascular access associated bacteraemia rates

Vascular access	Bacteraemia rate (per 1,000 dialysis days)	Source
TCVC	1.4	Observed rates
AVF	0.3	Taylor et al. 2002
AVG	0.6	Taylor et al. 2002

Table 8.2: Baseline costs for interventions in health economic model. All costs are quoted in pounds Sterling (£).

Intervention	Cost per event (£)	Source
Temporary Line Insertion	£209.0	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract
TCVC Insertion	£524.7	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract
TCVC Removal	£32.6	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract
AVF creation- 1st attempt	£1 072.0	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract Cost of bed days: Authors' estimate
AVF creation- 2nd attempt	£1 381.0	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract Cost of bed days: Authors' estimate
Combined ecAVG and AVF implantation	£1 982.0	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract Cost of bed days: Authors' estimate Device cost of ecAVG (Acuseal): W.L. Gore Associates
ecAVG implantation	£1 768.7	Staff cost per hour: Curtis, 2012 Consumables: NHS Greater Glasgow and Clyde purchasing contract Cost of bed days: Authors' estimate Device cost of ecAVG (Acuseal): W.L. Gore Associates
Ultrasound	£56.0	NHS Reference Costs 2011-2012
Fistuloplasty – Radiological	£1 957.0	NHS Reference Costs 2011-2012
Thrombectomy – Radiological	£1 957.0	NHS Reference Costs 2011-2012
Thrombectomy – Surgical	£3 451.0	NHS Reference Costs 2011-2012
Sepsis episode treatment	£9 148.0	Hockenhull et al. 2008

8.3. RESULTS

8.3.1. Patient demographics

79 patients were assessed prior to TCVC insertion (mean age: 62.8 ± 13.1 years; 51.4% male) requiring 101 TCVCs and 40 temporary lines over 6 months. Table 8.3 outlines basic patient demographics. Reasons for TCVC usage were as follows: problems with existing AVF (22.7%), problems with existing TCVC (48.5%) and need to commence HD without functioning AVF (28.7%) (Figure 8.2).

Table 8.3: Demographics of patients having TCVC inserted. Results reflect a mean ± SD or as a percentage and number of the total population unless otherwise stated

Age (years)	62.4 ±12.7
Sex (percentage male)	65.8% (n=52)
Cause of renal failure	
Diabetes	35.4% (n=28)
Hypertension	15.2% (n=12)
Glomerulonephritis	12.7% (n=10)
Interstitial nephritis	21.5% (n=17)
Other	15.1% (n=12)
Time on haemodialysis (years)	3.8 ±2.3
Number of previous TCVCs (median)	4 (range: 0-21)
Co-morbidities	
Hypertension	75.9% (n=60)
Previous myocardial infarction	27.8%% (n=22)
Previous cerebrovascular event	12.7% (n=10)
Diabetes	44.3% (n=35)
COPD	30.4% (n=24)

8.3.2. Delays and complications associated with TCVCs

Patients had a median delay of 7 days in hospital for TCVC implantation (range: 0-27). 35 had discharged delayed solely due to delays in TCVC insertion (median time: 6 days). 34.7% of TCVCs (n=35) had significant complications (including 17 episodes of culture proven bacteraemia and 13 flow-related problems) during the 6-month follow-up period.

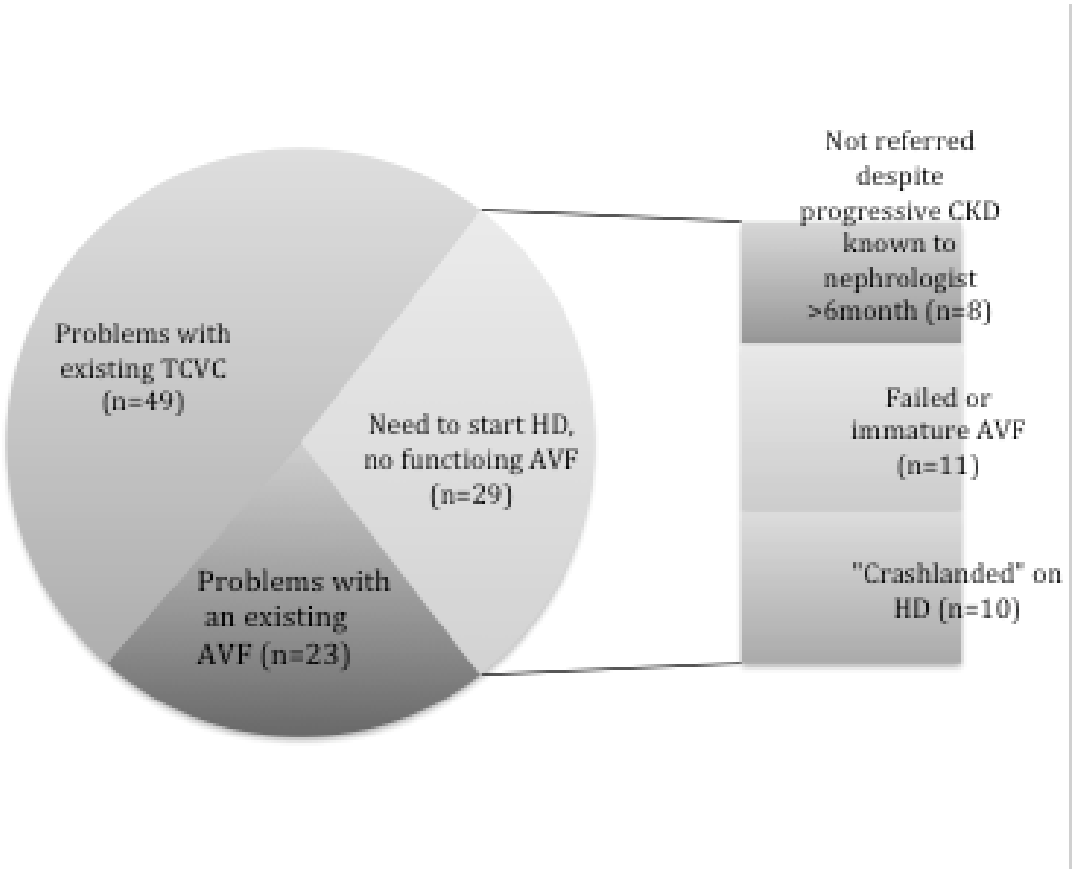


Figure 8.2: Indications for TCVC insertion. The majority of patients requiring TCVC insertion were already on haemodialysis (most having problems with an existing TCVC with a smaller number having problems with an AVF). 28.7% of patients needing TCVC were incident haemodialysis patients (who were either referred late for vascular access creation or "crashlanded" onto dialysis.

Table 8.4: Complications of TCVCs. Results are presented as absolute number observed and (where relevant) number per patient per year.

	Number of episodes (total)	**Number of episodes (per patient/ year)**
Complication		
Culture-proven line sepsis	17 (all lines replaced)	1.4 per 1,000 cathter days
Suspected or proven line sepsis	19 (all lines replaced)	1.6 per 1,000 catheter days
Poor flows	13 (5 new lines)	
Cracked line	1 (replaced)	
Accidental removal	3 (all replaced)	
Bed days	357 days	11.9 days/ patient/ year
Intervention		
IV vancomycin	198 doses (15 patients)	
Urokinase infusion	56 infusions (11 patients)	
New TCVC	28 lines	
Temporary line	5 lines	

8.3.3. Definitive vascular access

56 AVF access creation procedures were performed during the first 6 months after TCVC insertion. Median time from referral to actual AVF procedure was 79 days and 57 days thereafter for AVF maturation (until first successful cannulation). 7 patients (8.8%) died during the follow-up period and were removed from the analysis at the time of their death. 1 death was the result of proven line sepsis. 31 patients successfully dialysed through their AVF at some point during the first 6 months, but many failed early, and only 16 patients had a functioning AVF capable of giving sustained dialysis at 6 month follow-up.

8.3.4. Acceptability and practicality of an alternative ecAVG strategy

ecAVG were a clinically suitable alternative to TCVC in 66 of the 79 patients (83.5%). 64 patients (81%) would have been suitable for a strategy of ecAVG and AVF. A total of 13 patients were not clinically suitable for ecAVG for the following reasons: acute illness which would have precluded ecAVG (n=5); chronically too frail or unfit for ecAVG (n=11). 12 (11.8%) would have required temporary access to permit HD for hyperkalaemia or fluid overload prior to ecAVG insertion.

53 patients would have accepted ecAVG as an alternative to TCVC. 13 patients declined ecAVG (the majority also declined an AVF) at initial and 6 months interviews, however these were different sets of patients. This meant that 81% of patients were anatomically suitable for an ecAVG ± AVF, and 72% of these patients would have accepted this as a treatment option (Figure 8.1a). Table 8.5 outlines the acceptability of ecAVGs to patients at outset and at 6-month follow-up.

In all but two cases, the emergency CEPOD theatre was available within 4 hours. In these two cases a theatre slot would have been available within 24 hours and there would have been no need for additional temporary access.

21.2% of ecAVG would have been sited in the forearm, 69.7% in the upper arm and 9.1% in the thigh. ecAVG would have been the final definitive access option in 23.4%.

Table 8.5: Reasons for ecAVG refusal at initial interview and after 6 month follow-up. 13 of 66 patients (19.7%) declined ecAVG at each time point, however, these were not the same 13 patients and opinions were affected by experience with TCVC. Patients who had TCVC for a short period of time with rapid AVF maturation felt that ecAVG may have been unnecessary, while patients who initially would not have wished ecAVG but then experienced complications of TCVC usage, subsequently wished for ecAVG instead.

