UNIVERSITY OF MANCHESTER

Clinical Investigation of the Arteriovenous Access for Haemodialysis

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine (MD) in the Faculty of Medical and Human Sciences

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Abstract

Dr Milind Nikam, Submission for Doctor of Medicine (MD), University of Manchester
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Vascular access (VA) is one of the most important determinants of outcomes in haemodialysis (HD). Poor VA outcomes have a significant adverse impact on patient experience, morbidity and mortality and also result in significant burden on the health economy. An arteriovenous fistula (AVF) is accepted as the best HD vascular access. However AVF prevalence is variable and AVFs are associated with a high early failure rate. A small but significant number of AVFs experience late failure further down the line.

The purpose of this project, broadly, was to understand VA outcomes, focusing specifically on AVFs. This project involved a series of clinical studies that were specifically designed by the student researcher to investigate various time points in the life cycle of AVFs – from creation and maturation - to its use and subsequent failure. The MANVAS, OPEN and Coil embolisation studies focus on the early phase of AVF development and maturation, whilst, the VA in Home HD study investigates the impact of intensive self-use in a non-healthcare setting. It is followed by the prospective thrombosed vascular access study focusing on the late phase of VA failure. The MANVAS study, a prospective cohort study, was set up with an aim to follow up patients undergoing AVF formation with a view to defining the natural history and maturation process of AVFs, and determine factors which affect outcomes – demographic, clinical, and biological. The OPEN study was designed to investigate poor maturation due to anastomotic failure by the intervention of the Optiflow^{TM} device. The results suggest high maturation rates that were significantly better than those reported in the literature. The coil embolisation study demonstrated that the intervention of coil embolisation is a safe and effective treatment option for failing AVFs with accessory draining veins. The Vascular Access in Home Haemodialysis (HHD) study demonstrated that VA outcomes are significantly better in HHD patients and unadjusted patient survival in the HHD cohort was associated with incident VA. The thrombosed access study is a prospective longitudinal study designed to assess the effectiveness of endovascular access salvage and investigation of factors that impact longer-term access survival. One of the major aims of the study was to analyse outcomes related to prompt restoration of flow for patients presenting with acute failure of fistulae and grafts. The study showed that timely endovascular salvage is highly effective in restoring immediate patency but long-term outcomes remain poor. It also confirms poor outcomes of grafts as compared to AVFs and demonstrates that progression to thrombosis in AVFs portends poorer prognosis. The endovascular technique of balloon maceration, compared to outcomes reported in the literature, appears to be equally safe and effective with no increased risk of clinically significant pulmonary embolism.

The clinical studies in this thesis provide a unique insight into the different aspects of the lifecycle of an AVF, and pave the way for an improvement in our fundamental understanding of the natural history and biology of AVFs.

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Abbreviations

ADV: Accessory draining vein

AE: Adverse event

ACEI: Angiotensin converting enzyme inhibitors

ARB: Angiotensin receptor antagonists

ADMA: Asymmetric diethyl-amine

ASN: American Society of Nephrology

AVA: Arteriovenous dialysis access

AVF: Arteriovenous fistula

AVG: Arteriovenous graft

BM: Bone marrow

BMP: Bone morphogenic protein

CAD: Coronary artery disease

CI: Confidence intervals

CKD: Chronic kidney disease

CMFT: Central Manchester Foundation Trust

CRN: Clinical Research Network

CRP: C-reactive protein

CIED: Cardiac implantable electronic device

CVS: Central vein stenosis

DM: Diabetes mellitus

DOPPS: Dialysis outcomes and practice patterns study

DVT: Deep vein thrombosis

ePTFE: Expanded polytetrafluoroethylene

eNOS: Endothelial nitric oxide synthase

EC: Endothelial cell

EPC: Endothelial progenitor cell

ERA: European Renal Association

EDTA: European Dialysis and Transplant Association

ESRD: End stage renal disease

FAST: Failed arteriovenous haemodialysis access salvage therapy

Hb: Haemoglobin

Hct: Haematocrit

H&E: Haematoxylin and eosin

HD: Haemodialysis

HFM: Hemodialysis Fistula Maturation study

HHD: Home haemodialysis

HIF-1: hypoxia inducible factor (HIF-1)

HSC: Haematopoietic stem cells

HO-1: Haem-oxygenase 1

IGF-I: Insulin like growth factor – I

IHD: In-centre haemodialysis

iNOS: Inducible nitric oxide synthase

IRAS: Integrated research application service

JAS: juxta-anastomotic stenosis

KDOQI: Kidney disease outcomes and quality initiative

MANVAS: Manchester Vascular Access Study

MCP-1: Monocyte chemoattractant protein-1

miR: microRNA

MMP: Matrix metallo-proteinase

mRNA: Messenger RNA

MRSA: Methicillin resistant Staphylococcus aureus

NIHR: National Institute of Health Research

NIH: Neo-intimal hyperplasia

NO: Nitric oxide

NRES: National Research Ethics Service

OPEN study: Optiflow™ Patency and Maturation study

PCR: Polymerase chain reaction

PD: Peritoneal dialysis

PEUU: Polyester urethane urea

pmp: per million populations

PTA: percutaneous transluminal angioplasty

PVD: Peripheral vascular disease

R&D: Research and Development

RCT: Randomised Controlled Trial

RRT: Renal replacement therapy

SAE: Serious adverse event

SE: Standard error

SVIR: Society of Vascular and Interventional Radiology

spKt/V: single pool Kt/V

QoL: Quality of life

TIMP: Tissue inhibitor of metallo-proteinases

TGF-β: Transforming growth factor – beta

tPA: recombinant tissue plasminogen activator

UKRR: United Kingdom Renal Registry

US: Ultrasound

USRDS: United States Renal Data System

URR: Urea Reduction Ratio

VEGF: Vascular endothelial growth factor

VA: Vascular Access

VSMC: Vascular smooth muscle cell

WSS: Wall shear stress

To the memory of my beloved father

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Preface

This thesis follows the 'alternative' journal paper format. The journal format has been adopted mainly because it encourages publication in peer-reviewed journals. It is also the most suitable format for my research. My aim was to investigate the different clinical touch points in the life of an arteriovenous fistula (AVF) created for haemodialysis. This required setting out studies to investigate different, clinically relevant, but poorly researched, time points in the life cycle of an AVF in order to understand and thereby improve vascular access outcomes. The distinct study designs and clinical settings suited the alternative format presentation adopted for this thesis.

The inherent multidisciplinary nature of the clinical context of AVF meant that the studies required collaboration with relevant stakeholders. For each completed and proposed study, I have therefore outlined the nature of the collaboration and my own contribution in the study design and methodology chapter for each study.

Chapter 1: Introduction

1.1 Background

Haemodialysis (HD) is a life-saving and life-sustaining treatment for patients with advanced renal failure. It is the most prevalent dialysis treatment modality and is identical to transplantation in terms of patient numbers, the latter modality considered to be the gold standard in renal replacement therapy. Optimal delivery of haemodialysis has been shown to result in improved patient outcomes. However, the delivery of optimal HD is critically dependent on access to the bloodstream via a reliable vascular access. The three main types of vascular access are – dialysis catheters, native arteriovenous fistulae (AVFs) and artificial arteriovenous grafts (AVGs).

An ideal vascular access should provide good blood flow, be relatively free from complications and be durable. An AVF has the potential to meet all these criteria amongst all access types. They are therefore, the preferred haemodialysis vascular access.

However, AVF outcomes are unsatisfactory and plagued by high primary failure rate. This has been reported to be as high as 50% in some series.[1] However, in the longer term AVFs perform much better compared to AVGs and catheters.[1, 2] Kidney Disease Outcomes and Quality Initiative (KDOQI) guidelines recommend that 40% incident and 50% prevalent HD patients should undergo dialysis with an AVF.[3] The UK Renal Association (RA) guidelines recommend a much more ambitious target of 65% for incident and 85% for prevalent patients.[4] However, high primary failure of AVFs is a major hurdle towards achieving this goal.

The natural history and maturation of AVFs is not well understood. Moreover there is lack of consistency in practice of definition and time of use of mature AVFs. There have been new insights into the causes of early fistula failure and some interventions have been tested, but these have not shown sufficient clinical promise, that would recommend their routine clinical use.[5] Successful interventions to overcome the clinical problems are unknown and not studied extensively. An understanding of factors that define successful natural history for AVFs may provide valuable insight that may help achieve better clinical outcomes in vascular access.

1.1.1 End stage renal disease and renal replacement therapy

In 2010, the incidence of ESRD in the UK was 107 pmp (per million populations). Close to 70% of these patients would be receiving HD at 90 days.[6] The number of patients receiving RRT in the UK in 2010 was greater than fifty thousand, of which 44% were on haemodialysis.[7] Moreover, the 2009 UK Renal Registry report suggested around 5 pmp increase in the incident haemodialysis population in the UK.

Corresponding data from the United States Renal Data System (USRDS) have shown rising incident rates of ESRD since the 80's. The current trend however suggests that ESRD incidence has reached a plateau since the early 2000's.[8] The prevalence of ESRD in the USRDS population still seems to be rising, although with a lower annual percentage (figure 1-1).[8]

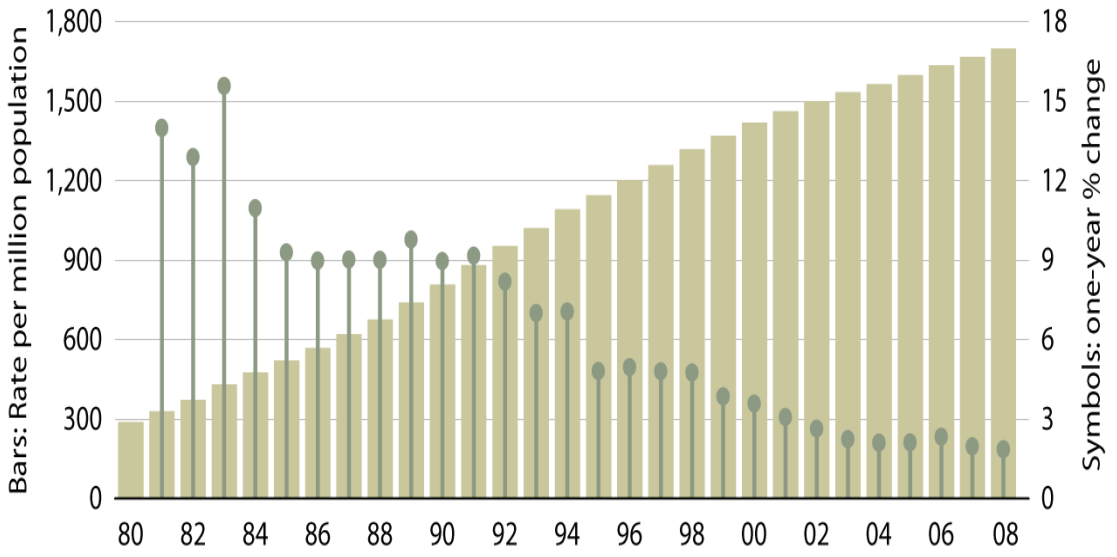

Figure 1-1: USRDS data demonstrating adjusted prevalence rates and annual percentage change in ESRD patients (adjusted for age, gender and race).[8]

Despite the apparent slowing down in the incidence of ESRD and reduction in the percentage growth in prevalent ESRD population, the number of patients on HD is rising on a global scale.[6] In the UK, the prevalence of ESRD has steadily risen from 1982 to 2008 (figure 1-2). It can be seen from figure 1-2 that the rise in HD prevalence is much more striking as compared to other modalities - from 1998 to 2008 the number of patients on HD doubled.

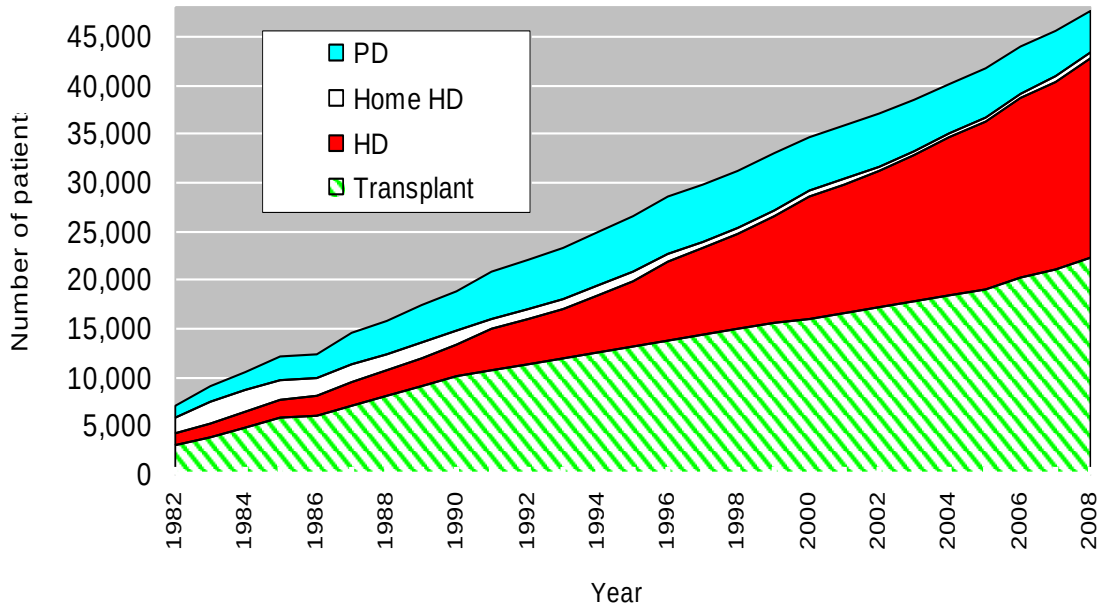

Figure 1-2: Change in RRT prevalence between 1982 -2008. Reproduced from renal registry 2009 report.

Mortality and morbidity in ESRD

ESRD carries a high mortality. The figure below illustrates the relative risk of death of all patients on RRT compared to the general UK population.[9]

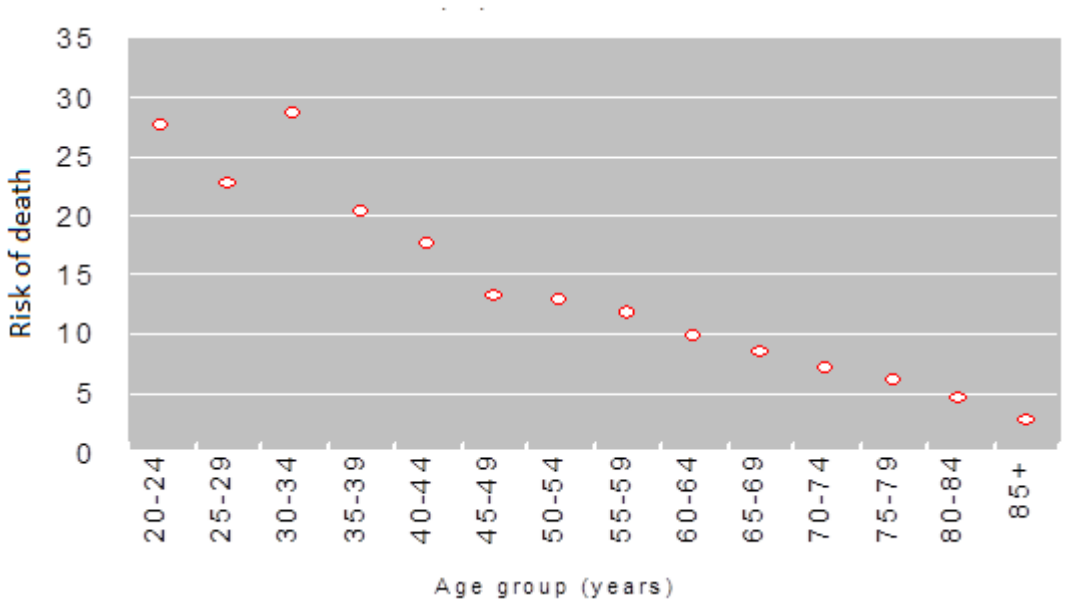

Figure 1-3: Relative risk of death of all prevalent RRT patients in 2008 compared with the UK general population in 2007.[9]

Amongst all RRT modalities, incident patients on HD carry the highest mortality, although direct comparisons within these groups may not be appropriate due to selection bias. In 2007, the one-year after-90-day survival, adjusted to age 60, for incident HD patients was just over 87%.[9] By the end of two years, more than a quarter of prevalent dialysis patients in the UK would have died.[9] The adjusted relative risk of mortality for HD population from the Dialysis Outcomes and Practice Patterns study (DOPPS) for the UK was 1.39 for all patients and 1.84 for those between age groups of 18-64.[10]

Higher mortality in CKD/ESRD patients exists across the globe. The 2010 USRDS report suggests that fortunately mortality amongst ESRD patients is falling since the 80's, but still remains unacceptably high when compared to the general population. The mortality in general, is highest in the first year of starting RRT, with a notable exception of patients starting PD.