Initial interview		**6 month interview**	
Reason for declining ecAVG	**Number of patients (n=13)**	**Reason for declining ecAVG**	**Number of patients (n=13)**
Did not want either AVF or AVG • Previous failed attempts • Prior AVF rupture • Cosmesis • Convenience of TCVC	**10** 5 1 2 2	**Did not want either AVF or AVG** • Previous failed attempts • Prior AVF rupture • Cosmesis • Convenience of TCVC	**8** 4 1 2 1
Did not want ecAVG	**1**	**Did not want ecAVG**	**1**
Concerned renal failure not permenant	**2**	**Concerned renal failure not permanent**	**-**
		Wishes to switch to PD	**1**
		Happy with new AVF and would not have wished ecAVG	**2**
		Multiple failed access attempts	**1**

8.3.5. Budget impact analysis

Over a 6-month period, total treatment costs per patient were £5 882 in the TCVC strategy and £4 954 in the ecAVG strategy, delivering potential savings of £927 per patient in the ecAVG arm. Although ecAVGs had higher procedure and re-intervention costs reflecting longer procedure time and device costs (£3 014 vs. £1 836), these were offset by significant reductions in septicaemia treatment costs (£1 322 vs. £2 176) and in-patient waiting time bed costs (£619 vs. £1 870) (Table 8.6).

Table 8.6: Health economic analysis highlighting relative intervention and complication costs of standard practice (TCVCs) and the novel strategy (ecAVG). All costs are quoted in pounds Sterling (£).

	TCVC+AVF (A)	**ecAVG+AVF (B)**	**Difference (A-B)**
Initial Procedure Costs per Patient	857	1 372	-515
Re-intervention Costs per Patient	978	1 641	-663
Bed Day Costs per Patient (Represent referral delay while waiting for TCVC implant)	1 870	619	1 251
Sepsis Treatment Costs per Patient	2 176	1 322	854
Total Cost	5 882	4 954	927

Figures 8.3, 8.4 and 8.5 are graphical models demonstrating how the overall cost savings (or otherwise) of an ecAVG strategy may change if various factors in the model (TCVC bacteraemia rate, delay for TCVC insertion or proportion of patients using ecAVG as their definitive access option) changed. For example, the observed bacteraemia rate for TCVCs was 1.4 per 1,000 catheter days. At this rate, the estimated cost savings of an ecAVG strategy are £927 per patient at 6 months follow-up. Figure 8.3 illustrates that if the TCVC-associated bacteraemia rate were to reduce to 1.0 per 1,000 catheter days, ecAVGs would continue to derive a lesser cost saving of £548 per patient. Similarly Figure 8.4 demonstrates a lesser cost saving of £228 per patient if the delay waiting for TCVC insertion reduced for 7 to 3 days, while Figure 8.5 demonstrates greater cost savings with the ecAVG strategy if the proportion of patients using ecAVG as their definitive access option were to increase.

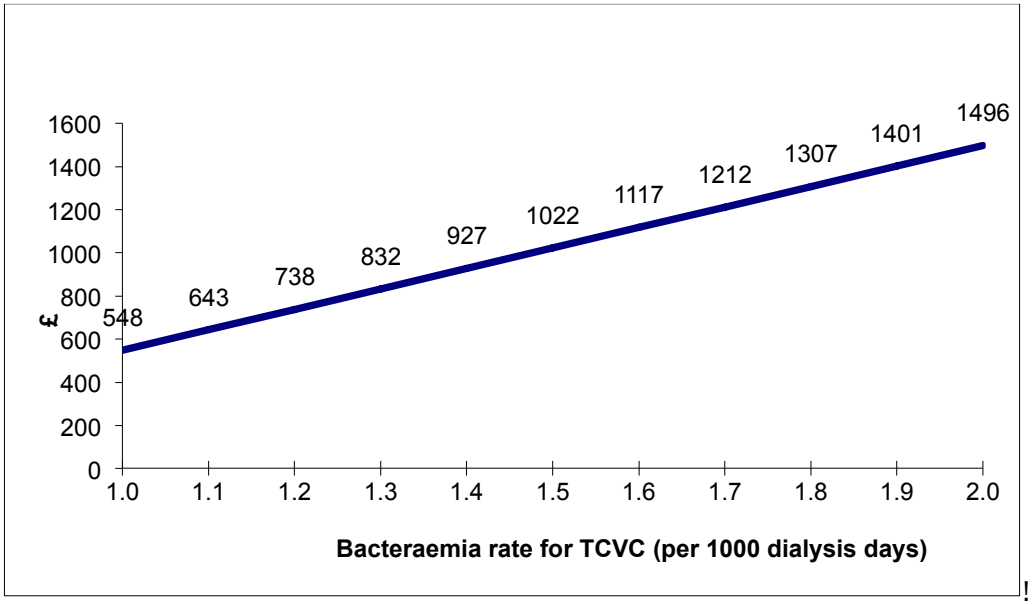


Figure 8.3: Graphical model reflecting varying cost savings if bacteraemia rate amongst TCVC patients were to change. For example, the observed bacteraemia rate for TCVCs was 1.4 per 1,000 catheter days. At this rate, the estimated cost savings of an ecAVG strategy are £927. If the TCVC-associated bacteraemia rate were to reduce to 1.0 per 1,000 catheter days, ecAVGs would continue to derive a lesser cost saving of £548. All costs are in pounds Sterling (£).

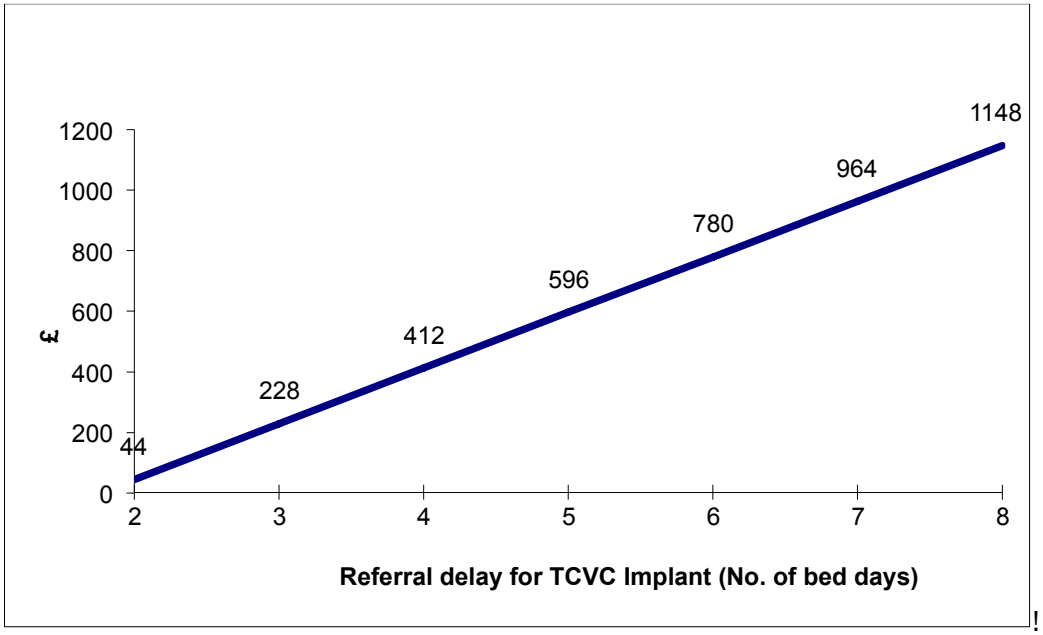


Figure 8.4: Graphical model reflecting varying cost savings if delays associated with TCVC insertion were to change. For example, the observed delay for TCVC insertion was 7 days. At this rate, the estimated cost savings of an ecAVG strategy are £927. If the delay for TCVC insertion were to reduce to 3 days, ecAVGs would continue to derive a lesser cost saving of £228. All costs are in pounds Sterling (£).

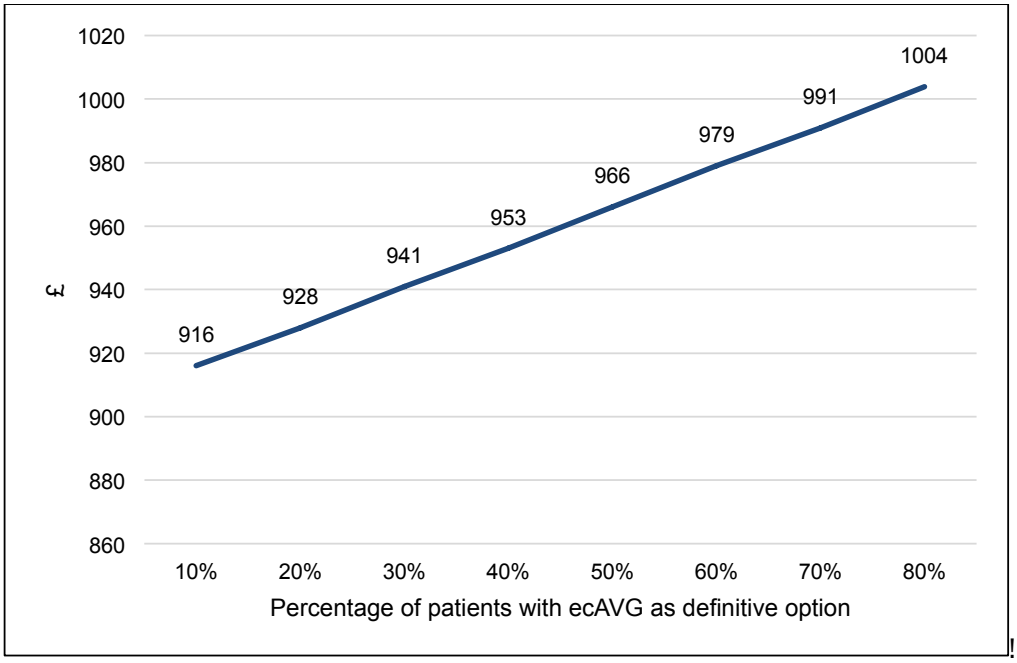


Figure 8.5: Graphical model reflecting varying cost savings if the percentage of patients using ecAVGs are their definitive access option were to change. For example, the observed proportion of patients using ecAVGs as their definitive option was 21%. At this rate, the estimated cost savings of an ecAVG strategy are £927. If this proportion were to increase to 40%, estimated cost savings would be higher at £953. All costs are in pounds Sterling (£).

8.4. DISCUSSION

This study demonstrates that ecAVGs may provide a viable alternative to TCVCs in patients requiring urgent vascular access for haemodialysis. It has been demonstrated that ecAVGs are acceptable to patients and practical to insert within the confines of our busy NHS practice. Moreover, when offset against delays and complications (particularly infective) associated with the current TCVC usage, ecAVG have been shown to deliver cost-savings of nearly £1 000 at 6 months over TCVCs.