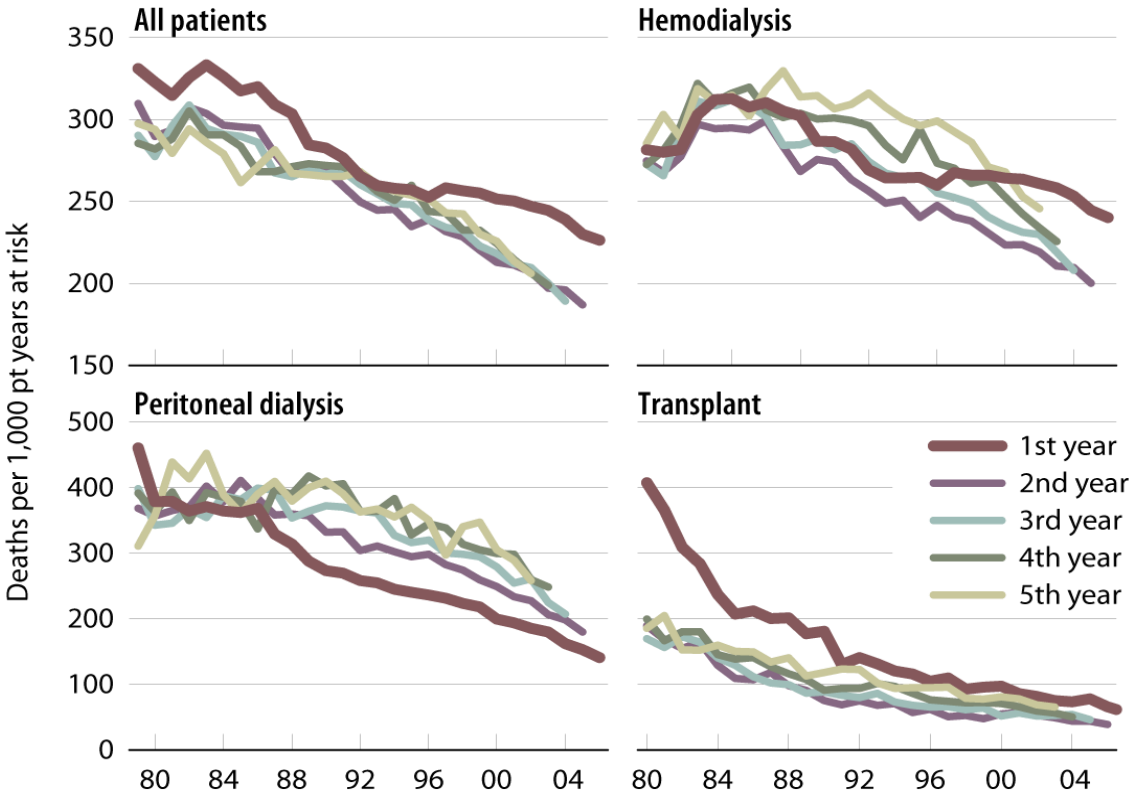

Figure 1-4: USRDS data demonstrating adjusted mortality rates by modality and year of treatment.[8]

Rates of hospitalisation remain very high in dialysis patients. Hospital stay is one of the most expensive components of HD.[11] Furthermore, once admitted dialysis patients seem to have longer hospital stays compared to the general population. Thus, ESRD has a significant impact on patients' lives and not surprisingly, poor quality of life (QoL) scores and depression is highly prevalent in dialysis patients.[12]

Causes of mortality and morbidity in ESRD

Infection is the second most important cause of death in dialysis patients (excluding treatment withdrawal), only preceded by cardiac disease (figure 1-5). Infection is also the leading cause of hospitalisation in ESRD patients; this observation being much more striking in HD patients.[8] HD patients are much more likely to develop

bacteraemia/septicaemia compared all other ESRD patients.[8] Also, HD patients account for a disproportionately larger share of MRSA bacteraemia episodes. Vascular access dysfunction remains one of the most important causes of hospitalisation in HD patients.[8, 10, 13] There is some evidence that the incidence of infection as a cause for hospitalisation seems to be on a rise amongst HD patients, whilst CVD related morbidity may be falling.[8]

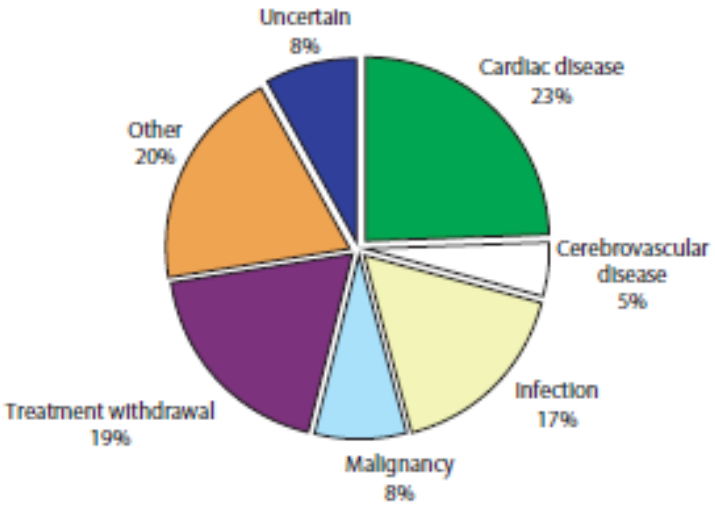

Figure 1-5: Causes of mortality amongst dialysis patients (adopted from the UKRR report 2013)

1.2 Vascular access for haemodialysis

Haemodialysis involves removal of patient's blood from the intravascular compartment, circulating it through an extracorporeal circuit (the dialysis 'machine') and returning the 'purified' blood back into the patient's intravascular system. Optimal access to the patient's intravascular system is thus vital to deliver efficient haemodialysis. An ideal vascular access should be safe, efficient and durable. Once mature, an AVF has the potential to meet these requirements. Hence the growth in ESRD and HD populations has been paralleled by an increasing focus on vascular access, which in turn has exposed the inherent lack of knowledge in this area.

1.2.1 Historical perspective

Not surprisingly, the history of vascular access closely follows the history of haemodialysis itself. Haas performed the first HD in a human subject in 1924. Initially, he used glass cannulas to access the radial artery and the cubital vein.[14] This was followed by surgical cut-down to access the radial artery and an adjacent vein.[14] Kolff in 1943 used similar repeated arterial and venous puncture technique to dialyse patients on his 'rotating drum kidney'.[14]

The first durable access was developed by joint efforts of Quinton, Dillard and Scribner (Seattle, USA) popularly known as the 'Scribner shunt', to be first used in 1960.[14] The Scribner shunt consisted of two tapered Teflon tubes which were inserted into the artery and the adjacent vein.[15] This access, for the first time, allowed dialysis availability over the long-term and as an outpatient treatment. Despite its wide use,

it was not without problems - recurrent thrombosis and infection were major problems, often necessitating device removal and replacement at another site.[15]

In 1961, Shaldon (London, UK) introduced handmade catheters for dialysis use. These were initially arterio-venous and paved the way for later development of veno-venous catheters, which are still used in practice today.[14]

The first native AVF use was reported by Brescia, Cimino and colleagues in 1966.[16] They anastomosed the radial artery to cephalic vein at the wrist and after maturation period used the newly formed AVF for repetitive punctures. The first surgically created fistula for the purpose of haemodialysis was placed on 19 February 1965, followed by further 14 operations. Twelve out of these 14 AVFs gained primary function, giving a rather low primary failure rate, even by present standards. These fistulae were able to deliver blood flows between 250 – 300 ml/min and there were no reported episodes of clotted AVFs. It was noted that the efferent vein became more prominent and thick walled as time passed. They termed this process as 'arterialisation' – more commonly termed as maturation in this age. The radio-cephalic AVF still remains one of the most widely used AVFs and goes with eponymous name of Brescia-Cimino fistula. Dr Appell, the surgeon in this team, had initially used the side-to-side anastomosis technique. The end-to-side anastomosis, where the end of the vein is anastomosed to the side of the feeding artery, is the most commonly used technique today.

In 1972, newer forms of grafts were being described, the most important being the expanded polytetrafluoroethylene (ePTFE) graft. This allowed creation of AV

vascular access in patients who did not have suitable veins. These AVGs required much less 'maturation' period and could be used in 2- 4 weeks. Their use expanded rapidly and became the most widely used AV dialysis access in the USA. However their take on rate was insignificant in the rest of the world - they are expensive and prone to frequent problems such as recurrent thrombosis, anastomotic stenosis due to neo-intimal hyperplasia (NIH) and infection. Unlike natural AVFs, grafts do not offer longevity, and their average cumulative survival is only 2 – 3 years.[15]

Tunnelled semi-permanent catheters, developed in the late 1980s also became an instant success until the shortcomings (poor flows, recurrent thrombosis, recurrent infection, central vein stenosis, etc.) became apparent.[15]

1.2.2 Types of vascular access

Native arteriovenous fistulae

An AVF is created by joining an artery to an adjacent vein (figure 1-6). It is the most commonly used permanent access type in the UK. Following the anastomosis, the high pressure and high flow from the artery is transmitted to the low pressure and low flow vein, which, in favourable conditions, undergoes a process of adaptive transformation, also known as maturation. This process, normally takes about 6 weeks after which the AVF can be cannulated.

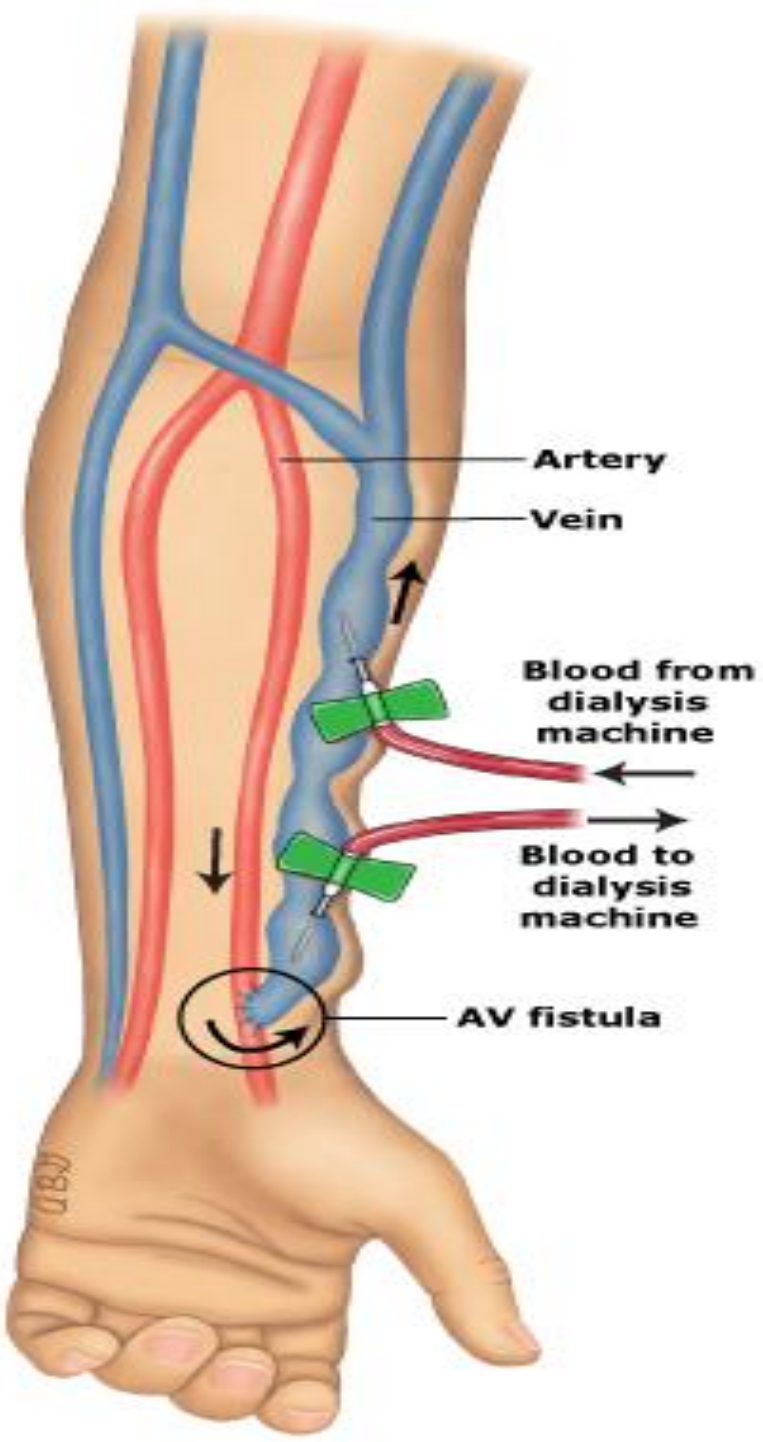

Figure 1-6: Diagrammatic representation of a radio-cephalic AVF

Synthetic arteriovenous grafts

The Scribner shunt was the first synthetic graft. An AVG (figure 1-7) acts as a conduit joining the feeding artery to the draining vein. The graft material is tunnelled under the skin joining the artery and the vein. This implanted portion of the graft is used for cannulation.

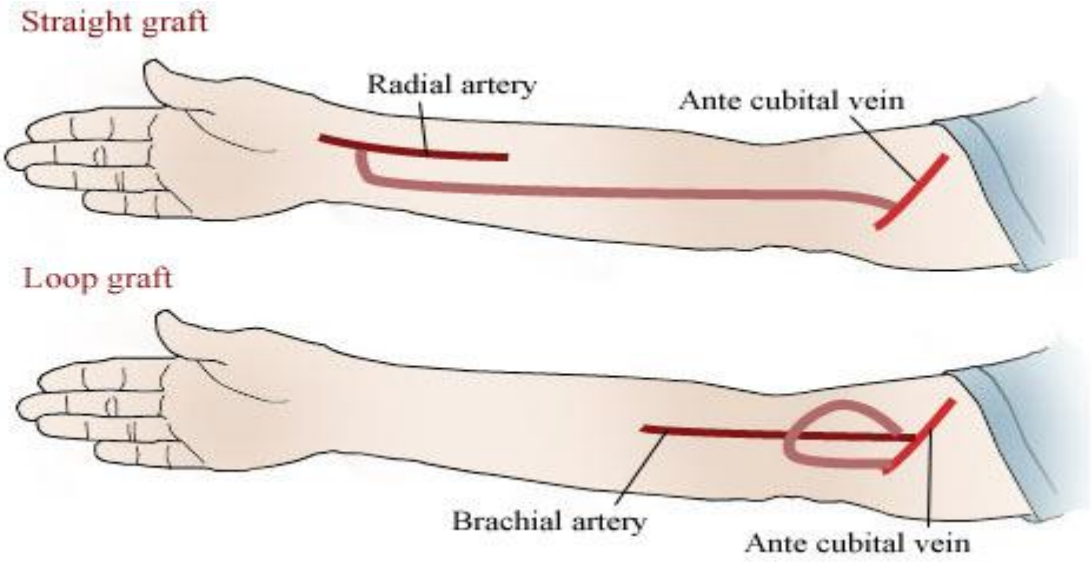

Figure 1-7: Diagrammatic representation of synthetic upper limb AVGs

Various biological and synthetic materials can be used as a graft. Biological materials include autogenous long saphenous vein, human umbilical vein and bovine carotid artery. Various synthetic materials have been used such as Dacron or ePTFE, the latter being the most common. Various modifications of the commonly used ePTFE grafts are available for use.