A strategy of line avoidance is the holy grail of vascular access. Both short-term risks of infection and long-term risks of central venous stenosis associated with TCVC usage are associated with access loss, morbidity and mortality for patients on haemodialysis (Bray et al. 2012; Thomson et al. 2007; Agarwal et al. 2007). Despite concerted efforts to decrease TCVC usage, it has not been possible to reduce prevalent TCVC usage below 30-35% in most units (Massoud et al. 2006; Lynch et al. 2011a). With "Fistula First" in the United States and governmental tariffs in the England and Wales, there are now financial incentives to minimise TCVC usage (Lynch et al. 2011a; Sharif & Baboolal, 2011; NHS Information Centre, 2014). This study demonstrates that there may be cost savings to be derived simply from the policy of TCVC replacement with ecAVG itself.

Clinically, early cannulation grafts have been used for a number of years, however published literature on their use, and indications for their use, is sparse (Tozzi et al. 2014a; Berard et al. 2015). In most cases they continue to be used in situations analogous to conventional AVGs, where there are no alternative autologous options. Our, recently published, observational data (described in Chapter 7) demonstrates the successful use of ecAVGs as a "bridge" to autologous AVF maturation or transplantation in selected patients (Aitken et al. 2014b). However, this is the first study to propose the use of ecAVG as an alternative to TCVCs for the entire dialysis population. Such a change would necessitate a paradigm shift in current nephrology thinking and resource allocation.

The approach adopted in this study is one of autologous primacy, with both ecAVG and TCVC used, wherever possible, only as a stop-gap until native AVF maturation. We advocate this approach because of the well-recognised lower infection and better long-term patency rates provided by native AVF (Bray et al. 2012; Thomson et al. 2007). It should be noted however that only 16 patients had autologous access at 6-month follow-up. This seems low and, given the 30-35% primary failure rate quoted in most studies of de novo

AVF (Rayner et al. 2004; Dember et al. 2008) could be seen to limit the generalisability of or results. However we believe this observation is representative of "real-world" practice and is probably comparable to other studies trying to achieve vascular access in prevalent patients (Rayner et al. 2004; Aitken et al. 2014c). The recent DAC multicentre study found that more than 60% of AVFs were not suitable for cannulation at 4- 5months (Dember et al. 2008). Furthermore dialysis via a TCVC is recognised as a risk factor for early AVF failure (Rayner et al. 2004) with Weber and colleagues (2009) achieving 81% primary patency in patients who had AVF created prior to commencing dialysis, compared to only 44% patients in patients who had AVF created after commencing on haemodialysis. This highlights that the concept of short-term TCVC for only 6-8 weeks to permit AVF maturation, may be flawed and a slightly more robust, albeit temporary, vascular access may have benefits.

This work utilises the novel concept of a "virtual study" to compare "real-world" prospective data collected on standard practice (the TCVC cohort) to an innovative, but as yet unproven, hypothetical new treatment strategy arm (ecAVG). It allows real-time assessment of the practicality, feasibility and acceptability of the proposed new management strategy and can inform a health economic analysis. The model can be adapted to permit cost-analyses for business cases prior to implementation of a new treatment plan or, in our case, has been used to inform cost calculations for a future randomised controlled trial. The real-time data collection in the standard practice cohort, allows very accurate figures, often lacking from other health economic analyses, and modeling that allows manipulation of variables such as bacteraemia rates and waiting time for TCVC provides generalisability to other centres, which may have differing baseline rates for these factors.

The "virtual study" model uses real-life data to inform cost-analysis in the TCVC arm, however data in the ecAVG arm is extrapolated from the literature. Data collected from this "virtual study" was subsequently used to inform the randomised controlled trial (RCT) comparing TCVC vs. ecAVGs described in Chapter 9. We propose that similar studies could be used to support the conduct of other RCTs (either to demonstrate potential cost savings to sponsors, or to assist in grant applications). This study has informed the power calculation for our subsequent trial, which is unique in the fact that it could be manipulated and modelled to take into account changes in practice that might occur over time or between units. The "virtual study" can also inform potential recruitment to subsequent RCTs by assessing acceptability of the novel intervention and likely refusal

rates or eligibility criteria for future studies. This is particularly relevant in trials of heterogeneous patient groups, such as those on dialysis, where strict inclusion criteria may necessitate large number of patients to be screened to determine eligibility. For example, a recent *New England Journal of Medicine* study evaluating tissue plasminogen activator (tPA) in dialysis catheter malfunction, failed to recruit the intended 380 participants despite screening nearly 2,500 patients (Hemmelgarn et al. 2011). The "virtual study" allowed us to assess likely uptake to a RCT prior to beginning recruitment. Finally, the results from our "virtual study" were used to support the application for conducting a RCT to our NHS trust sponsor, indicating that the study will, at a minimum, be cost-neutral to the hospital. This allowed our research to progress without the need to seek additional funding. In an era where research costs can often be prohibitive and charitable funding is limited, demonstrating potential cost-savings achievable from conducting the research itself has proven very valuable in this case.

In conclusion, the "virtual study" is a novel research methodology that can be used to compare current standard practice to an alternative management strategy and model potential outcomes. We have used it to demonstrate that ecAVGs could provide a practical, acceptable and cost-effective alternative to TCVCs in patients requiring urgent vascular access for haemodialysis.

A RANDOMISED CONTROLLED TRIAL AND COST-EFFECTIVENESS ANALYSIS OF EARLY CANNULATIONS GRAFTS VS. TUNNELLED CENTRAL VENOUS CATHETERS IN PATIENTS REQUIRING URGENT VASCULAR ACCESS FOR HAEMODIALYSIS

9.1. INTRODUCTION

On the back of the "virtual study" described in the previous chapter, a formal randomised controlled trial comparing ecAVGs to TCVCs in patients requiring urgent vascular access for HD was proposed. We hypothesised that ecAVG would result in a lower bacteraemia rate than TCVCs and could potentially deliver cost-savings.

The timing of the randomised controlled trial was salient, in that it followed five years ofdeveloping experience with the Gore® ACUSEAL ecAVG. The technical lessons learned from evaluating our observational data (described in Chapter 7 of this thesis) were employed throughout the study period.

Data from the "virtual study" suggested that a strategy of ecAVG as opposed to TCVCs could deliver cost-savings of nearly £1,000 at 6 months (Aitken et al. 2016). This demonstration of potential clinical cost-savings permitted engagement with our hospital's Research and Development Department. After discussion, the randomised trial was allowed to commence without additional funding due to the potential financial benefits that the research could have for the clinical service.

The randomised trial subsequently described was therefore performed based on the same rationale previously described for the "virtual study" (Chapter 8). It also represents a culmination of the clinical experience gained and is the actualisation of an ethos cultivated through the virtual study.

9.2. METHODOLOGY

9.2.1. Study design and participants

This prospective single-centre randomised controlled trial was performed in the Department of Renal Surgery, Western Infirmary, Glasgow. The trial protocol was published prior to the trial commencing (Aitken et al. 2015c). It was an inclusive study. All

patients aged 18 years or older with established renal failure who required urgent vascular access for HD (i.e. needed to dialyse within 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 pre-operative imaging, anticipated life expectancy < 3months, existing AVF thought likely to be useable within 2 weeks, if they lacked capacity to provide informed consent, or declined participation in the study.

The study protocol was reviewed and approved by the West of Scotland Research Ethics Committee 4 (13/WS/0187). All trial procedures followed were in concordance with the Declaration of Helsinki, 1975 (revised 2000). All participants provided written informed consent. A Trial Steering Committee was convened prior to 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.

9.2.2. Randomisation

Patients were randomly assigned (1:1) by a computer-generated randomisation sequence and sealed envelopes to receive either TCVC ± AVF or ecAVG ± AVF. Due to the nature of the treatment and any subsequent interventions, it was not possible to mask the allocation of treatment to patient, surgeon or study investigator.

9.2.3. Recruitment

Patients were identified at time of referral to the Vascular Access Coordinator for urgent insertion of TCVC. All eligible patients were then approached by a member of the research team, the study discussed and, if agreeable, pre-operative imaging undertaken.

9.2.4. Procedures

9.2.4.1. Pre-operative planning

All patients underwent Duplex ultrasound of both arms (and legs where no suitable upper limb option was determined). Both the venous and arterial tree was assessed and a pre-operative plan made to site both ecAVG and native AVF (if possible). A minimum arterial cross-sectional diameter of 2mm was deemed necessary to sustain either AVF or ecAVG. Venous diameters of 2mm at the wrist and 3mm at the elbow were considered suitable for AVF (or forearm loop graft). A patent basilic/ axillary artery measuring at least 3mm was deemed necessary to site the venous outflow of an ecAVG. Care was taken in the choice of anatomical site for the ecAVG in order to preserve all possible sites for future autologous

access, with the site of native AVF favoured distally in the non-dominant arm. ecAVG was placed to accommodate optimal AVF placement. For example, a native left radiocephalic fistula and right brachioaxillary graft was favoured in a left-handed patient with good native vessels and no previous vascular access; whilst 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.

9.2.4.2. TCVC ± AVF

The TCVC ± AVF strategy reflected standard practice at our institution with TCVC insertion performed either by a radiologist or nurse specialising in TCVC insertion. A single dose of intravenous vancomycin was administered prior to line replacement.

Tunnelled Ash Split® (Medcomp, Harleysville, PA, USA) 14Fr double-lumen polyurethane haemodialysis catheters were inserted with 280mm (left) or 320mm (right) catheters inserted via a Seldinger technique under image guidance. A standard catheter care protocol was employed throughout the study period. This demanded complete sterile precautions during insertion and manipulation with an assistant or non-touch technique to manipulating 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/ discontinuation of dialysis. At the end of dialysis, chlorhexidine cleansing of the skin was performed prior to application of a new sterile dressing and an interdialytic lock with TauroHep500™ (TauroPharm GmbH, Waldbűttelbrunn, Germany) was utilised.