There is wide global variation in AVG use. In European countries and the UK, AVG is generally considered as the last resort AV access when all other native options

have been exhausted. Traditionally in the US graft prevalence has been very high. In Europe and the UK graft prevalence is under 5%.[17]

Dialysis catheters

The use of central dialysis catheters was first reported by Shaldon.[14] The technique involved using hand-made catheters to puncture the artery and vein. This approach was soon abandoned in favour of veno-venous catheters. The subclavian vein was most commonly used in the early days but lead to increased risk of central vein stenosis. Central vein stenosis can lead to significant limb oedema and can interfere with successful AV access creation, by impairing the venous return from the high flow access. The most commonly used sites are jugular veins for longer-term and femoral veins for temporary access.

Catheters are widely used and temporary catheters provide a good access when it is required at short notice. They are also often used whilst patients wait for their AV access to be formed or mature. In these situations 'cuffed' central catheters are preferred (figures 1-8 and 1-9). These can be tunnelled under the patient's skin and the cuff helps to stabilise the catheter's position by stimulating formation of a fibrous scar around itself. Tunnelling has also been shown to reduce infection compared to temporary catheters[18] and this has led to use of these catheters as long-term access in patients where AV access can't be formed or is not preferred.

There are various tunnelled dialysis catheter designs and products available. The Tesio® catheter are essentially 2 separate single lumen catheters thus needing 2 venotomies and tunnels such as the Tesio catheter (figure 1-8). More commonly used

catheters have both lumens within one catheter and these are available in a variety of tip designs - with split tip such as the Hemosplit® catheter or symmetrical tip such as the Palindrome®. The catheter design also has an impact on insertion techniques with ante- or retro-grade tunnelling. Antegrade tunnelling is often favoured for ease of use but retrograde tunnelling allows for more precise tip positioning.

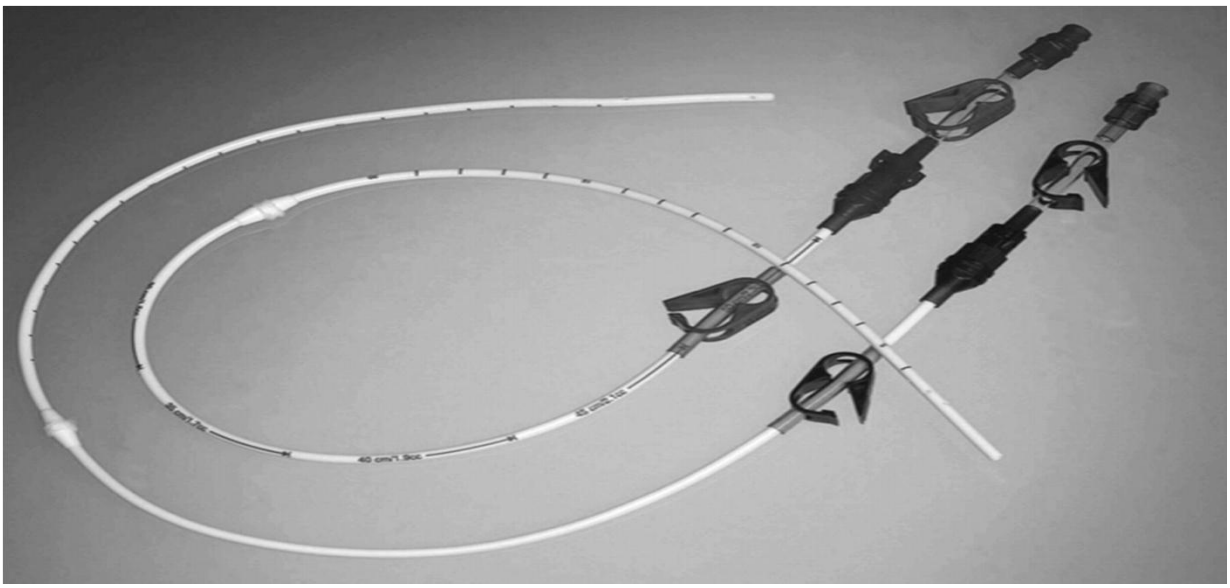

Figure 1-8: Tesio catheters

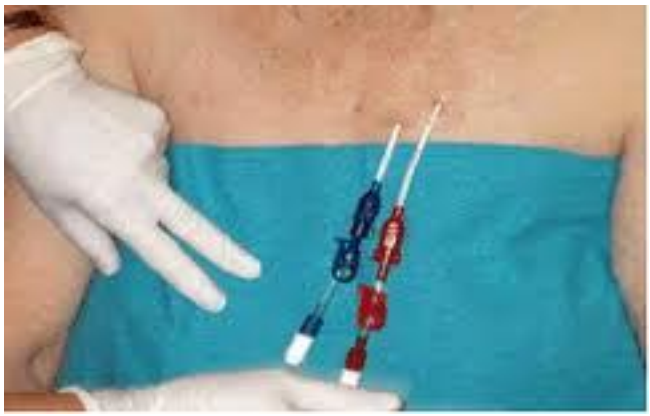

Figure 1-9: Tunnelled Tesio catheter in-situ

1.2.3 Complications of vascular access

Access failure

Access failure or inadequate function of the access can be classified as early or late. Early failure is defined as occurring within 4 days of insertion in case of catheters and within 3 months in case of AV access, to allow for maturation.[19, 20] In case of AVFs, the causes of early failure can be, vein stenosis (proximal and juxta-anastomotic), presence of accessory veins and arterial inflow problems.[19] More than one lesion may be found in more than a third of the cases.[19] The commonest cause for late access failure in case of AV access is vein stenosis followed by arterial disease.[21, 22] These lesions often lead to access thrombosis which is the common final mechanism of AVF failure.

In case of catheters, the common causes of failure are thrombosis, formation of fibrin sheath or mechanical causes such as, kinking or mal-position. Catheter failure that necessitates catheter replacement complicates 16% of catheters at a rate of 0.58 exchanges per catheter-year depending on catheter type.[23,24]

Incidence of early failure is much higher in AVFs compared to AVG and catheters. AVFs however, have a much higher cumulative patency compared to all access types. Radio-cephalic fistulae have 5 and 10 year cumulative patency in region of 53% and 45% respectively[25] compared to cumulative patency for PTFE grafts which at one, two, and four years is approximately 67% , 50% and 43%, respectively.[26] Moreover, AVFs also require far fewer interventions to maintain patency and function.[27, 28]

Infection

Infection rates are proportionately much higher in HD patients compared to other RRT modalities, much of which is attributable to vascular access. Infection is estimated to account for 20% of vascular access loss.[8]

Access related bacteraemia may lead to metastatic infections involving the spine (e.g. 'discitis'), joints, brain and other organ systems. It may also lead to development of infective endocarditis in a small proportion of patients, this complication being much more common in patients with catheters.[29, 30]

Catheters are the most likely of all three access types to get infected. Catheters are considered the main risk factors for MRSA bacteraemia and the estimated relative risk when compared to an AVF is 7 fold higher.[9] A venous catheter may act as the portal for the direct entry of organisms into the circulation. This is likely to be the primary mechanism as evident by the predominance of skin commensals as the most common pathogenic organisms in access-related bacteraemia. Catheters and AVGs can also develop a biofilm which leads to chronic infection. Bacteraemia secondary to another infection (e.g. skin or soft tissue, pneumonia) or procedures may result in colonisation of the catheter biofilm. Biofilm formation may delay the effectiveness of therapy or increase the risk of relapse.[31]

Steal phenomenon

Steal phenomenon results from shunting of blood ('stealing') from the extremity distal to the AV access resulting in distal hypoperfusion. Reversal of blood flow into the AV access is universal and becomes clinically relevant only in patients with

severe peripheral vascular disease.[32] Symptomatic steal syndrome has been reported in 20% of patients with 4% of these as severe cases requiring intervention. [33, 34]

Aneurysms and pseudo-aneurysms

Aneurysms result from repeated cannulation in the same area of the fistula. Repeated cannulation can lead to destruction of the vessel wall, which is replaced by collagenous scar tissue. This results in aneurysm formation due to poor physical properties of scar tissue. Aneurysms have a tendency to grow in size, as the wall shear stress is proportional to the diameter of the aneurysm. The major complications of aneurysm formation are rupture, infection and rarely embolism. Adequate imaging is crucial for delineating the extent of the lesion, identification of thrombi and also to detect predisposing lesions such as underlying stenosis.[35]

Pseudo-aneurysms are haematomas that form around a defect in the vessel wall and internally communicate with the vessel lumen. They tend to be a particular problem with ePTFE grafts, as the graft material tends to deteriorate over time. Depending on the size of the defect, smaller lesions (<5mm) can be treated with ultrasound guided direct compression with or without injection of thrombin and use of covered stents, whereas larger lesions often need surgical intervention. [36]

Central Vein Stenosis

Central vein stenosis (CVS) is a common problem in dialysis patients and is associated with catheter use. In some cases however, it only becomes apparent after creation of an AV access. AV access leads to high blood flow on the ipsilateral side, which the stenosed central vein fails to cope with, thus making the hitherto sub-

clinical problem, clinically apparent. In two studies, the incidence of central vein stenosis in dialysis patients was found to be more than 40% patients, although not all cases were symptomatic.[37, 38]

Risk factors for central vein stenosis are – subclavian vein insertion site, duration of catheter stay, number of catheter insertions, incidence of catheter infections, longer dialysis vintage and use of PICC catheters (peripherally inserted central catheter).[39, 40]

Cardiovascular implantable electronic devices (CIEDs) which include pacemakers and implantable cardioverter-defibrillators are increasingly found to be associated with central vein stenosis. CIEDs are frequently used in HD population because of the higher risk of sudden death in this cohort.[41] The exact prevalence of CIED use in HD patients is unknown. Two small single centre studies have found CIED prevalence to be 7% and 10% in their HD cohorts.[42, 43] Whilst the risk of developing CVS remains relatively low in the non-ESRD population,[44] [45] this becomes a very significant problem in HD patients with AV access. This proportion has been reported to be as high as 70% in one case series.[46]

The exact aetio-pathogenesis of central vein stenosis is not understood, but the likely mechanisms are thought to be mechanical irritation and endothelial injury.[47]

Other complications

Other complications include venous hypertension, seroma formation and high output heart failure.[48]

1.2.4 Cost of vascular access

Cost effectiveness of medical interventions influence clinical practice and treatment delivery. Cost efficiency is a composite of health care expense and clinical outcomes of a particular treatment option.[49] In USA alone, the cost of VA exceeds $1 billion dollars a year.[50] Costs of hospitalisation due to vascular access competes closely with the cost of cardiovascular hospitalisation.[8] A Canadian study estimated the annual per patient cost of maintaining VA to about 7000 Canadian dollars per year.[51]

The least expensive type of VA is an AVF.[11] The cost of access maintenance compared to an AVF was 5-fold higher for catheters and 8-fold higher in case of AVGs.[11] Not only is the cost of maintaining catheters and AVGs higher compared to an AVF, but the overall patient expenditure is also higher for other access types.

1.3 The Arteriovenous fistula

In their seminal paper reporting creation of AVFs for the first time, Brescia and Cimino described the procedure conducted in 14 patients. The AVF was created by side-to-side anastomosis of the radial artery to the adjacent cephalic vein. Twelve out the 14 patients had successful AVF.[16] This technique was further revised by Rohl et al (Heidelberg, Germany) by using a radial-artery-side-to-vein-end anastomosis.[14] This procedure was widely accepted and has become a standard procedure. Once created, an AVF needs to 'mature' so that it can be routinely cannulated with two needles and deliver blood flows enough to allow optimal dialysis over the total prescribed duration. The minimum blood flow required for haemodialysis is in the range of 350-450ml/min, whereas a mature AVF would typically have blood flow in the range of 500-2000ml/min. AVF use in prevalent HD patients in the UK was just over 65% as per the DOPPS III analysis.[17] AVF use in the UK is much higher than in the US where AVF prevalence is under 50%, but also much lower compared to other countries such as Japan where AVF prevalence is well over 90%.[17]

The ideal site for an AVF is distally in the non-dominant arm, thus conserving the proximal vessels for any further attempts at AVF creation, in case of AVF failure. Some studies have shown higher failure rate of distal (forearm) compared to upper arm fistulae.[52] This approach may lead to delay in having mature AVF, increased catheter use at dialysis initiation and more access interventions per patient.

Common sites for native upper limb fistula [15]

Forearm/Wrist

Radio-cephalic (Brescia-Cimino)

Snuff box radio-cephalic

Ulnar artery-basilic vein

Upper arm / elbow

Brachio-cephalic

Brachial artery-perforator vein

Brachial artery-basilic vein with transposition

1.3.1 Physiology of fistula maturation

Adequate maturation requires that the AVF has sufficient blood flow to support dialysis and prevent thrombosis. Anastomosis of the high-pressure arterial channel to the low-pressure and low-resistance venous channel, bypassing the resistance vessels in the distal extremity, leads to an immediate increase in the blood flow through the anastomosed vein. In case of a radio-cephalic fistula, the flow increases to around 300ml/min immediately from an average flow of 20ml/min in the radial artery. Within a week the flow increases to more than 500ml/min.[53] This increase in flow results, largely from dilatation of the inflow artery (figure 1-10). According to Pouseuille's law, blood flow (Q) is proportional to the product of the pressure gradient (ΔP) and the vessel radius (r) to the fourth power divided by viscosity (η) of blood.[32] Assuming steady blood flow, constant pressure gradient and viscosity, the artery would need to dilate by nearly 80%.[32] However, the arterial flow is pulsatile and the pressure gradient tends to increase following AVF creation. Furthermore, in about 75% of patients there is retrograde flow (towards the fistula) from the distal

artery and this retrograde flow accounts for up to 25% of inflow into the fistula (figure 1-10).[54]