First haemodialysiswas performed by trained nursing staff within the In Patient Renal Unit.Subsequent dialysis sessions were performed at regional outpatient dialysis units in the West of Scotland.

9.2.4.3. ecAVG ± AVF

Patients randomised to receive ecAVG ± AVF underwent anaesthetic assessment and surgery within 24 hours of randomisation wherever possible. Prophylactic vancomycin 1g intravenously (or teicoplanin if the patient was vancomycin allergic) was given preoperatively. All ecAVG implantations were performed by a single operating surgeon under either supraclavicular block or general anaesthetic.

The operative technique is summarised below, but employed all of the modifications described in Chapter 7. Alcoholic betadine was used for cleaning the skin and an Ioban™ skin covering (3M Healthcare, Bracknell, UK) applied to maintain strict asepsis. The vessels were exposed and controlled in a standard fashion. The Gore®ACUSEAL graft (W.L. Gore Associates, Flagstaff, AZ, USA) was then tunnelled in the subcutaneous fat using standard Kelly-Wick tunnellers. A 4-cm longitudinal venotomy was performed and the graft spatulated at the venous end in an attempt to minimise venous stenosis. A 4-6mm arteriotomy was made to accommodate the graft. Arterial and venous anastomoses were performed using continuous 5.0 Prolene. Colatamp™ (Tribute Pharmaceuticals, Milton, Ontario, Canada) was inserted prior to wound closure to minimise 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 post-surgery. Sharp needles (17G), low flows (200 to 250mL/min) and minimal heparin were used for first cannulation. Full aseptic technique was employed for cannulation and direct pressure 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 one-week of intravenous vancomycin post-operatively. Heparin, warfarin and anti-platelet agents were administered at the discretion of the operating surgeon. All patients who re-presented with thrombotic complications were anti-coagulated with warfarin unless contraindicated. All ecAVGs underwent surveillance ultrasound and angiography at 3 months and at 3 monthly intervals thereafter. Any stenosis (on either imaging modality) in the context of access dysfunction was considered clinically significant, prompting angioplasty±stenting (for recurrent lesions). In the event of thrombosis aggressive attempts at declotting were made by a combined surgical and radiological approach.

9.2.4.4. Autologous AVF

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

ecAVG if possible, otherwise every effort was made to provide the patient with opportunity of AVF creation on the next available theatre list (within 1-2 weeks). The ecAVG/TCVC was utilised for haemodialysis until the AVF was mature enough to cannulate. The decision to perform first cannulation of the AVF was taken by the clinical team (normally ~6 weeks after creation) following 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. In the majority of cases it was left *in situ* but on occasion was removed or ligated if required/wished. TCVCs were removed by the surgical team after six successful AVF cannulations as is standard practice.

9.2.5. Follow-up

Patients were reviewed on day 1, day 7 and at 3 and 6 months. Additionally 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 and/or urokinase infusions, access complications (bacteraemia, local infection, thrombosis, stenosis, poor flows) and re-interventions (new access creation/ insertion, thrombectomy, angioplasty). Quality of life data were collected at time of entry to the study and 6-month follow-up.

9.2.6. Outcome measures

The primary outcome measure was culture-proven bacteraemia at 6 months, defined according to the Centre for Disease Control (CDC) as laboratory confirmed positive peripheral blood cultures in association with clinical symptoms of access infection or failure to identify infection at a secondary site (Centre for Disease Control, 2015).

Secondary outcomes were local infection, thrombosis, stenosis, re-interventions (including thrombectomy, antibiotics and urokinase locks), additional vascular accesses, quality of life, whether or not the access provided a "personal vascular access solution"(Aitken et al. 2014a), length of inpatient hospital stay, and death at 6 months. Local infection was also defined according to CDC definitions as proven (laboratory confirmed positive cultures from local swabs) or suspected (clinical signs and symptoms but no positive culture) (Centre for Disease Control, 2015). Thrombosis was defined clinically as the absence of thrill or bruit from a graft and inability to dialyse via it, or the inability to dialyse via, flush,

or aspirate from a TCVC. Health-related quality of life (HR-QoL) was evaluated using the EuroQoL-5D (EQ-5D) questionnaire (Szende et al. 2007).

9.2.7. Sample size calculation

A reduced incidence of systemic bacteraemia in the ecAVG ± AVF group was postulated. Using previously published bacteraemia rates for TCVCs and ecAVG in our own institution (Thomson et al. 2010; Aitken et al. 2014b), it was calculated that 53 patients would be needed in each group to provide 80% power to detect a reduction in the incidence of systemic bacteraemia from 24% to 5% at six months follow-up with α level 0·05. In order to account for attrition/ loss to follow-up of 10%, we aimed to recruit 118 patients (n=59 per arm).

9.2.8. Statistical analysis

All analysis was performed on an intention-to treat basis. Any patient randomised but who withdrew from the study prior to the procedure was replaced by another patient but continued to be followed-up 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 bacteraemia rates are presented both as a proportion of the total population (and risk ratio) and as a rate per 1,000 access days. Having confirmed normal distribution, treatment groups were compared using *t*-tests for continuous variables and χ^2 tests for categorical variables.

Additionally, a cost-effectiveness analysis was performed 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 2013-2014 NHS Reference Costs, Scottish Health Service Costs 2014-2015 and Personal Social Services Research Unit: Unit Costs of Health and Social Care 2015 (Department of Health, 2015; Curtis, 2015). All costs e.g. 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 summarise the average cumulative total costs per patient from trial initiation to 6-months of patient follow-up.

This trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN 80588541).

9.3. RESULTS

Between December 5, 2013 and February 5, 2015, 121 patients were randomly assigned to ecAVG ±AVF group (n=60) or TCVC ±AVF group (n=61). 13 patients (10·7%) died during the follow-up period. No other patient was lost to follow-up (Figure 9.1).

Table 9.1 shows baseline characteristics of randomised patients. 31·4% of patients (n=38) commenced dialysis for the first time (of whom 39·4% (n=15) were "crashlanders" i.e. known to a nephrologist of <90 days prior to starting dialysis). The remainder of patients had previously been on renal replacement therapy via another modality or vascular access which had failed (Table 9.2). AVF was the ultimate intended vascular access in 62·0% of patients (n=75), with the intention of long-term AVG in 33·1% (n=40). A total of 52 AVF in 34 patients were also made during the follow-up period.

There was a significantly higher culture-proven bacteraemia rate in the TCVC ±AVF cohort (0·97 per 1 000 catheter days) compared to the ecAVG ±AVF cohort (0·19 per 1,000 access days) with 16.4% of patients (n=10) developing culture-proven bacteraemia during the first 6 months in the TCVC ±AVF arm compared to 3·3% (n=2) in the ecAVG ±AVF arm (risk ratio 0·2 95% CI 0·12, 0·56; P=0·02). Mortality was also higher in the TCVC ±AVF cohort with (16·4% [n=10] vs. 5% [n=3](risk ratio 0·3 95% CI 0·08, 0·45; P=0·04)). No patient died as a result of access-related complications (including access-related sepsis). One patient died from a perioperative myocardial infarction (MI) in the ecAVG ±AVF arm.

Median waiting time for TCVC insertion was 6 days (range: 1-21 days). Median waiting time for ecAVG insertion was 14 hours (range: 1- 168 hours) (P<0·001). Twice as many patients in the TCVC ±AVF cohort required a bridging temporary line than in the ecAVG ±AVF cohort (49·2% [n=30] vs. 25·0% [n=15]; P=0·006). Median length of hospital 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<0·0001). Four patients in the ecAVG arm had perioperative complications: MI (n=2); venous hypertension and limb swelling (n=1); pseudoaneurysm (n=1). Four patients had failed attempts at TCVC insertion and one had initial attempts at insertion abandoned due to flash pulmonary

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

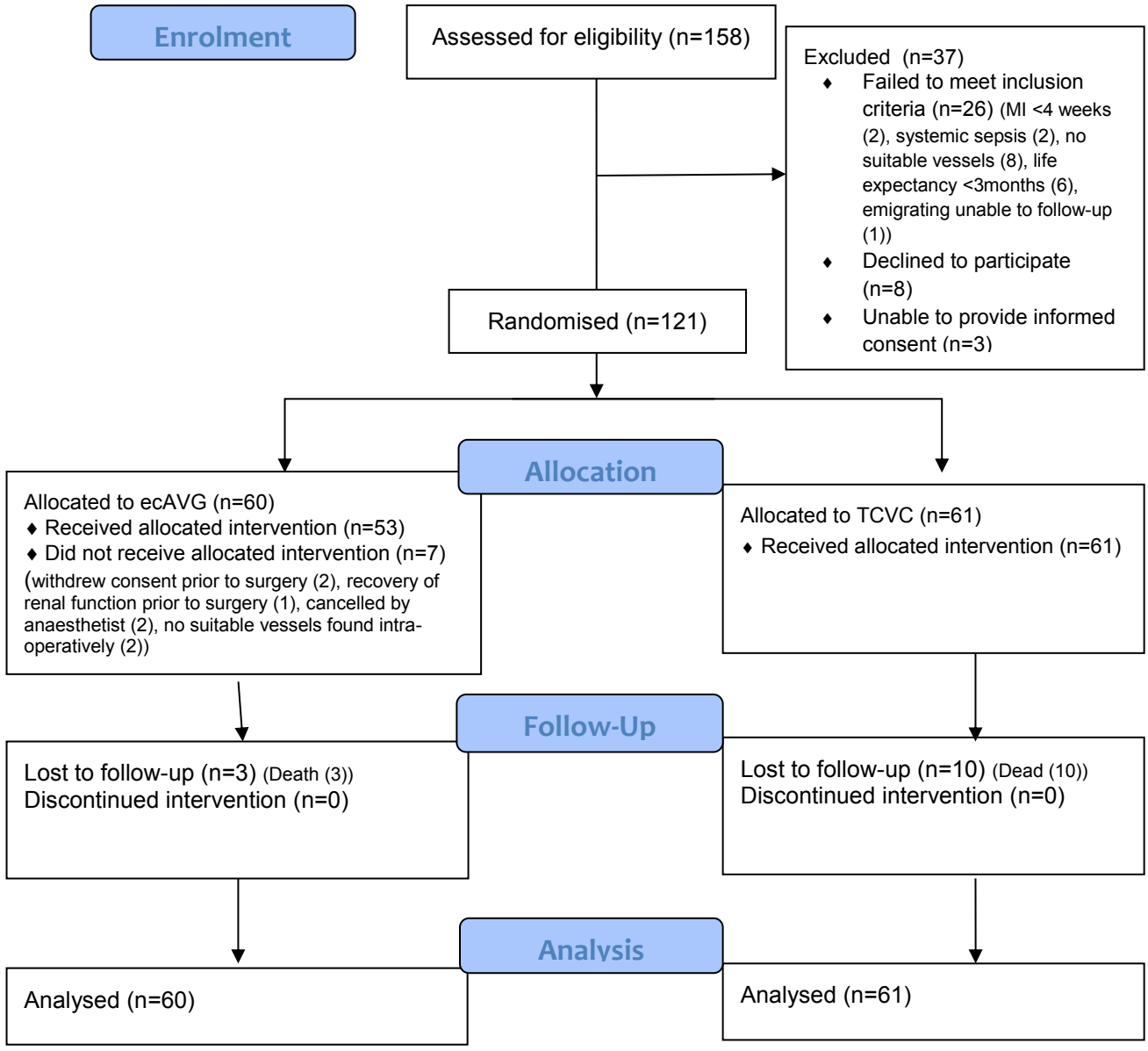


Figure 9.1 Trial flow and CONSORT diagram of assignment to ecAVG or TCVC

Table 9.1: Baseline characteristics of patients randomised to ecAVG or TCVC. Data are presented as n (%) or mean ± SD unless otherwise stated.

	Overall patient population (n=121)	**AVG (n=60)**	**TCVC (n=61)**
Age (years)	57·8+/-15·6	54·5+/-15·3	60·9+/-15·5
Sex (% male)	66 (54·5%)	32 (53·3%)	34 (57·4%)
Primary renal disease			
Diabetes	30 (24.·%)	19 (31·1%)	11 (18·3%)
Multisystem	17 (14·0%)	4 (6·6%)	13 (21·7%)
Interstitial	28 (23·1%)	15 (24·6%)	13 (21·7%)
Glomerulonephritis	26 (21·5%)	12 (19·7%)	14 (23·3%)
Unknown	20 (16.1%)	20 (18·0%)	9 (15·0%)
Co-morbidities			
Diabetes	39 (32·2%)	22 (36·7%)	17 (27·9%)
IHD	25 (20·7%)	13 (21·7%)	12 (19·7%)
CVA	20 (16·5%)	10 (16·7%)	10 (16·4%)
Hypertension	43 (35·5%)	20 (33·3%)	23 (37·7%)
Obesity	19 (15·7%)	10 (16·7%)	9 (14·8%)
Access modality at time of randomization			
Failing transplant	5 (4·1%)	3 (5·0%)	2 (3·4%)
HD	67 (55·3%)	38 (63·3%)	29 (48·3%)
PD	7 (5·8%)	3 (5·0%)	4 (6·7%)
Pre-dialysis	42 (34·7%)	16 (26·7%)	26 (43·3%)
Time on dialysis (median, IQR)	3·4 (2·5, 5·2)	3·4 (3·2, 6·8)	3·2 (1·8, 6·2)
Previous vascular access (median, range)			
AVF	2 (range:0-6)	2 (range: 0-6)	1 (range: 0-6)
TCVC	1 (range: 0-43)	2 (range: 0-43)	0 (range: 0-25)
Access modality at time of randomization			
AVF	29 (24·0%)	18 (30·0%)	11 (18·0%)
AVG	8 (6·6%)	7 (11·7%)	1 (1·6%)
PD	6 (5·0%)	3 (5·0%)	3 (4·9%)
Pre-D/ failing transplant	47 (38·8%)	19 (31·1%)	28 (45·9%)
TCVC	30 (24·8%)	13 (21·7%)	17 (27·7%)

Table 9.2: Indications for requiring "urgent" vascular access. Data are presented as n (%).

Indication for needing access	Number (%)
Acute-on-chronic renal failure Late presentation Problems with AVF maturation Rapid progression to end-stage	 14 (11·6%) 5 (4·1%) 4 (3·3%)
Failed transplant	6 (5·0%)
Problematic AVF/ AVG Aneurysm/ rupture Thrombosis Infection	 17 (14·0%) 28 (23·1%) 1 (0·8%)
Problematic TCVC Thrombosis Infection	 13 (10·7%) 12 (9·9%)
Failed PD	6 (5·0%)
Crashlander	15 (12·4%)

Access complications and their implications are outlined in Table 9.3. 34 episodes of graft thrombosis were observed in 16 patients (26·7%). Patients in the TCVC ±AVF arm spent an average of 4·7 days/ patient in hospital for access-related complications compared to 2·7 days/ patient in the ecAVG ±AVF arm (P<0·001). The total number of hospital days were reduced in the ecAVG ±AVF cohort in the 6 months following graft insertion compared to the 6 months prior to ecAVG insertion (4 days (IQR 3,7) vs. 8 days (IQR 4,12); P=0·02). A similar trend was not seen in the TCVC ±AVF cohort (10 days (IQR 8,14) vs. 8 days (IQR4,10)). Initial HR-QoL scores were comparable at entry to the study (total EQ-5D: 67 ± 12 vs. 67 ± 14; P=0·89). However at 6-month follow-up, patients in the ecAVG ±AVF cohort had better HR-QoL scores (74 ± 18 vs. 63 ± 16; P=0·001).

At six-month follow-up only 23·3% (n=14) of patients in the ecAVG ±AVF arm and 16·4% (n=10) of patients in the TCVC ±AVF arm were dialysing via autologous AVF. 34 patients were still awaiting further attempts at achieving autologous access at the end of 6-month follow-up. In the ecAVG ±AVF cohort 50% (n=30) were still using their ecAVG. In the TCVC ±AVF arm 52·5% (n=32) of patients were still dialysing via a TCVC. The ecAVG was deemed to be a "personal vascular access solution" (i.e. it was still being used for access, had served as a "bridge" to AVF maturation or transplantation or was the vascular access at time of death) in 73·3% of patients (n=44). 68·9% (n=42) in the TCVC ±AVF arm could consider the initial TCVC to be their "personal solution".

Table 9.3: Other vascular access complications and the implications of these including interventions and need for alternate vascular access. Data are presented as number of episodes per patient in 6 months (n). * All of these complications resulted in access loss unless otherwise stated. ** Of the 36 episodes of stenosis requiring intervention 26 were venous, 7 arterial, 1 cephalic arch and 2 central veins. @ One patient required urgent graft ligation for steal syndrome. The other cases were clinically relative mild and did not require urgent intervention. Three further grafts were ligated but this was after alternative access in the form of AVF had been established.

Complication	Episodes per patient in 6 months (n)
TCVC ARM	
Infection	
Systemic proven	0·16 (n=10)
Systemic suspected	0·07 (n=4)
Access removed	0·26 (n=15)
Additional hospital days	2·49 (n=152)
Days with antibiotic treatment	3·16 (n=193)
Thrombosis/ inadequate flow*	0·15 (n=9)
Urokinase	0.27 (n=17)
Line displaced*	0·07 (n=4)
Additional vascular access	
AVF	0·38 (n=23)
Tenckhoff catheter	0·03 (n=2)
AVG	0·08 (n=5)
Temporary line	0·16 (n=10)
TCVC	0·32 (n=32)
AVG ARM	
Infection	
Systemic proven	0·03 (n=2)
Local proven	0·1 (n=6)
Local suspected	0·03 (n=2)
Access removed	0·05 (n=3)
Additional hospital days	0·7 (n=42)
Days with antibiotic treatment	3·37 (n=160)
Thrombosis/ stenosis**	
Thrombosis	0·57 (n=34)
Stenosis	0·6 (n=36)
Surgical thrombectomy	0·52 (n=31)
Surgical revision	0·12 (n=7)
Angioplasty	0·5 (n=30)
Stent	0·12 (n=7)
Revision with additional graft (inc HeRO)	0·03 (n=2)
Graft erosion*	0·03 (n=2)
Steal syndrome*@	0·08 (n=5) (4 grafts were ligated)
Wound dehiscence	0·02 (n=1)
Pseudoaneurysm (re-exploration)	0·02 (n=1)
Additional vascular access	
AVF	0·48 (n=29)
Tenckhoff catheter	0·02 (n=1)
AVG	0·03 (n=2)
Temporary line	0·12 (n=7)
TCVC	0·27 (n=16)

In the ecAVG ±AVF arm, 32 patients (52.1%) had AVF planned as their definitive vascular access at the start of the study. 8 of these AVF (25%) thrombosed immediately, 6 were deemed unsuitable to ever provide dialysis and 4 required an additional procedure to try to achieve functional patency. Of the 14 patients with failed AVF, 9 had a second attempt at AVF creation during the study follow-up. Only 14 patients (23.3%) were using their AVF at 6 months. With regards to relative placement of ecAVG and AVF in patients having both created (n=32), 15 were deemed to have a radiocephalic fistula option, 14 a brachiocephalic option and 3 only had a mid forearm or lower limb autologous option at the time of graft placement. 21 patients had placement of a contralateral brachioaxillary graft, 8 had an interposition graft (into an otherwise defunct fistula), two had forearm loops and one a leg graft. In both the patients with forearm loops, the ecAVG was utilised 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 to TCVC ±AVF arm (£11 393 vs £9 692, P=0.24). 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 (£2 011 vs. £453, P=0.02). Re-interventions made up the largest proportion of costs in the ecAVG ±AVF arm (average £1 042 re-intervention costs per patient) (Table 9.4).

A comparison between the findings of the "virtual study" (Chapter 7) and the randomised controlled trial has demonstrated that the overall cost savings of AVGs were greater in the RCT than in the "virtual study" (-£1,702 vs. -£927). The estimated costs of TCVC, TCVC infection and bed days as a result of TCVC complications were lower in the "virtual study" than in reality in the RCT. Similarly, bed day utilisation and procedural costs (especially re-intervention costs) were higher in the AVG in the RCT compared to the estimated costs of the "virtual study" (Table 9.5).