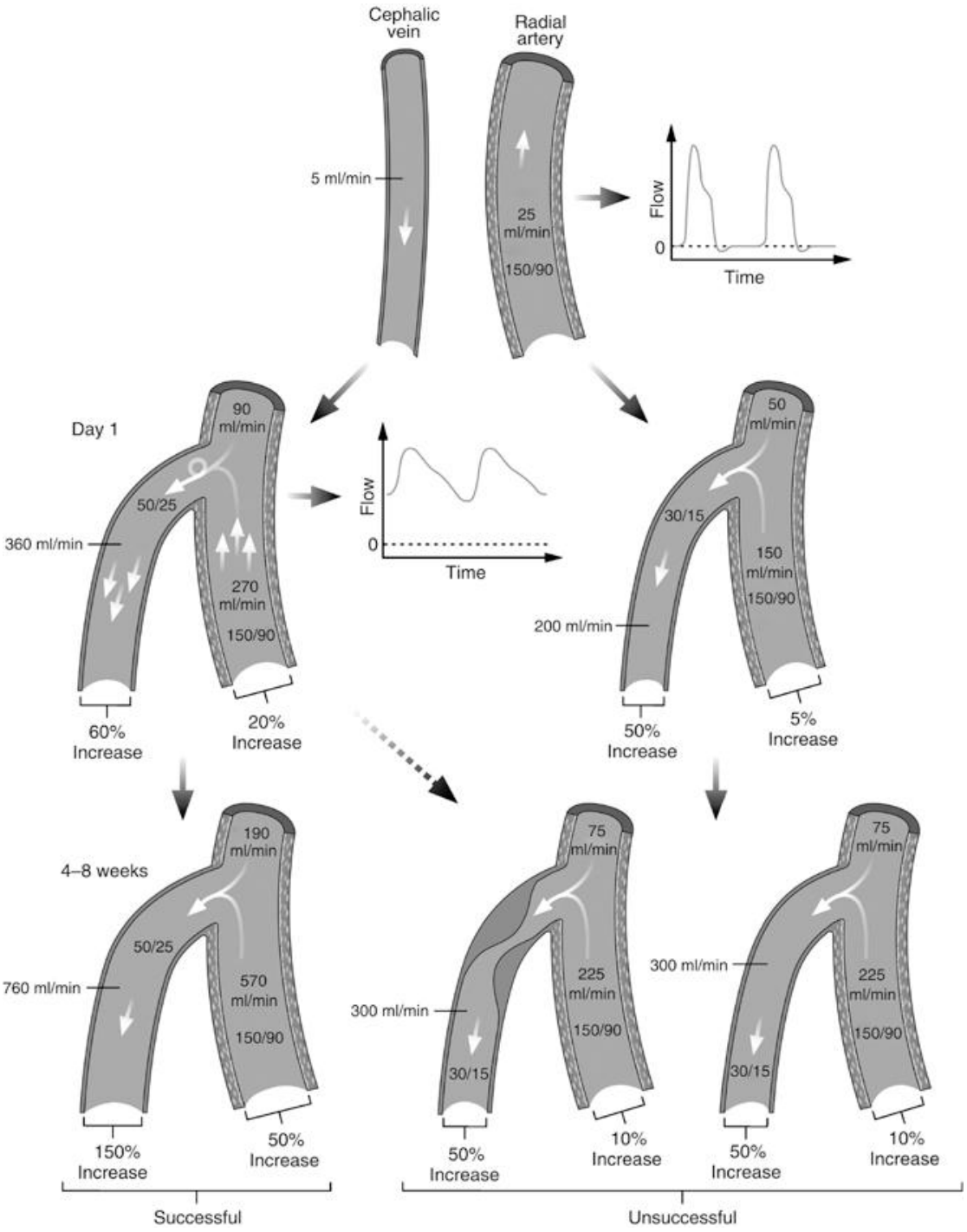

Figure 1-10: Overview of fistula maturation: Figure temporally depicting the typical pattern of successful and unsuccessful AVF maturation in radio-cephalic fistulae. Reproduced with permission from reference 35

Increase in flow needs to be coupled with arterial and venous dilatation and remodelling. Increase in blood flow velocity and resultant increase in wall shear stress (WSS) serves as the major stimulus for arterial vasodilatation and remodelling.[32,55] As a result of these stimuli, release of endothelial nitric oxide (NO) and other vasodilators occurs which results in immediate arterial dilatation and restoration of shear stress. Further dilatation and remodelling of the artery is achieved by breakdown of the elastic lamina. This is mediated by reactive oxygen species and matrix metalloproteinase (MMP) up-regulation,[32] this in turn is NO dependent.[56]

Whereas arterial dilatation is required for successful AVF maturation, vein dilatation is the clinically more apparent and desirable consequence. Venous adaptation to increased flow has been studied to a much lesser extent than arterial adaptation. Initial vein dilatation is the result of an increase in venous pressure, but subsequent dilatation is likely to be a response to normalise flow-induced increase in WSS.[32] Vein wall thickening is characterised by neointimal hyperplasia (NIH). NIH has traditionally been thought of as a pathological entity, as it is the underlying histo-pathological lesion in vein stenosis. Yevzlin et al in a recent paper have suggested that NIH to certain degree, is a prerequisite to successful maturation.[57] Successful maturation requires an appropriate balance between NIH and dilatation. Excessive NIH with little dilatation, and little or no NIH would impair AVF maturation (figures 1-11 and 1-12).[57]

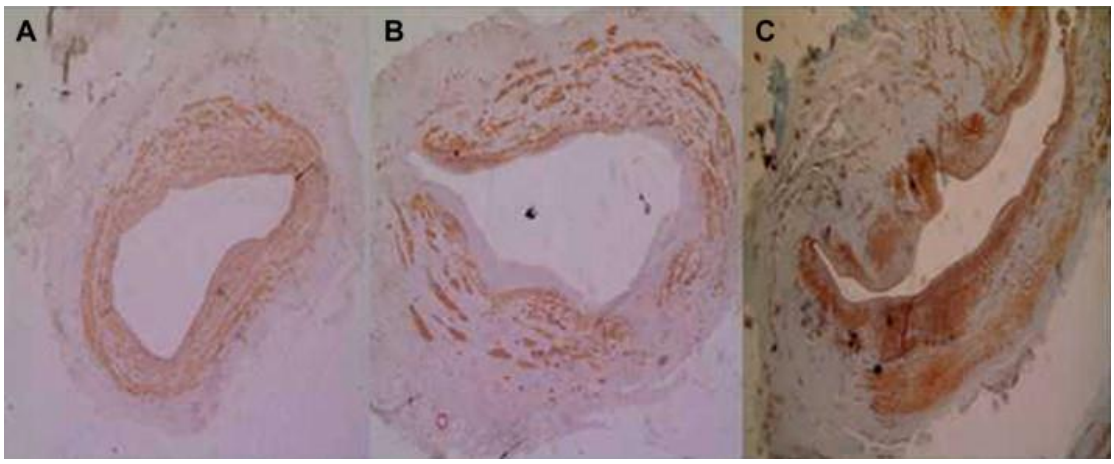

Figure 1-11: NIH lesions of various degrees in a porcine model of AVF. (A), Mild NH; (B), moderate NH; (C), severe NH with luminal compromise. Reproduced with permission from reference 39

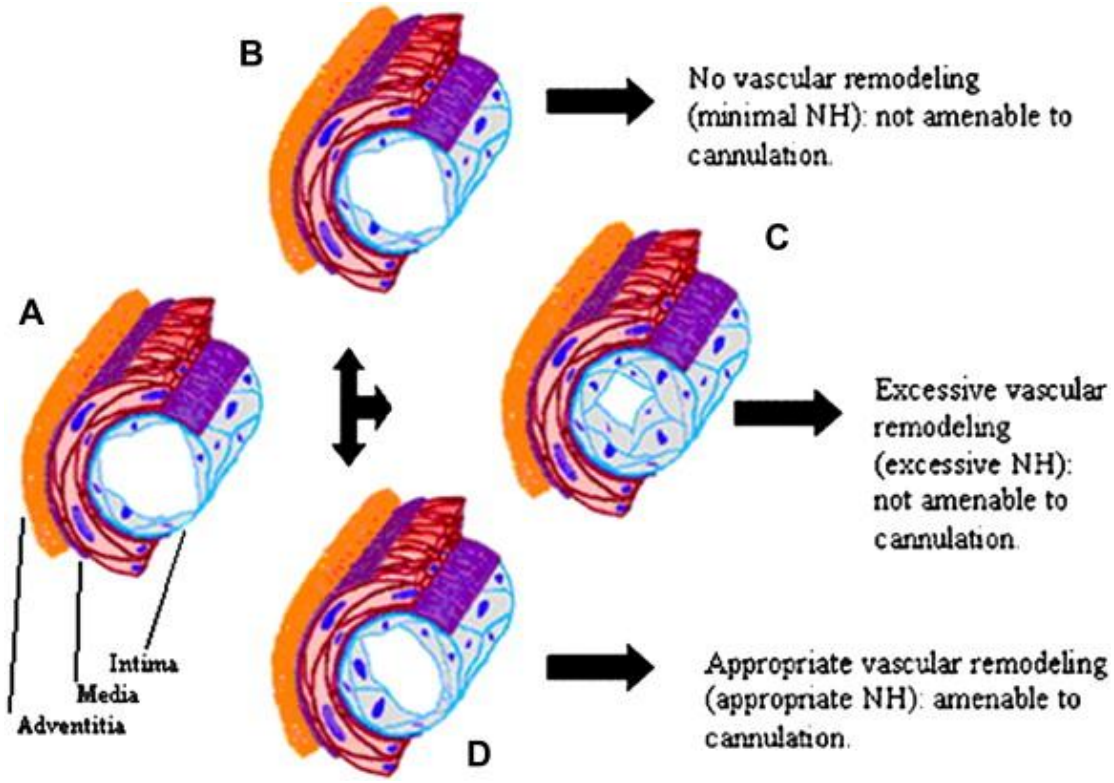

Figure 1-12: Figure depicting impact of NIH on AVF maturation. Reproduced with permission from reference 39

Other examples of vein arterialisation

Much of the initial knowledge of NIH came from coronary bypass vein grafting. This analogy provides us with useful insights in VA failure. Saphenous vein grafts, in

addition to arterial conduits, are still commonly used in coronary bypass. NIH occurs in vein grafts within weeks after grafting.[58, 59] Post-operative events that precipitate vessel injury are similar in an AVF (surgical trauma, ischaemia, endothelial injury and increased WSS). This is followed by apoptotic vascular smooth muscle cell (VSMC) loss but eventually leads to increased vascular wall thickness,[60] followed by cell proliferation (smooth muscle cells, myofibroblasts), cell migration (medial VSMCs, adventitial myofibroblasts into the intima), extracellular matrix deposition and inflammation, all culminating in vessel wall thickening. Identical changes are seen in peripheral vascular disease where vein grafts are employed. NIH formation leads to development of atherosclerosis eventually leading to graft stenosis and occlusion.

There are some key differences between these models of arterialisation and an AVF. Firstly, in an AVF unlike in coronary vein grafts, the capillary circulation is entirely bypassed. This leads to a different haemodynamic profile as the resistance to flow is further reduced. Secondly, although uraemia may exist in coronary vein graft arterialisation model, it is universal in an AVF model.

Lee et al have recently demonstrated presence of NIH lesions in veins of uraemic subjects prior to AVF creation.[61] These changes may be a reflection of chronic volume overload leading to an alteration in haemodynamic profile along with the presence of uraemia.[57, 61] Presence of these changes may be clue to the significance of factors such as uraemia.

1.3.2 Fistula failure

1.3.2.1 Early failure

This is defined as an AVF which was never usable for dialysis or one which failed within 3 months of initial use.[19] The causes of early failure can be grouped into two categories – inflow and outflow problems.

Inflow problems

In order to mature, to maintain patency and support HD, the AVF needs good inflow of blood. Poor inflow could result from:

a) Abnormalities of the feeding artery: Anomalies or disease of the feeding artery such as selection of too small an artery or a heavily atherosclerotic artery.
b) Abnormalities of the anastomosis: Juxta-anastomotic stenosis (JAS) and anastomotic stenosis would impair fistula maturation by reducing the inflow into the draining vein. JAS is the most common pathological lesion in non-maturing AVFs.[19]
c) Systemic problems: Hypotension, pump failure, etc.

Outflow problems

a) Abnormalities of the draining veins: Choice of too small a vein or a vein that it is fibrotic or stenotic due to past trauma.
b) Accessory veins: Accessory veins may hamper AVF development by diverting blood flow away from the intended draining vein. Accessory veins are present in more than 40% of non-mature AVFs, often in combination with

JAS.[19] In one case series, ADVs were thought to solely account for non-maturation in 12% of patients.[19]

1.3.2.2 Late failure

Thrombosis is the final mechanism of late AVF failure and is much more common in grafts compared to AVFs.[62] Low flow is associated with AVF thrombosis in most cases. The commonest underlying lesion that leads to reduction in blood flow is vein stenosis. NIH is the primary pathological lesion that characterises vein stenosis.

Pro-coagulant disorders such as factor V Leiden, anti-cardiolipin antibodies, etc. can also contribute to fistula thrombosis. A study by Knoll et al estimated that with presence of each additional thrombophilic disorder, the odds of access thrombosis increased significantly (adjusted OR, 1.87; 95% CI, 1.34 to 2.61).[63] Other causes that may lead to thrombosis can be systemic (hypotension, hypovolaemia) or local due to external compression. There may be interplay of more than 1 factor as hypotension due to cardiac failure or hypovolaemia and pro-thrombotic disorders are frequently found to co-exist in dialysis patients.

Thrombosis resulting in acute fistula failure is a significant event and a major cause of morbidity and mortality for HD patients. Acute AVF failure can precipitate hospitalisation and often leads to a myriad undesirable consequences viz. disruption of dialysis schedules, hospitalisation with its related complications, need for alternative access, etc. Acute access failure thus can also have significant impact on patient's quality of life and lead to increased healthcare costs. It is estimated that 17-25% of hospital admissions in HD patients are secondary to access thrombosis.[13, 50]

More emphasis is now being placed on increasing overall AVF prevalence. Whilst we need to create more AVFs in a timely fashion, we also need to prevent permanent loss of AVFs due to thrombosis. Whilst surveillance of AVFs is recommended by national[64] and international guidelines[3], as a strategy to prevent AVF and graft thrombosis, evidence for these recommendations is unclear. Recent reviews suggest that benefit of vascular access surveillance, vis-à-vis the increase in cost and interventions, remains unproven.[65, 66] In case of AVFs, there are no proven primary prevention strategies to reduce incidence of thrombosis. In this context, effective treatment of thrombosed AVFs remains our only hope.[67]

Treatment of late failure

Salvage of AVFs and grafts, can be reliably achieved using surgical or endovascular techniques. Wherever available, endovascular salvage is preferred as it is effective, less invasive, logistically easier to organise and has lower complication rates.[68, 69] Moreover, most procedures can be performed as day case procedures, obviating the need for hospitalisation and also reducing the time from thrombosis reporting to intervention.

Effective treatment of access thrombosis needs to be delivered by those skilled and experienced in access interventions – usually interventional radiologists but increasingly other professional groups such as nephrologists and vascular surgeons trained in dialysis vascular access interventions have contributed in this area.[70, 71] Interventional treatment being universally expensive has significant impact on overall healthcare cost related to HD.

Thrombolysis

Thrombolysis can be achieved using fibrinolytic agents such streptokinase, urokinase or recombinant tissue plasminogen activator (tPA). Although thrombolysis alone has been tried for AVF salvage, the outcomes are generally poor and this practice has been largely superseded by use of thrombolytic agents in combination with other percutaneous techniques.[72-75]

When used in combination, thrombolytic agents can be used as bolus dose, as infusion thrombolysis or using the pulse-spray technique.[76]

Mechanical

Several mechanical methods of fistula or graft thrombectomy have been described. These include the simple balloon maceration technique (commonly used in our centre) and thrombo-aspiration to use of various thrombectomy devices such as the Arrow-Trerotola device, Angiojet device, Hydrolyzer device, Amplatz thrombectomy device, etc.[77] No single technique has been convincingly demonstrated to be more effective in comparison with others.[77] Operator preference, operator experience, local availability and cost are the usual factors which determine the technique that is employed. Balloon maceration and thrombo-aspiration techniques are significantly more cost effective as they do not involve use of expensive proprietary devices.

Challenges in care delivery for thrombosed AVFs and grafts

Avoiding delay:

Salvage treatment needs to be delivered in a timely fashion. Whilst time delay has not been convincingly shown to impact outcomes of endovascular salvage, time is nevertheless of critical importance, in view of the need for dialysis. Other than restoration of patency, avoiding hospitalisation and catheter use are the two most important goals of any service catering to patients presenting with acute access failure.

Availability of expertise:

Availability of interventional expertise can be a significant problem - especially for smaller renal units. It is not uncommon to hear reports of AVFs and grafts being abandoned after thrombosis in some units due to lack of skilled interventionists. Published reports of this practice, not surprisingly, are difficult to find. Therefore, optimal ways of care delivery for this cohort of patients need to be implemented and frequently audited. The design of the interventional set up and its framework may therefore influence the outcome of acute AVF failure and is a major limitation in clinical research. The study of natural history and interventions of acute AVF failure and its outcomes is only feasible in a clinical set up that is standardised and streamlined to overcome these factors.

1.3.3 Clinical pathophysiology of AVF maturation and failure

1.3.3.1 Clinical correlates of early fistula failure

Several studies have tried to identify risk factors for AVF failure. Table 1-1 below summarises the finding from some of the studies, which attempted to identify clinical correlates of AVF outcomes.

Study	Risk factors	Favourable factors	Note
Miller et al[52]	Female sex, older age, diabetes		Wide CIs
Lok et al[78]	White race, older age (>65), presence of PVD and CAD,		
Feldmann et al[79]	Older age, presence of CVD, dialysis dependency, smaller veins, radiocephalic AVFs, Mean arterial pressure <85	Larger heparin dose, end to side anastomosis	
Wong et al[80]	Radial artery and cephalic vein diameter <1.6mm		Associated with failure to maturation
Reilly et al[81]	Vein diameter <2mm and arterial diameter <2.9mm		Associated with early failure in RCFs
Thomsen et al[82]	Hypotension (SBP <110)		Associated with high early failure rate
Rayner et al[10]	Previous catheter use		2-fold higher risk of AVF failure

Table 1-1: Summary of clinical studies identifying clinical co-relates of AVF outcomes

1.3.3.2 Role of haemodynamics

WSS is the tangential frictional force applied by blood to the vessel wall. The mathematical formula is WSS = 4ηQ/πr3, where η = blood viscosity, Q = blood flow and r = radius of vessel. High WSS is the favoured haemodynamic profile for AVF maturation as this leads to endothelial quiescence and survival, and orientation of endothelial cells in the direction of flow. The endothelial cells secrete NO and other anti-inflammatory factors.[55, 83] This results in positive remodelling of the vessel – dilatation with minimal NIH.[22]

Low blood flow and hence, low WSS results in endothelial activation and secretion of pro-inflammatory factors, thus leading to vascular constriction and NIH. Pattern of WSS may also influence vessel adaptation. Laminar WSS as opposed to oscillatory WSS, leads to a favourable endothelial response.[22, 84]

Whilst WSS seems to influence intimal thickening, circumferential or transmural pressure has been shown to correlate with medial thickening.[85]

1.3.3.3 Cellular, cytokine and genetic determinants

Endothelial function

Optimal endothelial function is critical for AVF maturation and function. As outlined earlier increase in WSS and vascular injury resulting from AVF creation, in favourable conditions, leads to NO secretion by the endothelium resulting in immediate arterial dilatation. Further dilatation and remodelling is achieved by MMP up-regulation and reactive oxygen species, but this is dependent on NO secretion by the endothelium.[56]

Role of uraemia

Endothelial function is impaired in uraemia.[86] There are several plausible mechanisms – oxidative stress,[87] chronic inflammatory status[88, 89] and uraemic toxins such as ADMA (asymmetric diethyl-amine).[90] Uraemia has been shown to result in worse AVF outcomes in mice models compared to normal mice.[91]

Role of vascular / endothelial injury

Dialysis needling is a unique model of repetitive and regular vascular injury. Needling can result in direct endothelial injury, but the presence of needle itself, the resulting disturbance to flow, and the blood jet can all contribute by making the blood flow more turbulent.[92] Endothelial injury can also result from surgery and interventional procedures such as angioplasty.[93, 94]

Abnormal haemodynamic shear stress

A study by Davies et al on cultured endothelial cells (ECs) examined the influence of flow patterns on endothelial cell characteristics.[95] They observed the effect of flow patterns on ECs in culture. In static or no flow condition, endothelial cells show polygonal conformation, in laminar flow they undergo ellipsoidal conformation and under turbulent flow conditions the cells drop out due to cell lysis and death in cultured cells (figure 1-13).

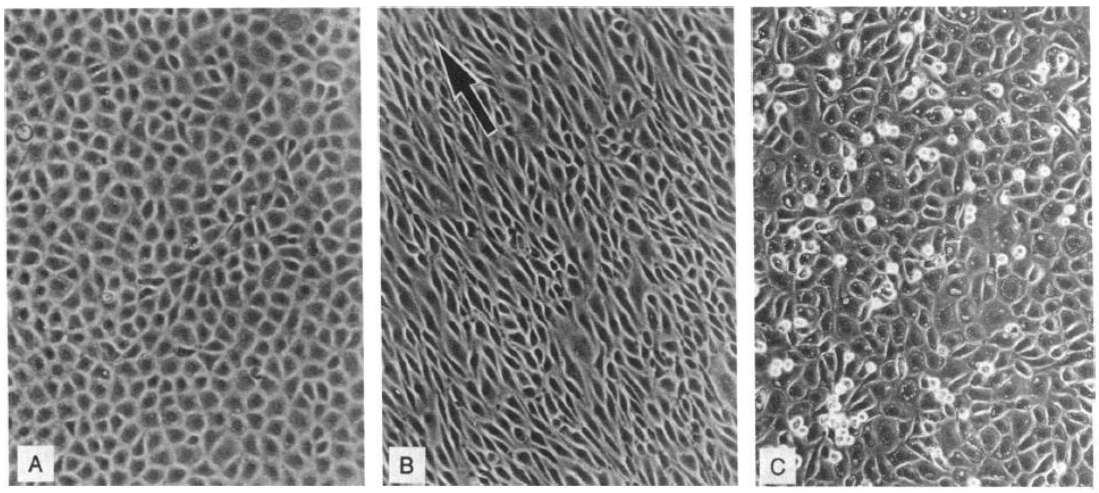

Figure 1-13: Influence of flow pattern on ECs in culture A - Static (no flow), B - Laminar Flow, C - Turbulent flow. Reproduced with permission from [95]

Further evidence for role of haemodynamic shear stress comes from study by Krishnamoorthy et al.[96] Using pig AVF models, the authors have demonstrated the different WSS profiles that result from straight or curved AVF configuration. They have also shown that changes to the WSS profile correlated with histological changes highlighting the importance of flow pattern, which is in-turn dependent on the anatomical configuration.[96]

Endothelial progenitor cells (EPCs)

EPCs are circulating bone marrow derived stem cells, which can differentiate into various cell types including endothelial cells. They play a role in vasculogenesis and vascular remodelling following vascular injury, by promoting rapid endothelisation.[97, 98] Endothelial progenitor cells (EPCs) and their concentration in the blood has been linked to defective vascular remodelling.[99, 100] Various studies have shown reduced EPC numbers and EPC dysfunction[101, 102] in patients with CKD, which may explain poor vascular remodelling after AVF formation.

1.3.3.4 Genes and Cytokines in AVF failure

The molecular mechanisms involved in maturation have been investigated in cell culture and animal models. eNOS mRNA and protein expression is up regulated in bovine aortic endothelial cells in response to chronic increases in WSS.[103] In addition, increased expression of eNOS mRNA occurs as an acute response to AVF creation.[104] eNOS activity also seems to modulate vessel remodelling in the later phase, as evidenced by absence of MMP-9 induction in eNOS deficient mouse model.[105] Uraemic toxins may inhibit NOS activity by reducing the expression of iNOS (inducible NOS).[106]

MMPs lead to breakdown of extracellular matrix – this has beneficial effect causing dilatation of the feeding artery; but can also lead to migration of smooth muscle cells leading to development of NIH. There is a reduction of NIH in a porcine AVG model by inhibition of MMP using oral nonspecific synthetic inhibitor BB2893.[107] Misra et al also demonstrated differential expression of MMPs in a porcine model of venous stenosis of AVG. They observed that AVG placement resulted in early expression of VEGF-A and pro-MMP-9, followed by subsequent rise in pro-MMP-2, active-MMP-2, VEGFR-1 and 2, and TIMP-1. They concluded that the latter may contribute to development of venous stenosis.[108]

Haem-oxygenase 1 (HO-1) may play a positive role in protecting vascular health and may promote AVF maturation by its anti-oxidant and anti-inflammatory properties.[109] HO-1 knockout mice have poorer AVF outcomes as a result of increased NIH and venous thickening and higher incidence of AVF occlusion.[110] Lin

et al found that a longer length polymorphism with (GT)n ≥30 in the HO-1 gene was associated with a higher frequency of access failure and a poorer patency of AVF in HD patients.[111] HO-1 knockout mice were observed to have significant induction of MMP-9.[110] In the later phase of AVF development, MMP-9 may promote NIH by allowing the smooth muscle cells to migrate from the adventitia to the intima.

Monocyte chemoattractant protein-1 (MCP-1 or CCL2), a member of the chemokine family (C-C) has been linked to atherogenesis.[112] In a recent study of murine model of AVF, Juncos et al demonstrated that MCP-1 might contribute to development of AVF failure. MCP-1 expression was markedly up regulated in the venous segment of AVF in these animals and they also found higher fistula patency in murine models with a genetic deficiency of MCP-1.[113]

Increased expression of transforming growth factor - β1 (TGF-β1) along with insulin like growth factor – I (IGF-I) in stenotic lesions of AVFs has been shown.[114] Genetic polymorphisms in the gene region encoding the signal sequence of TGF-β1 are linked with AVF failure.[115] Antibodies against TGF-β1 reduce the size of intimal lesions in a carotid artery balloon injury model in rats.[116] Even at low concentrations, TGF-β1 increases the synthesis of extracellular matrix proteins such as fibronectin, collagens and PA-1 in vascular smooth muscle cells, endothelial cells and fibroblasts.[117, 118]

Chymase, a chemotrypsine-like serine protease, is involved in conversion of Angiotensin I to Angiotensin II and also conversion of the latent form of TGF-β1 to its active form. Recently, plasma chymase concentration has been found to correlate

with chymase expression in vessels with NIH lesions.[119] In a dog arteriovenous fistula model, Jin et al, showed that chymase and TGF-β positive mast cells markedly accumulated, selectively, in the areas of severe NIH.[120] Furthermore, selective inhibition of chymase by NK3201 resulted in reduced expression of chymase and marked reduction in TGF-β expression and NIH.[120]

It is likely that the end result is determined by a complex interplay between the various biological mediators along with other known and unknown factors and / or events.

1.3.3.5 Role of practice patterns

Across the world, there is a huge variation in access type and outcomes. VA care patterns can change in response to changes in publicity and policy.[121] Evidence for this comes from the observation of increase in AVF placement in response to the Centre for Medicare and Medicaid Services' Fistula First campaign.[121] Thus, service delivery patterns and care process related factors are important modifiable determinants of AVF outcomes. Practice pattern variations in vascular access are determined by local preference, in addition to patient-related factors. Considerable challenges remain in attempting to deliver optimal vascular access practice patterns across the globe. Factors that may affect AVF outcomes are pre-operative evaluation, patient and staff education, incentive structures, surgical practices, clinician and unit preferences, access surveillance, AVF salvage service provision, access cannulation practices and finally the patient's own preferences and perceptions. Optimal processes that deliver the best outcome are not well known. Some of these factors are considered in the design of the clinical studies.

Chapter 2: Study design and methods

2.1 Study design and methods

Summary of research plan

AVF is the first choice and most optimal form of vascular access for HD available to us today. However, AVF outcomes are far from satisfactory. Despite significant progress, there lies a gap in our understanding of the biology and natural history of AVF maturation and its failure. Knowledge of factors that influence AVF outcomes is critical to our efforts in improving outcomes.

Due to the lack of effective therapies to improve AVF outcomes, the focus has to be on better understanding of the basic process of AVF maturation and failure.

The primary objective of this MD project was to design clinical research to investigate and improve our understanding of vascular access especially AVFs and examine the role of various management or intervention strategies to improve AVF outcomes.

2.1.1 Vascular access research programme

A programme of research in vascular access was set up in the Department of Renal Medicine and Manchester Institute of Nephrology and Transplantation in collaboration with the Faculty of Life Sciences at the University of Manchester. The Renal Network Service and facilities in Greater Manchester, delivered through a hub and spoke model across two centres (Manchester Royal Infirmary and Salford Royal Hospital) serve a population of 3 .5 million and have a prevalent population of 900 patients undergoing haemodialysis in centre, at a satellite unit or at home with an average AVF prevalence of 70% and at least 300 AVF surgeries undertaken each

year. The arteriovenous fistulae are created in the two main renal hubs by a common dedicated team of transplant surgeons. An initial evaluation of the processes in the patient pathway, current practice patterns and baseline clinical performance was undertaken to define the study population.

Aims and overview of the project

The clinical patient base population for this thesis was prevalent and incident haemodialysis and CKD stage 5 patients approaching haemodialysis who are in need of or have existing AVFs or grafts. The studies were designed such that various stages in the natural history of AVFs were addressed, to capture the spectrum of significant clinical events encompassing creation to maturation, subsequent VA use and failure (figure 2-1).

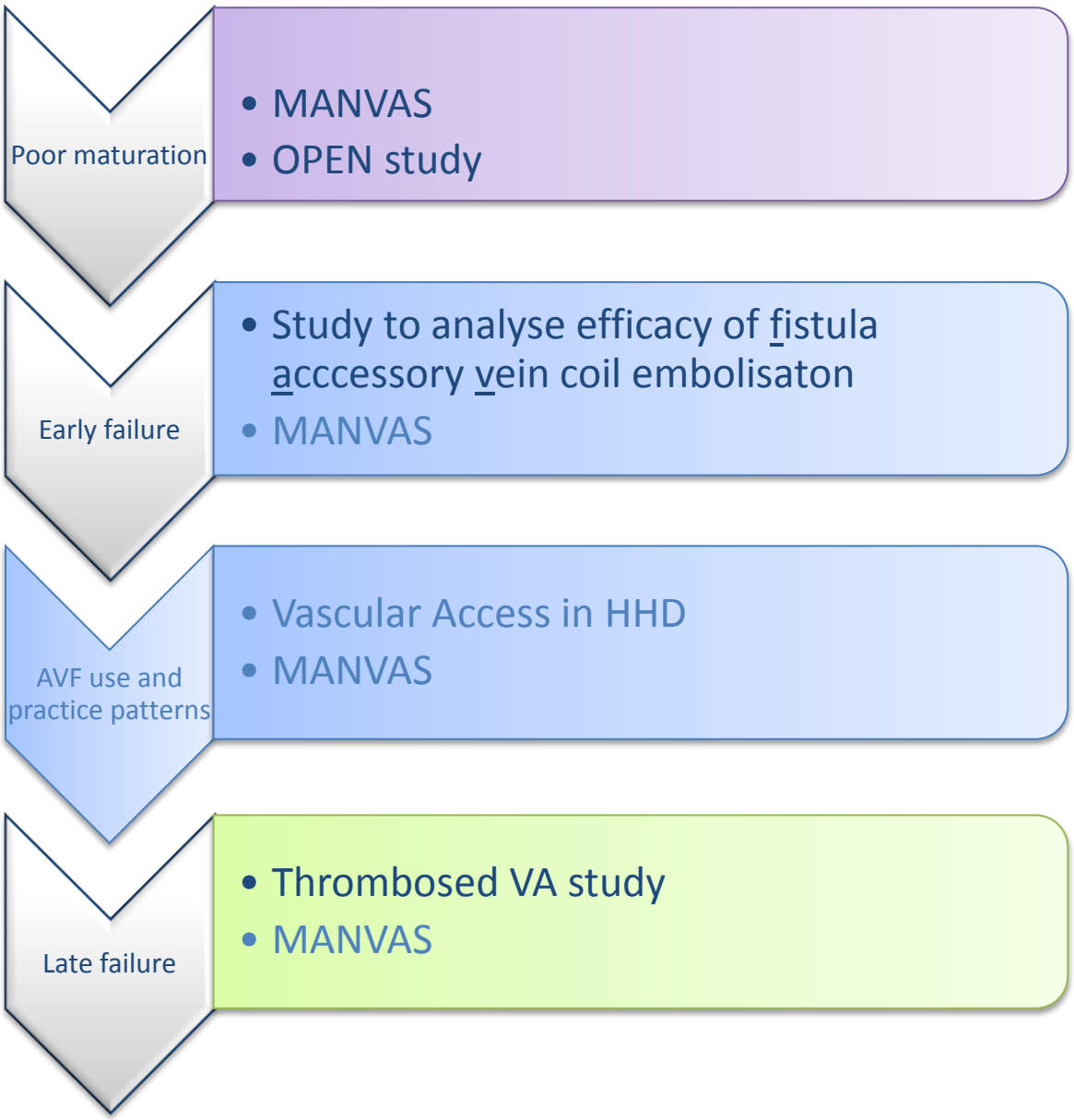

Figure 2-1: Clinical research studies undertaken during the MD, represented schematically alongside natural history of an AVF

2.2 Clinical studies undertaken during the MD

2.2.1 The MANVAS study

The Manchester Vascular Access study (MANVAS) is a prospective observational study to understand the natural history of AVFs and its maturation. The aim of the study is to describe natural history of AVFs and identify factors which can predict or influence outcomes. The study protocol design, ethics application, and NIHR CRN portfolio adoption application were all conceived, completed and led by myself as a part of this MD project. This multicentre longitudinal study is on-going and designed to evaluate long term outcomes. An analysis of available datasets of an initial cohort of study subjects is presented in this thesis.