Table 9.4: Average costs per patient at six-months follow-up by treatment group. All costs are calculated in 2014-2015 pounds Sterling. *The other costs category refers to peritoneal dialysis catheter insertions and transplants.

	AVG	TCVC	Difference (AVG-TCVC)	P value
N	60	61		
AVG procedure costs	£2 432	£212	£2 220	<0.001
AVF procedure costs	£426	£465	-£40	0.7
TCVC costs	£390	£1 824	-£1 434	<0.001
Temporary line costs	£62	£121	-£60	0.003
Index TCVC bed days	£244	£4 222	-£3 978	<0.001
Infection costs	£453	£2 011	-£1 558	0.02
AVG or AVF intervention costs	£1 042	£85	£957	<0.001
Bed day costs	£3 781	£1 965	£1 816	0.004
Other costs*	£862	£487	£375	0.52
Average total costs per patient at 180 days	**£9 692**	**£11 393**	**-£1 702**	**0.24**

Table 9.5: A comparison between findings of the "virtual study" and the RCT

	Virtual study Difference (AVG-TCVC)	Randomised controlled trial Difference (AVG-TCVC)	RCT-virtual study
AVG procedure costs	£764	£2 200	**£1 463**
AVF procedure costs	£25	-£40	**-£65**
TCVC costs	-£265	-£1 434	**-£1 169**
Temporary line costs	-£9	-£60	**-£51**
Index TCVC bed days	-£972	-£3 978	**-£3 006**
Infection costs	-£854	-£1 558	**-£704**
AVG or AVF intervention costs	£663	£957	**£294**
Bed days	-£279	£1 816	**£2,095**
Other additional costs	£0	£375	**£375**
Average total costs per patient at 180 days	**-£927**	**£-1 702**	**-£775**

9.4. DISCUSSION

The study has demonstrated that the incidence of culture-proven bacteraemia in patients requiring "urgent" vascular access for HD was higher in those dialysing via a TCVC than those using an ecAVG. There was also a higher mortality rate observed in the TCVC±AVF cohort. ecAVGs were found to be cost-neutral with the initial outlays and costs of re-intervention offset against lower costs conferred from the treatment of sepsis and treatment delays.

This is the first randomised controlled trial comparing TCVCs to AVGs, however there is a significant quantity of observational data supporting the findings of this study. The higher mortality rate in patients dialysing via TCVCs is well described (Bray et al. 2012; Malas et al. 2015; Thomson et al. 2007). The survival difference between the access modalities emerges early in the life of the vascular access and is only in part attributable to infectious deaths (Bray et al. 2012; Thomson et al. 2010). Recent retrospective data collected from over half a million patients via the US Renal Data System indicates that cardiovascular and all-cause mortality are higher in patients dialysing via TCVC (Malas et al. 2015). In our study, whilst no patient died as a result of access-related bacteraemia, a clear difference in mortality rates was observed as early as six-month after insertion of the vascular access.

Similarly, many large observational cohort studies concur with our finding of a higher culture-proven bacteraemia rate in TCVCs than AVGs. Three-fold higher rates of bacteraemia are commonly reported for TCVC than AVG (Taylor et al. 2002; Thomson et al. 2007). Data from these population-based studies is inherently vulnerable to selection bias with frailer, sicker patients more likely to dialyse via a line (Thomson et al. 2010). Additionally it can be difficult to compare infection rates between populations, and there are few observational studies comparing bacteremia rates between access modalities within the same population (Thomson et al. 2010). The magnitude of difference observed in the cohort studies is however similar to that observed in our series, adding validity to our results. It should be acknowledged that most of the reported bacteraemia rates for AVGs relate to traditional poly-tetrafluoroethylene (PTFE) grafts and not ecAVGs. Previously published small case-series of ecAVGs report slightly lower culture-proven bacteraemia rates of 0·2-0·3 per 1,000 access days (Aitken et al. 2014b; Glickman et al. 2015; Chiang et al. 2014). The rate of culture-proven bacteraemia observed in this study was also lower than previously published in both ecAVG ±AVF and TCVC ±AVF cohorts. We attribute this to good practice, with strict infection control measures employed both 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 of this study both clinically applicable and generalisable to a wide variety of patients. Conversely however, the population is very heterogeneous. It may be that there are specific subgroups of patients more or less likely to benefit from ecAVG/ TCVC. The study was underpowered for any subgroup analysis. One such subgroup of interest is the "crashlanders". It had been anticipated that this would be a study principally of "crashlanders", however in actuality less than one-third of patients were new-starts onto dialysis. De novo dialysis patients pose unique challenges. The National Kidney Foundation Vascular Access Report (2012) found that 60% of "crashlanders" still had their TCVC six months after commencing dialysis and AVF maturation rates are poorer in patients already on HD via a TCVC (Weber et al. 2009; Brunori et al. 2005), supporting the adage "start with a line, stay on a line". It is essential to optimise the initial vascular access as legacy of bad access decision-making may have lifelong implications for patients. For these reasons we hypothesise 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 randomised trials. Dember and colleagues (2008) found that 60% of AVF remained unsuitable for use five months after creation and reflects the difficulties creating autologous access in a contemporaneous dialysis patient cohort. These patients run the risk of surgical fatigue with second and subsequent AVF having lower success rates, longterm line use leading to central vein stenosis, and ultimate patient refusal of further perceived futile attempts at vascular access (Aitken et al. 2014a; Nica et al. 2013). Although the high thrombosis rate of AVG is well recognised (Akoh, 2009; Schild et al. 2007), there is good observational data to suggest that the cumulative patency rates of AVGs are at least comparable to AVF up to two years accounting for the high early primary failure of AVF (Lok, 2007; Allon & Lok, 2010). Whilst, 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.

Prior to embarking on the study, the authors had concerns that 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 (initially

inspired by trying to minimise autologous options lost as a result of central vein stenosis from inappropriate TCVC use). In reality however, we did not find this to be the case. Of the 32 patients having both ecAVG and AVF made, one had lower limb ecAVG and 8 had interposition grafts into already defunct AVF, so no potential autologous option was compromised. In two cases, a forearm loop ecAVG was actually used to mature the outflow vein for subsequent successful AVF creation. We therefore, despite our initial concerns, have been relatively reassured that, in this study, ecAVG placement has not compromised any future options for autologous access placement.

More than a study of ecAVGs versus TCVCs *per se*, this study is considered a comparsison of strategies and approaches to vascular access provision. A change in practice has been evaluated, with a move away from TCVC as default to an ethos that considers alternative options to permit line avoidance. Such a change in practice requires a concerted, team-based approach to minimise inertia in the system, as evidenced by the fact that, with effort, ecAVG could be inserted within 14 hours of referral compared to a 6 days wait-time for 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 patient had an access placed (either TCVC or ecAVG) without considering what their "exit strategy" from that access was (i.e. 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, who traditionally placed TCVCs in all of these patients, towards 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 in order to achieve a line-minimisation culture. Significant education of nephrology and nursing colleagues is also required to ensure correct cannulation technique and minimise graft complications. Furthermore, it must also be acknowledged (as we have observed moving forward adopting the findings of this study into clinical practice), that adoption of such a monumental strategy in vascular access provision on a large scale requires significant redistribution of resources (both manpower and monetary) to reflect the additional pressures placed on the surgical service.

Locally, the timing of the randomised controlled trial was critical. The protocol and implementation built on five years of exponential experience with ecAVGs and the lessons learned from this e.g. a long venous anastomosis to reduce outflow stenosis and the

importance of education and graft care to minimise infective complications and pseudoaneurysm formation (as described in Chapter 7). Furthermore, the "virtual study" (Chapter 8) provided a financial incentive to consider an alternative to the *status quo*. Perhaps most importantly however, the study came at a time when the mind-set of clinicians within the unit was beginning to change. The study was certainly driven by a small number of committed "early adopters"(Rogers, 1962), but was generally received positively by clinicians and dialysis nurses who recognised difficulties with current standard practice and were keen to engage with any research that might lead to an alternative. This attitude certainly aided in recruitment. Additionally, the RCT itself has actually guided and shaped clinical practice moving forward. Rather than the paradigm shift previously described and anticipated, we have observed a mission creep (Anon., 2016), with ecAVG slowly becoming our local standard of care for patients requiring vascular access urgently. There has been significant stakeholder engagement at a clinical level, with nephrologists now referring directly to the surgical service for ecAVG rather than TCVC. Currently however, this *ad hoc* approach remains sporadic and under-resourced. Large-scale implementation of this practice will require significant redistribution of resources and funding. As described, an access practice with a large number of ecAVG requires a commitment and provision to deal with the complications, especially thrombosis, expectantly. This requires investment in surgical services to provide adequate flexible theatre time and manpower without detracting from an elective service, which should still maintain an ethos of fistula primacy. In summary, this study highlights how research that answers an important clinical question, can be rapidly disseminated into a clinical environment. Moreover, the simply conducting the study, appears to have improved clinical outcomes with a reduction in overall *Staph.aureus* bacteraemia rates from 1.75 per 1,000 catheter days in September 2011 to 0.45 per 1,000 catheter days in September 2015 (P. Thomson, personal communication), a observation that, at least in part, can be attributed to an overall shift in the prevalent vascular access modality from TCVC to AVG.

In conclusion, this study demonstrates that a strategy of ecAVG ±AVF for patients requiring urgent vascular access for haemodialysis reduces culture-proven bacteraemia rate and mortality at 6-months compared to 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, within the wider context of provision of cure through renal transplantation. The successful delivery of this philosophy can help patients receive a more optimally tailored, “personalised vascular access solution”.

CONCLUSION

10.1. CONCLUSIONS

Vascular access is the 'key modifiable risk factor' (National Kidney Care Vascular Access Report, 2012, pp.6) for mortality in patients on HD. Despite this, it remains underrepresented in the nephrology literature with fewer than 60 randomised controlled trials published in the worldwide literature prior to initiation of this thesis (Kian & Asif, 2010; Inston & Jones, 2014). A niche audience, heterogeneous patient population and multiple non-standard outcome measures often hinder publication of studies of vascular access in high impact journals (Lok & Oliver, 2003). The relative dearth of existing evidence presented a blank canvas and unique opportunity for the work presented in this thesis however.