2.2.2 The OPEN study

The Optiflow Patency and Maturation Study (OPEN) study was a prospective controlled pilot study designed to evaluate the safety and efficacy of the Optiflow™ device intervention addressing a major factor limiting maturation. All the study details including design, methodology, analyses and outcomes are described in the OPEN manuscript section in this thesis.

Candidate's role and involvement: I was responsible for study design, preparation of protocol, NRES ethics submission, study enrolment in the primary centre, overseeing data collection, data analysis and preparation of the manuscript.

2.2.3 Coil Embolisation study

Accessory draining veins (ADVs) can be found in up to 40% non-maturing AVFs and are considered to be the sole cause of non-maturation in over 15% cases.[19]

However, currently published studies on coil embolisation also report outcomes of patients having lesions other than ADVs in their AVFs. Moreover, all the reports focus on role of ADVs solely in early fistula failure (non-maturation).

The coil embolisation study was a retrospective study designed to analyse the initial outcomes and the results of longer term follow-up of patients who underwent endovascular coiling of accessory draining in AVFs. It also evaluates the role of ADVs in early as well as late failure of AVFs.

All the study details including design, methodology, analyses and outcomes are described in the coil embolisation manuscript section in this thesis.

Candidate's role and involvement: I was responsible for study design, patient identification, data collection, data analysis, writing the manuscript and manuscript submission.

2.2.4 Vascular Access in Home HD

Home HD has significant advantages over conventional thrice-weekly in-centre HD. [122-126] Availability of optimal vascular access is even more critical in Home HD self-care setting. Few recent reports have highlighted the importance of need for awareness towards VA issues in patients on HHD. [126, 127] However, there is distinct lack of literature on this topic.

VA in HHD is a study designed to outline the trends of VA outcomes from one of the largest HHD programmes in the UK with a wide spectrum of patients treated over a 5-year period. The aim is to determine incidence, prevalence, access patency

rates, practice patterns of VA use and its complications in a challenging clinical setting.

All the study details including design, methodology, analyses and outcomes are described in the VA in HHD manuscript section in this thesis.

Candidate's role and involvement: I was responsible for study design, patient identification, data collection, data analysis and preparation of the manuscript.

2.2.5 Acute vascular access failure studies

2.2.5.1 A prospective study of thrombosed haemodialysis vascular access and outcomes of endovascular salvage therapy

AV access failure as a result of thrombosis or occlusion is a common event and often leads to several undesirable events. Endovascular salvage techniques are the most commonly utilised ways of rescuing failed AV accesses. Whilst initial results are acceptable, longer-term results of endovascular salvage are quite poor. However, there are very few prospective studies reporting outcomes of thrombosed access salvage and those that are published have very small numbers. Moreover, very few studies have attempted to analyse factors which affect long term outcomes after salvage therapy.

In view of the length, the study is reported as 2 separate manuscripts. The first manuscript reports the epidemiology of access failure and salvage, along with long term outcomes of VA salvage. The second manuscript investigates risk factors and a risk scoring analysis developed to help predict outcomes of VA salvage.

All the study details including design, methodology, analyses and outcomes are described in each of these manuscripts in this thesis.

Candidate's role and involvement: I was responsible for generating the hypothesis, study questions, study design, patient identification, data collection, data analysis and writing the manuscript. Dr Jim Ritchie, my nephrology colleague helped me with statistical analysis for the second manuscript, in particular with developing the risk scoring system.

2.2.5.2 Meta-analysis of randomised trials comparing surgery versus endovascular therapy for thrombosed arteriovenous fistulas and grafts

Despite popularity of EVS for thrombosed VA, the jury is still out in terms of the best form of therapy. We, therefore, undertook a systematic review of the randomised trials comparing surgery to endovascular therapy. Surgical intervention forms a key part of vascular access interventions and therefore the above study was accompanied by a meta-analysis of randomised control studies comparing radiological and surgical interventions undertaken for the first time in vascular access salvage.

Candidate's role and involvement: This meta-analysis was conducted in collaboration with the co-authors, Mr Kuhan and Mr Antoniou, my vascular surgery colleagues, who were the primary authors in this publication. My role was instrumental in undertaking the literature search, analysing the studies that met the inclusion criteria, providing interventional and clinical nephrological input in the analysis, write up and review of the final manuscript. The manuscript was published in the Cardiovascular and Interventional Radiology Journal in June 2013.

Chapter 3: The MANVAS study

The Manchester Vascular Access Study (MANVAS): A prospective observational study to understand the natural history and identify factors associated with dialysis fistula maturation*

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* This manuscript requires study completion and more datasets after which it will be submitted as a completed manuscript for publication.

3.1 Abstract:

Background:

The Manchester Vascular Access study (MANVAS) is a prospective observational cohort study to understand the natural history of AV access for haemodialysis and its maturation. It was designed to examine the clinical, radiographic, and biological factors that affect outcomes or can help predict outcomes of AVFs.

Design, setting, participants and measurements:

I have led the development of the MANVAS study concept , design, write up, funding arrangements, training and infrastructure setup, and subsequent data collection during the tenure of my research. All patients undergoing AVF creation and satisfying the inclusion/exclusion criterion are prospectively recruited in the study. Extensive baseline information on demographics, co-morbidities, dialysis history, vascular access history and medication use is collected. All participants are required to undergo pre-operative vascular mapping and post-operative ultrasound / Doppler (US) follow up scans on their AVFs. Detailed surgical information is collected and participants are followed up for data collection related to any vascular access events, interventions, complications, use and HD information.

Results

The study was accepted on the National Institute Health Research Clinical Research Network (NIHR CRN) portfolio (study identification number 12048) and the scheduled completion date is 18 June 2015. I have analysed all datasets available (on 40 participants) at the time of writing this thesis. Mean age at the time of AVF

creation was 55 (± 15) years and 68% participants were men. Successful maturation was observed in 59% cases. Analysis of post-operative US examinations revealed that brachial artery flow rises rapidly after AVF creation, in those which mature. Successful maturation was associated with brachial artery volume flow ≥300ml/min measured at 2 weeks post AVF creation.

Conclusion

The MANVAS study aims to provide unique prospective data on natural history of AVF and its outcomes. It will test association of demographic, clinical and ultrasound variables with AVF outcomes. Moreover, the study will provide extensive data on UK practice patterns and may inform important clinical decision such as timing of post-operative follow up ultrasound examination.

3.2 Manuscript

3.2.1 Introduction

Native AV fistulae (AVFs) are the preferred vascular access due to reported low complication rates and greater longevity. The recently released UK Renal Association guidelines recommend that a target of 65% of incident patients should commence HD using an AVF.[64] High primary failure or non-maturation of AVFs is a major deterrent in achieving this target. In some series this has been reported to be as high as 40 – 50%.[62, 128] But once matured, they have a relatively longer operational life and a lower complication rate, especially from infections, when compared to prosthetic grafts (AVGs) and dialysis catheters.

MANVAS Study rationale

Despite the emphasis on placing AVFs, catheter use in incident patients has actually risen.[8] This is likely to be due to low maturation rates and problems with AVFs development in the early phase (3-12 months). Almost a third of patients dialyzing with a fistula will have a catheter placed within the succeeding 6 months.[129] Morbidity of AVFs in the early phase after maturation is also not well understood. Events in the early phase of AVF formation may influence long term AVF outcomes. However the natural history of AVF, especially in the early phase is poorly studied.

So far only a few factors which influence maturation outcomes of AVFs have been identified. Evidence for or against some of these factors is controversial (table 1-1). Many of these are non-modifiable and thus not amenable to therapeutic approaches. Factors such as vein diameter have been identified as a major determinant of

outcome but despite routine preoperative vein mapping, to circumvent the problem, the rate of AVF maturation remains abysmally low. Knowledge from recent interventional trials such as the Dialysis Access Consortium trial[5] has emphasised the importance of gaining better understanding of the natural history of AVF maturation. It is a complex process that involves firstly, several upstream and downstream haemodynamic changes and subsequently, structural adaptions of the vasculature and potentially the myocardium. These steps in-turn involve several biological processes.[32, 53] Thus, there is a need for robust prospective studies which specifically address the gaps in our knowledge of the process of maturation, identify factors affecting its outcomes and help develop further research concepts.

3.2.2 Study design and methodology

This is a non-interventional prospective observational cohort study. The study participants are adult (18 years and above) patients with advanced kidney disease (end stage kidney disease or chronic kidney disease stage 4/5) who have opted for haemodialysis and are having an AVF formed. The study aims to recruit up to 250 patients in total across the participating centres.

Primary hypothesis

Better understanding of the natural history and biology of AVFs, will help identify the factors affecting maturation.

Study procedures

Table 3-1 below describes study procedures that are carried out as part of MANVAS study and how these procedures are expected to help satisfy the study objectives, answer research questions or help in further research.

Subject selection

Inclusion criteria

1. The participant is in need of upper limb AVF for haemodialysis
2. Participant is available and can return for follow up visits

Exclusion criteria

1. Inability to give consent and comply with the study follow up schedule
2. Lower limb AVF procedures
3. Procedures involving prosthetic grafts

Primary outcome:

Successful (unassisted) maturation defined as either A or B

A> Use of the AVF with two needles for 75% HD sessions within a 4 week period, of which four consecutive sessions in which the mean dialysis blood pump speed is ≥300ml/min AND/OR spKt/V ≥1.4 or URR ≥70% (adopted from HFM study protocol)

B> Vein diameter of ≥0.4cm and fistula blood flow of ≥500ml/min AND AVF deemed 'mature' or 'usable' by experienced dialysis / vascular access nurse.

Study procedures	Time	Study objectives and *role of the study procedure/s*
Baseline demographics, co-morbidities, medication usage and clinical attributes (collected at enrolment)	Enrolment	Identify predictive factors – *clinical ± therapeutic utility*
Pre-operative blood – serum and DNA	Enrolment	Design nested studies to evaluate role of genetic factors / biomarkers - *Biology of maturation*
Vascular mapping	Pre-operative	Understanding of vascular anatomy, association with outcomes – *clinical*
Detailed surgical history	AVF creation	Identify surgical factors / practices associated with outcomes – *clinical / care process*
Pre-operative vein tissue obtained during surgery	AVF creation	Understanding vascular anatomy – *clinical / biology of maturation*
Serial blood samples – serum and blood	2 weeks and 6 weeks	Design nested studies to evaluate role of genetic factors / biomarkers - *Biology of maturation*
Post-operative US Doppler scans	2, 6 and 12 weeks post-operatively	Vascular anatomical and haemodynamic changes, ultrasound features associated with outcomes – *clinical, understanding natural history and biology of maturation*
Clinical follow up – dialysis use, events , interventions, etc.	Post-operative clinical follow up	Use of AVFs, longer term outcomes, complications and interventions – *clinical, therapeutic, care process and understanding natural history*

Table 3-1: MANVAS study procedures and their expected role in satisfying the objectives

Secondary outcomes

VA use outcomes: assisted maturation (defined as patency rate in patients requiring with surgical or radiological intervention), radiological / surgical interventions, time to first use of access, time to successful maturation, time to abandonment of AVF, thrombosis, access related complications, access related hospitalization episodes

Ultrasound outcomes: Blood flow, diameter, depth, presence of lesions such as stenosis

Maturation at 6 week: Using a composite of US (flow ≥ 500ml/min and diameter ≥ 0.5 cm) and/or clinical endpoints (successful use on dialysis with two needles and dialysis pump speed of ≥ 300 ml/min) maturation will be assessed at 6 weeks.

Statistical methods

Parametric data are presented as mean ± standard deviation and non-parametric data as median [interquartile range]. Between groups, comparisons for categorical variables were made using Chi-squared test and ANOVA appropriate to the distribution of the data for continuous variables. For variables with non-normal distribution, independent samples Mann-Whitney U test was used.

Multivariate analysis using binary logistical regression (forward stepwise likelihood ratio) was used to identify factors associated with successful maturation. Choice of variables included in the multivariate model was based on results of univariate analysis and from clinical experience. Results are expressed as odds ratio (OR) [95% CI].

SPSS version 20 (IBM Inc, USA) licenced to the University of Manchester was used for all analysis.

Results of interim analysis:

At the time of writing this thesis, partial datasets are available for 40 patients enrolled in the study. Forty-one AVFs were created in these 40 patients with one patient having 2 AVFs created. Mean age (± SD) at the time of AVF creation was 55 (±15) years. Over a third of patients undergoing AVF creation were males (68%). Only 3 patients had planned 2-step surgical procedures. Thirty per cent patients were diabetic. Other than renal disease, hypertension was the most prevalent co-morbidity in this cohort (>70%). Prevalence of previous or current smoking history was also high at 60%. Thirty six per cent patients were active on the transplant list at the time of AVF creation.

In 85% patients, the study access was the first fistula or graft. In over 40% patients, there was an indwelling tunnelled dialysis catheter at the time of surgery (internal jugular vein). However, in none of these patients was the AVF placed in the side ipsilateral to the tunnelled catheter. Patient characteristics depending on site of access created are presented in table 3-2 below.

Variable	Forearm group (n=24)	Upper arm group (n=16)	P value
Age	54.5 ± 17	55.7 ± 12	0.44
Proportion of males (%)	80	50	0.04
Previous AV access (%)	94	66	0.048
Indwelling catheter (%)	56	78	0.62
Diabetics (%)	27	37	0.4
Pre-operative arterial size (cm)	0.26 ± 0.1	0.36 ± 0.1	0.04
Preoperative vein size (cm)	0.21 ± 0.08	0.31 ± 0.1	0.33

Table 3-2: Comparison of clinical characteristics in the forearm vs upper arm AVF group

Pre-operative vein mapping

All patients underwent pre-operative vascular mapping. Mean artery and vein sizes were 0.29 (±0.11) cm and 0.25 (±0.09) cm, respectively.

AVF creation surgery and types of AVFs placed

All patients in this cohort underwent AVF creation under local anaesthesia. The responsible consultant surgeon performed the anastomosis in 22% cases and in another 15% the consultant surgeon performed the anastomosis in conjunction with trainee surgeons. In 63% cases, the anastomosis was performed by non-consultant grade surgeons. Over 80% AVFs were created in the non-dominant upper limb. Sixty-one per cent of patients had AVF created in the forearm region.

Follow-up

One patient was transplanted early after AVF creation and 1 patient withdrew from the study for personal reasons. Complete follow up data for analysing maturation as an outcome were available on 36 patients. Using a composite of US (flow ≥ 500ml/min and diameter ≥ 0.5 cm) and/or clinical endpoints (successful use on dialysis with two needles and dialysis pump speed of ≥ 300 ml/min), 59% AVFs could be classified as mature (n=20). Fifteen of these patients had successful dialysis and rest (n=5) were not on HD at the time of assessment. Median time to first needling from date of creation was 13 weeks. Comparison of clinical attributes in mature vs non-mature AVF cohorts is presented in the table 3-3 below.

Higher rate of maturation was observed in the dialysis group as compared to the pre-dialysis group although this observation did not reach statistical significance.

Variable	Maturation at 6 weeks		P value
	Mature (n=20)	Non-mature (n=16)	
Age ± SD	56.4 ± 14.9	52.5 ± 18.2	0.58
Males (%)	57	80	0.16
Caucasian race (%)	64	70	0.97
Proportion of diabetics (%)	64	68	0.81
Smokers (%)	57	30	0.73
Indwelling catheter (%)	29	50	0.41
Pre-dialysis (%)*	50	79	0.09
Forearm location (%)	64	55	0.33
Presence of thrill post-operatively (%)	79	95	0.23
eGFR (pre-dialysis cohort) ± SD (ml/min)	8.3 ± 3.7	11.5 ± 4.6	0.54
Haemoglobin (g/dL) ± SD	11.8 ± 1.2	11.3 ± 1.4	0.47
Albumin (g/L) ± SD	39.8 ± 3.8	38.3 ± 6.5	0.33

Table 3-3: Comparison of clinical features in the mature vs non-mature group

Post-operative US follow up

Consistent with reports in the literature, our data shows that blood flow in brachial artery rises rapidly after AVF creation. In the participants in whom all 3 scan data was available, the changes to brachial artery flow are depicted in the figure 3-1

below. Comparison of ultrasound features in the mature vs non-mature AVF is presented in table 3-4.

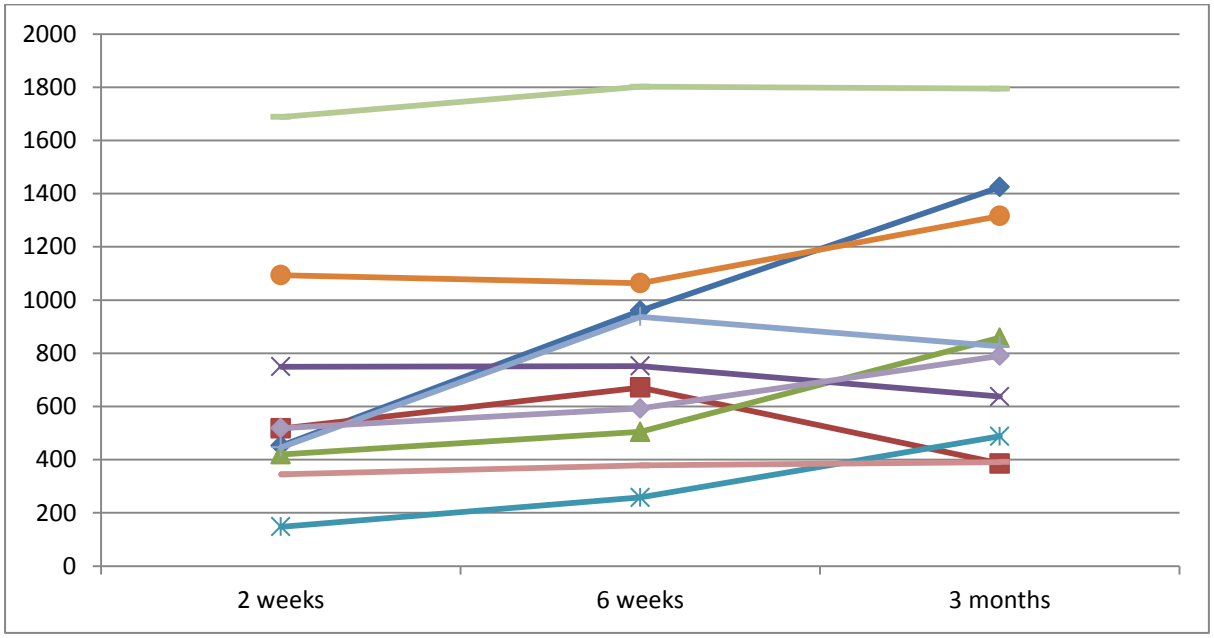

Figure 3-1: Serial changes to brachial artery flow on US. X-axis depicts flow in ml/min

Ultrasound variable	Maturation at 6 weeks		P value
	Mature (n=20)	Non-mature (n=16)	
Preoperative arterial size ± SD (mm)	3.3 ± 0.1	2.8 ± 0.1	0.2
Preoperative vein size ± SD (mm)	2.5 ± 0.1	2.5 ± 0.05	0.4
Presence of arterial calcification on pre-op US (%)	25	17.6	0.59
Brachial artery flow at 2 weeks ± SD (ml/min)	580 ± 243	322 ± 245	0.025
Brachial artery flow at 6 weeks ± SD (ml/min)	576 ± 442	171 ± 228	0.02
AVF volume flow at 2 weeks ± SD (ml/min)	580 ± 243	417 ± 218	0.06
Maximum AVF diameter at 2 weeks ± SD (mm)	6.1 ± 0.14	6.7 ± 0.43	0.8
AVF volume flow at 6 weeks ± SD (ml/min)	739 ± 420	512 ± 408	0.17
Maximum AVF diameter at 6 weeks ± SD (mm)	7.2 ± 0.2	7.6 ± 0.6	0.9

Table 3-4: Comparison of ultrasound features of mature vs non-mature AVFs

Features on ultrasound at two weeks

Significant changes can be detected on US as early as 2 weeks after AVF creation. Mean AVF diameter at 2 weeks was 6.2 ± 2.4 mm. Mean change in vein diameter at the 2 weeks US was 3.3 ± 2.1 mm. Mean blood flow in the brachial artery at 2 weeks was 490 ± 269 ml/min.

Results of multivariate analysis

Multivariate analysis was performed using binary logistical regression to investigate clinical factors associated with successful maturation at 6 weeks and US features of success maturation. Variables included in the model were age, gender, diabetic status, site of fistula, pre-operative artery size, pre-operative vein size, mean AVF flow, AVF diameter and brachial artery flow.

Only brachial artery flow ≥ 300 ml/min at 2 weeks was associated with higher maturation rate (OR 14, 95% CI 1.4 – 150, p=0.035) as was flow > 400 ml/min at 6 weeks (OR 7, 95% CI 1.5 – 32, p=0.013)

Complications

Early failure or non-maturation often associated with presence of thrombosis was the most common complication of AVF formation followed by wound infection (10%, n=4). One patient experienced arm oedema ipsilateral to the side of AVF creation, which persisted for >2 weeks.

3.2.3 Discussion

Vascular access complications lead to significantly poor patient survival and increased hospitalisation.[50] Our understanding of the biology/physiology and clinical history of AVF maturation is deficient in a number of areas. There remains considerable variation in clinical practice across various centres worldwide, and in the UK. There is no consensus even in definition of what constitutes 'a mature AVF'. The MANVAS study is one of first large scale multicentre prospective epidemiologic study to be conducted in the UK and Europe. The study brings together a variety of approaches to further our understanding of AVFs and help develop other clinical and biological research on this topic.

In this interim sub-cohort analysis of MANVAS study, no differences in traditional clinical phenotype of maturing vs non-maturing AVFs could be detected. This finding highlights the current difficulties faced by clinicians in risk stratification. Brachial artery flow at 2 weeks after AVF creation was found to be strongly

associated with higher maturation rate. In view of the relatively small numbers in this interim analysis, the CIs for the OR are expectedly wide. However, this finding is still potentially significant and suggests that important haemodynamic changes can occur very early in the course of AVF creation, an observation previously noted in the literature.[53]

High blood flow in an AVF is likely to be marker of good endothelial function. High blood flow is directly proportional to wall shear stress (WSS) and high WSS leads to endothelial quiescence and survival. This is the favoured profile for AVF maturation.[22, 55, 83] Furthermore, increase in blood flow requires vessel dilatation (Pouseuille's law) which in-turn is dependent on endothelial function and secretion of mediators such as NO. Clinically, higher blood flow in the brachial artery is required to ensure high flow in the fistula, which is an essential pre-requisite for maturation and supporting dialysis. Thus detection of high brachial artery blood flow is marker of favourable upstream biological events and may be a harbinger of desirable downstream events which ultimately lead to fistula maturation.

In the absence of other non-invasive techniques, ultrasound examination remains the only available modality to assess these vascular changes. Traditionally follow-up ultrasounds have been performed around 6 – 8 weeks to assess for maturation. Whilst brachial artery and AVF flow at this time point is also associated with maturation[130], valuable time is lost by this stage in identifying poorly maturing AVF, thus resulting in an increase in catheter incidence.

If the association between brachial artery blood flow and maturation is confirmed in the larger MANVAS cohort and other populations, it would be an extremely useful clinical tool for timely prediction of maturation outcomes. This would in turn help to plan timely interventions.

The higher rate of maturation in the dialysis group compared with the pre-dialysis group, although not reaching statistical significance may be a clinically significant finding. Uraemia impairs endothelial function[86] and is associated with worse AVF outcomes in animal models.[91] Improvement in the uraemic state due to dialysis may be the explanation for this observation. This observation highlights the importance of understanding biological mechanisms underlying AVF maturation

3.2.4 Conclusion

The MANVAS study can yield valuable data on AVF natural history, maturation and outcomes in an UK setting. The non-interventional observational study design will reflect natural clinical practice patterns and outcomes in a non-trial multidisciplinary setting. Data from pre-operative and post-operative US examinations will be invaluable in determining associations with important clinical outcomes. The study and its findings will also help develop further research in this area.

In this interim analysis, presented on a sub-cohort, brachial artery volume flow data indicate favourable haemodynamic parameters associated with good outcomes occur early in the course of natural history. Moreover, very early (2 week) brachial artery volume flow measurement post AVF formation may be a strong determinant

of good outcomes, and this finding must be confirmed in larger numbers in the study. If confirmed this would be a valuable metric in predicting success and for planning timely interventions.

Chapter 4: The OPEN study

Creation of arteriovenous fistula using the novel the Optiflow™ device – Results from the Optiflow™ Patency and Maturation (OPEN) study†

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4.1 Abstract

Background:

Arteriovenous fistulae (AVFs) maturation remains a significant clinical problem with reported early failure rates of up to 60%. Sub-optimal haemodynamics and variable surgical skills and technique are widely believed to contribute to majority of AVF non-maturation. The Optiflow™ is a novel anastomotic device placed in-situ which has the potential for improving haemodynamics and reducing the dependence on surgical skill for creating successful mature AVFs. The OPEN study (Optiflow PatEncy and MaturatioN) is a prospective controlled pilot study designed to investigate the safety and performance of the Optiflow™ device.

Design, setting, participants and measurements:

AVFs were created using the Optiflow™ device in an end-to-side configuration using a 3 or 4mm device. Forty-one patients underwent AVF formation using the Optiflow™ device and 39 age and gender matched control subjects using standard technique. Patients were recruited prospectively and followed for 90 days following AVF creation. Maturation was defined as an outflow vein with diameter ≥ 5mm and blood flow ≥500ml/min measured via Doppler ultrasound. Patency was determined by clinical evaluation as presence of audible bruit throughout the cardiac cycle, which is present at least 8 cm downstream to the anastomosis.

Results:

Primary unassisted maturation rates at 14, 42 and 90 days were 76%, 72% and 68% respectively for the Optiflow group and 67%, 69% and 75% respectively in the

control group (p-ns). The primary patency rate at 90 days for the Optiflow and control group was 78% and 82% respectively (p=ns). The outcomes of the 4mm device group were superior even when adjusted for pre-operative vessel size. When compared to the control group there was a trend to earlier maturation in the 4mm device group, after adjusting for pre-operative vessel sizes.

Conclusions:

The high maturation rates in the fistulae created using device (Optiflow™) are encouraging. Maturation results for both the device and control groups were highly favourable when compared to historical unassisted maturation rates of approximately 50%. The Optiflow™ appears to be safe, effective and successful in creation of AVFs with high maturation rates.

4.2 Manuscript

4.2.1 Introduction

Haemodialysis (HD) is a lifesaving and life sustaining treatment. Effective HD requires a reliable, long-term and safe vascular access. Native AV fistulae (AVFs) are the preferred vascular access in view of the low complication rates and longevity. AVFs are however, plagued by high early failure rates. In some series this has been reported to be as high as 40-60%.[1, 5, 62, 131] But once matured, they have a relatively longer operational life and a lower complication rate, especially from infections, when compared to prosthetic grafts (AVGs) and dialysis catheters.

Failed or inadequate vascular access is a significant cause of morbidity and mortality in haemodialysis patients.[50] The standard technique for creating an arteriovenous fistula (AVF) involves a hand sutured surgical anastomosis between the artery and vein. The outcome is dependent upon the surgical technique, vessel characteristics, regional anatomy, and healing response of the patient, all of which can be highly variable. Studies also indicate that operator experience has a major impact on procedure success with less experienced surgeons having hazard ratios more than triple those of their more experienced colleagues. [132-137]

Optiflow™ (Bioconnect Systems, Ambler, Pennsylvania, USA) is a novel anastomotic connector made of highly non-thrombogenic siliconised polyurethane, designed to standardise the surgical creation of AVFs (figures 4-1 and 4-2). The device is intended to optimise the haemodynamics of the anastomotic region, and to "shield" the juxta-anastomotic area from adverse effects of shear stress.

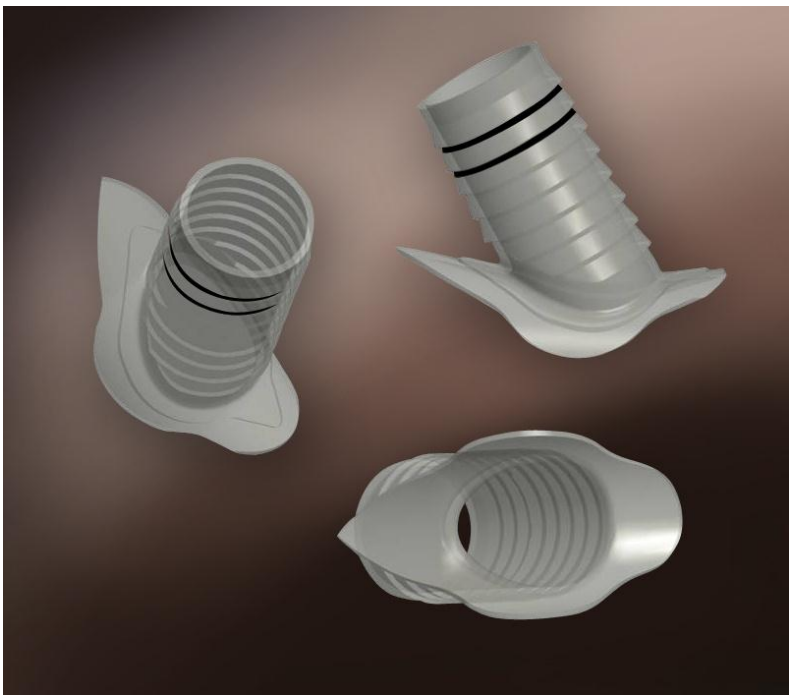

Figure 4-1: Schematic representation of the Optiflow device

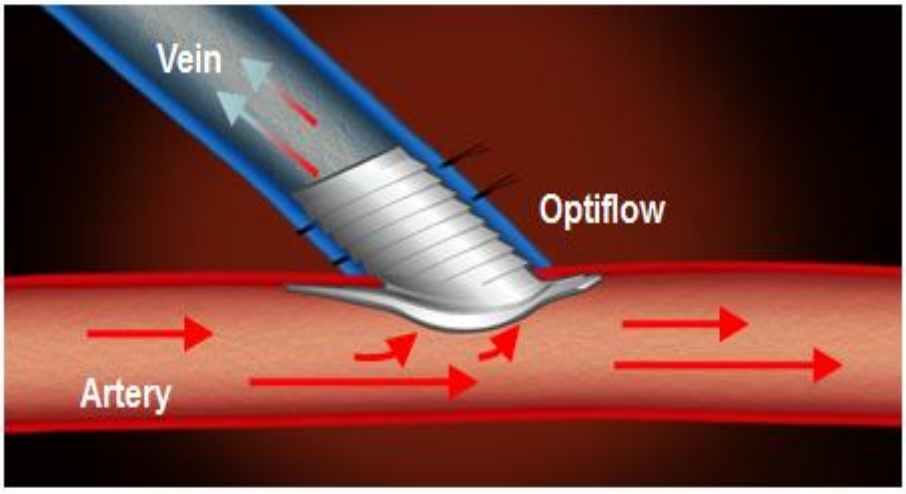

Figure 4-2: Schematic diagram of an in-situ Optiflow device

4.2.2 Materials and Methods

Study population

The Optiflow Patency and Maturation (OPEN) study was set up as a pilot study to evaluate the safety and efficacy of the Optiflow™ device (CE) in creating AVFs. The study design was a multi-centre non-randomized prospective controlled study. The main objective was to evaluate the safety and performance of the Optiflow anastomotic connector in comparison to AVFs using standard hand-sewn surgical techniques without the device. The pilot phase was intended to demonstrate safety, performance and early experience of use in the clinical setting, but not powered to detect differences between the two study groups.