Contrary to the previous precedent, research in vascular access actually lends itself very well to randomised controlled trials (Inston & Jones, 2014). A high early AVF failure rate (30-40%) (Dember et al. 2008) means that it is possible to adequately power a study for an end-point of immediate thrombosis with fewer than 100 patients. The overwhelming importance of early maturation on long-term outcomes necessitates only short follow-up period to achieve clinically relevant results. It is possible to instigate RCTs of interventions, devices and operative technique that are not subject to the same especially stringent regulations and legislation as would be a drug study (Medicines and Healthcare Products Regulatory Agency, n.d). Furthermore, as an awareness of the potential role of AVGs refines, industry support is likely to assist in the funding of larger multicentre RCTs, which are expensive to run. It is vital that such studies remains clinician led and industry-supported, to ensure that the most appropriate and clinical relevant questions are asked.

This thesis includes three novel randomised clinical trials of vascular access (operative technique, anaesthetic technique and a new device/product) each of which, unlike many other studies in renal medicine, had a positive result. The study presented in Chapter 6, which demonstrated superior patency at 3 months in AVF created under brachial plexus block compared to local anaesthesia, was recently published in the *The Lancet* and is one of only three vascular access publications ever published in a journal with impact factor >45.

The focus of this thesis has been on optimising vascular access in incident haemodialysis patients. It acknowledges the significant impact that vascular access has on early dialysis mortality and the legacy of poor early vascular access decision-making. The importance "getting it right from the start" cannot be overemphasised (Lok, 2007). Mortality rates on haemodialysis are highest within the first year, with catheter-related infection the principal cause of death among these patients (UK Renal Registry, 2014.; USRDS, 2006.; Pietro Ravani et al. 2013). Patients who start dialysis via a line are more likely to remain with a line (Weber et al. 2009; UK Renal Registry, 2014.; National Kidney Care, 2012.). Data from the UK Renal Registry indicate that 59.8% of patients starting on a TCVC continue to dialyse via a TCVC at 3 months (UK Renal Registry, 2014) and the presence of a CVC at the time of dialysis commencing is associated with poorer AVF maturation (Brunori et al. 2005). Central venous stenosis can occur with just a few days of line exposure and has significant impact on longevity of future vascular access (Agarwal et al. 2007; Moist et al. 2012; Jackson et al. 2014). Within this thesis five distinct areas of practice relevant to incident vascular access creation have been explored:

1. Central vein stenosis and avoidance of future problems.
2. Predicting maturation of autologous access.
3. Promotion of maturation of autologous access.
4. Individualising vascular access provision.
5. The problem of "crashlanders" .

Chapters 5 and 6 describe randomised controlled trials of modifications in operative and anaesthetic technique aimed at optimising maturation of autologous AVF. Interventions to improve AVF maturation should minimise the number of unnecessary vascular access procedures and improve autologous vascular access usage amongst incident patients. Previous observational studies have demonstrated that modifications to suturing technique may affect anastomotic haemodynamics and affect early AVF thrombosis rates (Hong et al. 2013; Moini et al. 2009; Zeebregts et al. 2004), however the study presented in this thesis is the first RCT of a suturing technique to demonstrate differential outcomes in AVF patency. It has shown improved early (6-week) patency rates in radiocephalic fistulae created using an interrupted suturing technique compared to a continuous suturing technique. Similarly, prior observational studies have demonstrated improved blood flow at 8 weeks in AVF created under brachial plexus block (BPB) compared to local anaesthesia (LA) (Sahin et al. 2011), however the results presented in Chapter 6 are the first to demonstrate improvements in the clinically relevant end point of primary patency

at 3 months in a randomised controlled trial comparing BPB to LA.

The importance of tailoring vascular access to the individual is repeatedly highlighted throughout this thesis. The concept of the arteriovenous fistula as a 'gold standard" vascular access (Fluck & Kumwenda, 2011) is challenged. Whilst, arteriovenous fistulae have traditionally been the access of choice, changing patient demographics and the evolution of graft technologies means that 'the subject is in a perpetual state of evolution (therefore) gold standards are, by definition, almost never reached' (Duggan, 1992 pp. 1569) and may necessitate refining the definition of 'gold standard' towards a more patient-centred strategy.

Chapter 2 describes the local experience in the West of Scotland with TCVC use and the changes that occurred following aggressive intervention to reduce line usage. These observational data demonstrated that, whilst in prevalent patients it was possible (with aggressive surgical intervention) to convert 20% of patients who were dialysing via a TCVC to an AVF, the majority (over two-thirds) were subjected to multiple failed interventions and associated morbidity with no resultant autologous AVF. This highlighted two important issues: firstly the difficulty in obtaining autologous access in prevalent patients after several failed attempts and the importance of getting it right from the start with incident patients; and secondly, that blindly enforcing a policy of "Fistula First" is not necessarily in the best interests of the individual patient (Drew & Lok, 2014). A fistula primacy at all costs approach will inevitably lead to inadvertent surgical fatigue and prolonged catheter dependence (Lok, 2007) and patient-centred care must therefore be considered "best practice" for vascular access provision (Drew & Lok 2014). The emphasis of the research in this thesis is directed towards finding pragmatic, patient-focussed solutions to clinically relevant problems. Likewise, Chapter 3 describes the legacy of poor vascular access decision-making in incident patients and highlights the difficulties in achieving sustainable vascular access in patients with bilateral central vein stenosis. A targetted and individualised approach is necessary in these patients with "end-stage" vascular access also. Despite the difficulties, lower limb vascular access and HeRO grafts can prove effective in these complex patients, however an "exit strategy" in terms of cure through renal transplantation (expedited or otherwise) is necessary for long-term survival in most of these patients.

Chapter 4 evaluated uraemia and renal function as a predictor for AVF maturation in pre-dialysis patients. No association was found between eGFR at the time of access creation and either short or long-term patency. However increasing serum urea was associated with

worse clinical patency at 6 weeks and poorer long-term outcomes from RCF, suggesting for that the timing of AVF creation in pre-dialysis patients may actually influence AVF outcome.

Chapters 7, 8 and 9 describe our work with ecAVGs and highlight the role that these novel devices may play in clinical practice, particularly in relation to incident haemodialysis patients and "crashlanders". The evolution of a practice is described from the initial case series, through modification of the technique, development of a concept in the "virtual study", to implementation in a RCT. The early case series with Gore® ACUSEAL highlights the versatility of the graft in a range of clinical settings including "end-stage" complex vascular access patients and as a "bridge" to alternative vascular access. The potential role of an ecAVG as an alternative to TCVC in "crashlanders" and incident patients requiring expectant vascular access was highlighted. Complication rates, particularly venous stenosis, infection and pseudoaneurysm, were high in the early patient cohort and modifications of operative and cannulation technique acquired through experiential learning and education have been described (Chapter 7). The "virtual study" (Chapter 8) represents progression of the concept of the role of ecAVGs by demonstrating, in a feasibility study, that ecAVG can provide an acceptable, practicable and cost-effective alternative to TCVCs. Finally the randomised controlled trial (Chapter 9) confirms a significantly lower rate of access related bacteraemia at 6 months in patients requiring "urgent" vascular access with ecAVG compared to TCVC.

Traditionally TCVC have been considered default in patients without mature autologous access who require to start haemodialysis. From the outset of the work with ecAVG it was anticipated that the implementation of ecAVG into clinical practice for this purpose would necessitate a "paradigm shift"(Rodriguez et al. 2000) in thinking on vascular access. In fact, a gradual "mission creep" (Anon., 2016) of practice change has been observed. In the past five years, as the combined local experience of ecAVG has grown, there has been a gradual shift away from TCVCs in favour of ecAVGs. This is an excellent example of how the research described in this thesis has rapidly shaped clinical practice. Moreover, I was surprised and intrigued to observe the almost symbiotic relationship between the research described in this thesis and practice development, particularly in relation to ecAVG. A few "early adopters" who modified the operative technique through experiential learning initially embraced the concept. Education was vital in those early stages. Further uptake and adoption of ecAVGs into routine clinical practice in our unit was expedited by the existence of the randomised trial. The clinical trial drew interest to an otherwise

underrecognised area of practice and many clinicians became engaged in discussion on the role of ecAVG. Whilst it is evident that the RCT could not have progressed were it not for a rapid expansion in the clinical service, it is also my belief that the service would not have expanded so rapidly were it not for engagement with the clinical trial. This highlights the importance of the integration of clinical research into clinical practice with gains and benefits evident for both parties. Research, quality improvement and practice development are not independent of each other and may actually draw mutually beneficial conclusions.

10.2. MOVING FORWARD: IMPLEMENTATION INTO CLINICAL PRACTICE

Locally, the findings of the RCTs on suturing and anaesthetic techniques have been almost universally adopted into clinical practice as examples of evidence-based medicine informing clinical practice. Resource issues regarding the availability of trained anaesthetists and additional time added to the procedure are currently limiting the universal adoption of BPB for simple AVF creation.

As described above, the implementation of an ecAVG practice has been exponential. The early adaptations to practice involved modification of operative or cannulation t*echnique*, however the latter changes relate to the evolution and modification of an entire *service*. Over the past few years, during which this research was conducted, the number of AVGs used in prevalent patients in the West of Scotland has increased from 0.8% (October 2011) to 5.9% (October 2016). Nearly 10% of incident patients now commence dialysis via an ecAVG (P. Thomson, personal communication). Such a change in practice has, and will, necessitate redistribution of resources, away for the radiology service, that traditionally inserted TCVCs, to the surgical service to support an increase in the number of ecAVG procedures. Furthermore, the unpredictable nature of the need to insert and thrombectomise grafts requires a previously unnecessary flexibility in access to theatre time and manpower. The ecAVG "package" is an excellent example of the importance of "process", rather than simply a procedure, in driving change and improving quality of care (Stevenson et al. 2007). Currently this remains a fluid situation and is likely to continue to evolve as the exact role for ecAVGs in clinical practice emerges.

As alluded to previously, the research presented in this thesis forms part of the work to develop a fledgling Vascular Access Service in Glasgow. The clinical and academic aspects of this service have developed in parallel. In 2011 only 42% of incident patients at our institution commenced HD via an AVF; the *Staph.aureus* bacteraemia rate was 1.8 per

1,000 access days; >10% of patients had bilateral CVS (the legacy of years of poor vascular access decision-making); and there was one Vascular Access Nurse Specialist (whose role it was to co-ordinate TCVC insertion). There was an ethos of absolute autologous primacy. Now, despite the fact that still fewer than half of our incident patients commence dialysis via an AVF, the *Staph.aureus* bacteraemia rate is only 0.8 per 1,000 catheter days; only 3% of patients have bilateral CVS; and there is a dedicated Vascular Access Multidisciplinary Team. The focus is now on individualised care with the aim to provide every patient a "personal vascular access solution". The local service has expanded rapidly and the team has taken a coordinating role in the improvement of vascular access services nationally with the publication of the Scottish Haemodialysis Vascular Access Appraisal (Oliver et al. 2015).

Personally, it has been an exciting time to be involved in vascular access research. Locally, the rapid expansion of a service has provided me with great scope to undertake varied research and also take an active role in service development and quality improvement. Globally, the last couple of years have brought increased recognition of the need for and opportunities that research into vascular access provides. Since 2011, there have been over 2,000 peer-reviewed publications (including 15 RCTs) on vascular access. 20% of the randomised controlled trials in the vascular access world literature in the past 5 years are presented in this thesis.

10.3. FUTURE RESEARCH

Our work on ecAVGs and incident patients has highlighted the lack of standardised definitions for access infection and functional patency in patients not yet established on dialysis. Whilst definitions of catheter-related bacteraemia (Taylor et al. 2002; Thomson et al. 2010) and functional patency in maintenance dialysis patients (Sidawy et al. 2008) are well established, terminology for graft infection and functional patency in pre-dialysis patients is not. In our studies, we have used a combination of the ultrasound-based "rule of 6s" (NKF-KDOQI, 2006) and clinician assessment to define functional patency in pre-dialysis patients. We found 100% concordance between the two measures; however both are arbitrary, historical and have not been validated. Similarly we have observed that, whilst systemic bacteraemia rates associated with AVGs are significantly lower than TCVCs, the pattern of infective complications differs significantly and would caution against using similar terminology to compare the differ access modalities as definitions of systemic bacteraemia are likely to underestimate the burden of infection associated with

AVGs. Instead we propose a range of terms to fully characterise graft infections: a. local *vs.* systemic; b. culture proven *vs.* suspected; c. temporal (early infections are commonly localised associated with post-operative haematoma; late infections are generally associated with inoculation from cannulation and often lead to systemic bacteraemia) (Kingsmore, 2016).

One of the limitations of current research in vascular access is the heterogeneous nature of the patient cohort. Whilst this is reflective of the "real-world" practice encountered by the clinician, the "dirty data" obtained from research in a mixed patient cohort limits reproducibility and can lead to difficulties in publication. (Certainly this author has often received feedback from reviewers that the variation in the patient cohort limits transferability and clinical applicability). Future research is likely to need to target more specific patient groups e.g. "crashlanders" or "end stage access". Clearly defined terminology for these patient cohorts will also be necessary, particularly since recruitment of patients from small, specific patient cohorts is likely to need greater collaboration and multicentre trials (thus far lacking in vascular access).

Future randomised controlled trials need to ask clinically relevant questions of the right patient groups. We have demonstrated the benefit of ecAVGs over TCVCs in provided immediate vascular access for dialysis, however it is likely the AVGs have an additional role in other clinical settings. The demographic of the dialysis population is changing. Elderly, co-morbid patients are now the norm (Scottish Renal Registry, 2015). Previously held-beliefs, for example the 'gold standard' standard arteriovenous fistula and start distally and work proximally when planning autologous access need to be challenged (Fluck & Kumwenda, 2011; NKF-KDOQI, 2006). The previously published RCTs comparing AVGs to AVFs failed to address true clinical problems, instead comparing BBF to forearm loop grafts (Keuter et al. 2008) and forearm loops with primary RCF in patients with suboptimal vessels (Rooijens et al. 2005). At the time, both studies found that the prosthetic graft required more interventions to maintain patency, adding support to the ethos of "Fistula First". Latterly however, the high primary failure rate of autologous access in an aging, co-morbid dialysis population, coupled with a resurgence in interest in the role of AVGs, mean that the scene may once again be set for a multicentre RCT of prosthetic versus autologous access.

In my opinion the following are the most important contemporaneous clinical questions in vascular access that could be answered via RCT:

1. Brachiobasilic fistula versus brachioaxillary graft in patients with no or failed cephalic options?
2. Pre-emptive AVF or “watch-and wait” (±ecAVG) for pre-dialysis patients over 70 years old
3. “Distal first” versus “single best option” for autologous access

It is my intention to continue clinical research in vascular access, taking forward these questions into multicentre randomised controlled trials in the coming year.

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APPENDIX 1: KIRKPATRICK'S MODEL OF TRAINING EVALUATION ADAPTED FOR ecAVG COURSE

The model uses four levels: reaction, learning, behaviour and results to evaluate the success of any training intervention. The description below outlines how the model was adapted specifically to evaluate outcome of the graft courses.

1. **Reaction**: Participants completed questionnaires immediately following the course and six weeks later to evaluate their reactions and response to the course. A combination of closed (outlined below) and open questions (with opportunity for free text responses) were used. Participants were asked to answer each response as strong agree; agree; neutral; disagree or strongly disagree.

The course was well organized
The course was clear and easy to understand
The course improved my knowledge concerning the subject
The course improved my skills concerning the subject
The course developed my ability to think critically about the subject
I will be able to apply the knowledge and skills from my course to my job
The course was a good use of my time
I would recommend the course to others

2. **Learning:** Nurses knowledge of arteriovenous grafts and early cannulation grafts was assessed prior to and following the course by asking five simple questions:

    - Can you describe the anatomy of a brachioaxillary graft?
    - Where is the venous outflow?
    - How should the graft be assessed prior to cannulation?
    - Which needles should be used to cannulate an ecAVG?
    - How long should you press for after the needles come out of an ecAVG?

    Additionally participants were asked to comment on what they had learned following the course. Common themes in the domains of knowledge, skills and attitudes were identified.

3. **Behaviour:** The transfer of skills back into the workplace was assessed. Surgeons and dialysis nurses were contacted 3 months following participation in the course. Surgeons were asked if they had inserted any ecAVGs in their practice and if so how many. Dialysis nurses were asked if had they cannulated any ecAVGs and did they do so on a regular basis (i.e. more than once a week)?

    Additionally, given that at the second course, a whole team of surgeons, nephrologists and vascular access nurses attended from Belfast an evaluation of

practice in Belfast prior to and following the course was assessed to evaluate dissemination of practice from one institution to another.

4. **Outcomes:** Prior to the course we perceived a relatively high rate of graft complications locally (as has been reported in the early Gore® ACUSEAL cohort (Aitken et al. 2014c)). The number of graft complications (infection, stenosis, thrombosis, pseudoaneurysm/ rupture) in the three years prior to (early cohort) and the six months following the course (later cohort) were compared to evaluate if change in behaviour translating into change in clinical outcomes.

APPENDIX 2: PHOTOGRAPHS FROM THE ecAVG COURSE

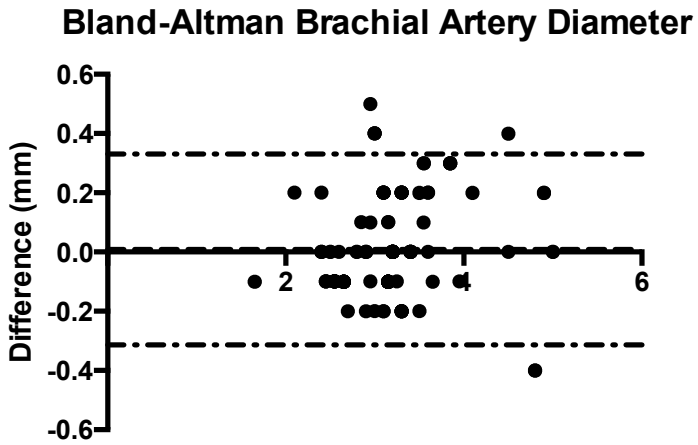
A model was used to demonstrate the anatomy of upper and lower limb grafts and highlight where needles should be sited.

Patients with grafts attended help teach vascular access examination skills

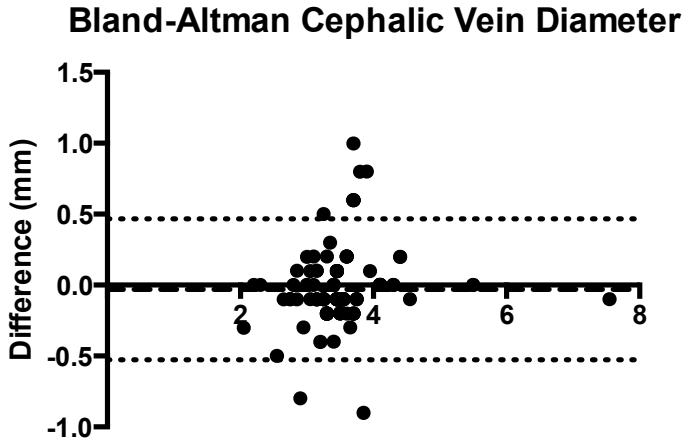
APPENDIX 3: BLAND ALTMAN PLOTS OF BRACHIAL ARTERY BLOOD FLOW AND VESSEL DIAMETER

Bland Altman plots showing intraobserver variability in the measurement of brachial artery diameter, cephalic vein diameter and brachial artery blood flow. Dashed line represents bias and the dotted-dashed line represents 95% limits of agreement. A. Brachial artery diameter (95% limit of agreement: -0.31, 0.33mm). B. Cephalic vein diameter (95% limit of agreement: -0.53, 0.47mm). C. Brachial artery blood flow (95% limit of agreement: -10.9, 7.6mL/min).

A.



B.



C.