The study received ethical approval from the UK National Research Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki and institutional good clinical practice framework. All participants underwent informed consent process in accordance with UK National Research Ethics Service requirements.

The study participants included all adult (18 years and above) patients with advanced kidney disease (end stage kidney disease or chronic kidney disease stage 4/5) who have opted for haemodialysis and planned for formation of AVF as part of routine standard care. Forty-one participants were recruited to have an Optiflow™ AVF in the treatment arm and 39 participants were recruited in the control arm (matched for age and sex). The patients in the control arm underwent AVF formation using standard surgical technique (end-to-side) AVF. All patients

underwent AVF formation in the upper arm / elbow region such that the brachial or proximal radial artery was used as the feeding artery (figure 4-3).

Study Design

The primary safety endpoint was the rate of serious adverse events (SAEs) during the follow-up period, approximately 90 days after surgery.

The primary performance endpoint was successful maturation, defined as an outflow vein, which is equal to or greater than 5 mm in diameter and with flow equal to or greater than 500 ml/minute as measured via ultrasound.

The secondary performance was patency as determined by clinical examination. Patency was defined as the presence of a bruit audible with a stethoscope throughout the cardiac cycle detectable along outflow vein at least 8 cm proximal (downstream) from the anastomosis. The key inclusion and exclusion criteria used to enrol patients for the study can be found in the supplementary material.

Failure to mature (FTM) risk score was calculated for each group as described by Lok et al.[78]

Surgical Procedure and Peri-operative Protocols (Figure 4-3)

Two dedicated surgeons created all Optiflow AVF's. The control AVFs were created by a team of highly experienced surgeons that included the former two surgeons. The surgical team were specifically trained to insert the device leading up to the study. All AVFs were created in the two study centres. Anastomotic technique was end-to-side in all cases and vessels with internal diameter of ≥ 3 mm were selected based on pre-operative vein mapping and intra-operative confirmation. All

participants undergoing AVF creation using the implant were given a pre-operative antibiotic (Amoxicillin/Clavulinic acid or equivalent) and were required to take aspirin (unless contraindicated) for the study duration. The patient pre-operative preparation and post-operative care was same for both the groups. Further detailed information on surgical technique for AVF creation using the device can be found in the supplementary material.

Figure 4-3: Intra-operative photograph of a newly created AVF using the Optiflow device

Statistical Analyses

SPSS version 20 (IBM Inc., USA) licenced to the University of Manchester was used for statistical analysis. Chi square test and independent sample t test was used to detect difference between the groups in case of variables which were normally distributed. For variables with non-normal distribution, independent samples Mann-Whitney U test was used. Multivariate analysis using binary logistical regression was used to identify factors associated with AVF success.

4.2.3 Results

Forty-three patients were enrolled in the Optiflow group and 39 into the control group matched for age and gender. Forty-one patients underwent AVF creation using the Optiflow device. Two cases were excluded as vein sizes were found to be unsuitable for AVF creation intra-operatively. In the Optiflow group, 11 patients had the 3mm device and 30 patients had the 4mm device. A single patient from the control group withdrew consent for study continuation before the 14 days ultrasound and follow up was performed. Patient characteristics for each group are presented in Table 4-1.

Characteristic	Optiflow™ group (n=41)	Control group (n=39)	P value
Males (%)	61	53	0.26
Age (mean ± SD)	67 ± 16	63 ± 15	0.24
Caucasians (%)	76	62	0.23
Vascular disease score (mean ± SD)	1.25 ± 1.09	1.09 ± 0.95	0.42
Lok (FTM) score	2.94 ± 1.76	3.27 ± 2.35	0.444
Study fistula as first vascular access (%)	45.2	35.9%	0.496
Diabetics (%)	57	56	1
Previous dialysis catheter use (%)	47.6	61.5	0.27
Pre-operative vein diameter (mean ± SD)	3.87 ± 0.6	3.71 ± 0.8	0.04
Pre-operative arterial diameter (mean ± SD)	3.9 ± 0.5	3.6 ± 0.8	0.007

Table 4-1: Patient characteristics in device and control groups

Time-point	Maturation rates in respective group (%)		p value
	Control group (n=39)	Optiflow group (n=41)	
14 days	67	76	0.31
42 days	68	72	0.84
90 days	76	68	0.47

Table 4-2: Unassisted maturation rates

Time-point	Patency rates in respective group (%)		p value
	Control group (n=39)	Optiflow group (n=41)	
14 days	89	93	0.09
42 days	87	88	0.77
90 days	82	78	0.18

Table 4-3: Unassisted patency rates

The average blood flow rates (± SD) at 14, 42 and 90 days were 961 ml/min (± 545), 957 ml/min (± 619), and 1087 ml/min (± 910) in the Optiflow™ group and 739 ml/min (± 354), 828 ml/min (±362) and 874 ml/min (±397) in the control group ($p>0.1$) respectively. The average diameters at 14,42 and 90 days, in the venous segment intended for cannulation were 6.1 mm (±1.1), 6.7 mm (±1.6), and 7.2 mm (±1.7) in the Optiflow group and 6.2 mm (±1.1), 6.8 mm (±1.3) and 7.4 mm (±1.6) in the control group ($p>0.1$) respectively. At 90 days, successful dialysis using the study fistula was achieved in 41% patients in the implant group and 42% patients in the control group.

Results for primary outcome of unassisted maturation for both groups are presented in table 4-2. Patency rates in both groups are presented in table 4-3.

In a multivariate analysis, using binary logistical regression gender was the only variable found to be associated with 42 day and 90 day unassisted maturation. Females appeared to a higher risk of AVF failure with hazard ratios at 42 and 90 days being 5.8 (95% CI 1.8 – 18.6, p=0.003) and 4.95 (95% CI 1.29 – 19, p=0.02) respectively.

Impact of implant size

The outcomes of 4mm devices were superior to the outcomes of 3mm device. Unassisted maturation at 42 days was 40% and 84% in the 3mm and 4mm implant size group ($p<0.01$). This effect persisted even when adjusted for preoperative arterial and venous diameter in a binary logistical regression model (OR 0.13, 95% CI 0.03 – 0.63, p=0.01, n =41)

When the outcomes (unassisted maturation) of control group were compared to those of 4mm device group (adjusted for pre-operative vessel sizes), there was a trend towards higher maturation rate and earlier maturation with the 4mm device, as depicted in table 4-4 below.

Time-point	OR	95% CI	p value	n
14 days	4.1	1.03 – 16.4	0.04	67
42 days	1.5	0.42 – 5.6	0.5	68
90 days	0.98	0.29 – 3.3	0.97	67

Table 4-4: Results of comparison of unassisted maturation rate between 4mm device and control group (adjusted for pre-operative vessel size)

Adverse events:

Twenty-three (23) SAEs were reported (14 in device and 9 in control group). Two instances of SAEs namely an episode of haematoma formation and an episode of post-operative bleeding were related to the AVF creation surgery. There were no SAEs related to device insertion. Acute thrombosis or failure was observed in 7% (n=3) of the patients in the implant group and 5% of the patients (n=2) in the control group. SAEs were defined as any untoward medical occurrence that results in death, is life threatening, or requires in-patient hospitalization or prolongation of an existing hospitalization. There were two SAEs classified as life threatening – an episode of pulmonary oedema and an episode of acute coronary syndrome. Neither event was classified as related to device insertion or AVF creation. One of study participants in the Optiflow group was re-hospitalised and reported as an SAE on four occasions for low haemoglobin, unrelated to the device.

4.2.4 Discussion

Arteriovenous fistulae are the most preferred HD access in view of the low complication rates, longevity and reduction in patient morbidity and mortality.[2, 27, 28, 138-141] However, primary or early failure in AVFs remains unacceptably high and

there are currently no effective therapies. The Dialysis Access Consortium (DAC) led trial, suggested the use of clopidogrel to reduce the rate the early thrombosis, but there were no significant difference in the treatment vs control group in the number of fistulae suitable for cannulation for dialysis between the two groups.[5]

It is believed that suboptimal haemodynamics, surgical technique, and the operating surgeon have a significant impact on maturation rates. There is significant evidence highlighting the impact of surgical skill and experience on success of arteriovenous fistula formation. [133, 136, 137]

Creation of the arteriovenous anastomosis is a fundamental first step towards a good outcome on haemodialysis. End-to-side is the most preferred technique since its first description by Rohl et al in 1968.[142] As available surgical skill and experience vary between kidney centres, optimal technique development is time dependent and can take years of practice. This variability can significantly influence AVF outcomes and may be an easily modifiable factor. Means of standardising anastomosis creation are therefore urgently needed. The Optiflow™ device provides a new opportunity for creating a standard anastomosis with a well-defined lumen size. The juxta-anastomotic area is one of the commonest areas of stenosis resulting in early failure of an AVF.[22, 143] Optiflow™ device can offer anatomical shielding of this critical important area and thus may also have an impact on early failure too.

The Optiflow™ device offers potential other advantages over standard surgical technique. By standardising anastomotic size and preventing future enlargement of

the anastomosis, the Optiflow™ device, in theory, may reduce the risk of steal and / or high flow fistula.

In both the study groups, surgeons highly skilled and experienced in formation of AVFs performed the fistula creation. This study was designed to provide initial data on safety and performance, but was not powered to detect differences between the two study groups. Whilst there is no statistical difference in the primary patency between the implant and control group, there was a trend towards higher average vein diameter, higher average volume flow at 42 days and improved patency in the implant group. However the outcomes of the 4mm device were superior hand-sewn technique in the control group even when adjusted for pre-operative vessel size. There was also a trend to earlier maturation in the 4mm device group when compared to the control group (adjusted for pre-operative vessel size).

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Study limitations

The primary endpoint was ultrasound measurements as opposed to successful cannulation. However, dialysis use of the study fistula was measured where possible and the ultrasound measurements obtained have been shown to correlate well with AVF cannulation success.[130] Confounding errors and selection bias in the groups cannot be reliably excluded. As this was a pilot evaluation of the technology, the patient numbers were relatively small. Larger study comparing long term outcomes will advance further knowledge and the potential of the application of the device in routine clinical practice.

4.2.5 Conclusions

The Optiflow™ device is a novel anastomotic connector and one of the first available technologies in improving creation and maturation rates of AVFs. This study demonstrates safety and efficacy of the Optiflow™ device as a technology for creation of AVFs. High success and patency rates with the use of the device comparable to highly skilled surgical practice provides the reassurance in the technology and underlines its potential role in standard clinical practice. The advantages of Optiflow™ device over standard hand-sewn fistulae such as an anastomotic area with well-defined lumen diameter, potential shielding of the juxta-anastomotic region and less dependence on available surgical expertise in AVF creation, is attractive and provides an exciting opportunity for improving AVF outcomes in haemodialysis. Larger studies are needed to establish the superiority of device assisted maturation over conventional hand-sewn fistulae and its impact in routine clinical practice.

4.2.6 Supplementary material

4.2.6.1 Inclusion criteria

All the following criteria must be met:

1. The participant requires long-term access for haemodialysis via an arteriovenous fistula in the upper extremity.
2. The participant is available and can return for follow-up visits during the 90-day study period.
3. The participant is a candidate for a hand-sewn fistula as determined by pre-operative and intra-operative assessment.
4. The artery and vein inner diameters of the participant at the intended access site are at least 3.0 mm as determined by pre-operative ultrasound and confirmed intra-operatively.
5. The anastomosis configuration is an end of vein to side of artery.
6. The participant has understood the Informed Consent and has agreed to participate in the study.

4.2.6.2 Exclusion criteria

A candidate for participation in the study must not have ***any*** of the following conditions or a history of the following

1. The participant has a known coagulation disorder (e.g. haemophilia or Von Willebrand's disease) including a history of deep venous thrombosis (DVT).
2. The participant has a history of two or more access site failures due to anatomical or pathological abnormalities of artery and/or vein.
3. The participant has a history of previous steal syndrome from a haemodialysis vascular access.
4. The participant is participating in another clinical study that may interfere with compliance to this study protocol.

5. The participant is scheduled to have surgery requiring general anaesthesia within 90 days after study enrolment.
6. The participant has a history of intravenous drug use.
7. In the opinion of the investigator, the participant is likely not to comply with the protocol or the participant has a medical condition that should exclude the participant from the study.
8. A transposition of the vein is anticipated for vascular access.
9. The participant has evidence of an active or suspected infection or a history of local or systemic infection within one month of screening.

4.2.6.3 AVF creation surgery

Anastomotic technique was end-to-side in all cases and vessels with internal diameter of ≥ 3 mm were selected based on pre-operative vein mapping and intra-operative confirmation. All participants undergoing AVF creation using the implant were required to have a prophylactic antibiotic (Amoxicillin/Clavulinic acid or equivalent) and were required to take an antiplatelet agent (unless contraindicated) for a minimum duration of 3 months post-procedure.

In cases of Optiflow™ fistulae, the brief description of creation is as follows:

Using standard techniques, the target artery and vein are exposed. The vein is ligated approximately 5 cm distal to the anticipated site of anastomosis and device implantation. Appropriate device size (3 or 4 mm) is selected based on measurement of the arterial and venous internal diameter. The vein is cut adjacent to the distal ligation and implant prepared by submerging in 0.9% sodium chloride solution.

Implant is carefully removed from the pre-assembled packaging instrument and loaded onto a retractable vein delivery instrument.

The implant is introduced into the vein using the retractable vein delivery instrument. The long flange of the device is aligned for properly into the artery.

The implant is secured in the vein with two independent 3-0 silk suture ties (one near the centre of the conduit and the other near the end of the conduit) ensuring that the suture is tied securely to the conduit.

The anvil of the implant is retracted on the vein delivery instrument ensuring that the implant remains within the vein and is properly positioned in the vein to create the anastomosis.

The vein/implant is aligned to the artery to determine the appropriate position for the arteriotomy. This location is marked with a sterile pen.

Flow in the artery is temporarily restricted followed by making a stab incision at the preferred site for the arteriotomy.

In case of a 3 mm implant the arteriotomy incision is enlarged to 1.5 mm. In case of a 4 mm implant the arteriotomy incision is enlarged to 2.5 mm

Arteriotomy is created using the appropriately sized aortic punch (2.0 mm punch for the 3 mm implant or 2.8 mm punch for the 4 mm implant).

A 6-0 Prolene stitch is inserted across the arteriotomy and is used later to secure the artery to the vein. The suture is not tied and left loose inside the artery so that it does not interfere with the delivery of the implant.

Using the template, the implant flanges are secured in the angled tipped forceps and then the long flange/forceps tip of the implant is inserted into the arteriotomy. While stabilizing the long end of the implant in the arteriotomy, the short flange of

the implant is carefully advanced into the arteriotomy such that the long flange faces opposing to the direction of blood flow (retrograde) and the short flange faces in the direction of blood flow (antegrade).

Using the longitudinal line on the vein as a reference, it is ensured that the vein is not twisted or kinked when the implant is inserted within the artery. After the flanges are completely within the artery, the implant is released and the angled forceps is removed.

The arteriotomy is tied using a 6-0 Prolene security suture ensuring that the suture is not under the short flange before tying.

Before cutting the free end of the suture, the end of the vein is secured with the remaining suture. This suture is then tied to secure the end of the vein to the artery making sutures the suture does not go through the implant

Flow in to the artery and vein is restored

The resulting end-to-side anastomosis is examined for leaks and to confirm flow through the anastomosis ("thrill"). The incision is closed as per standard surgical technique.

Chapter 5: The coil embolisation study

Arteriovenous fistula failure: Is there a role for accessory draining vein embolisation?‡

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5.1 Abstract:

Purpose:

Arteriovenous fistulae (AVFs) are accepted as the best form of haemodialysis vascular access (VA) but are plagued by high primary failure. Accessory drainage veins (ADVs) may account for up to 40% of these failures. Furthermore, they may also lead to low flow in 'mature' AVFs.

Methods:

We analysed the results of 42 patients who underwent endovascular coiling of ADVs at our centre over a 4-year period.

Results:

Indications were failure to mature in 34%, low flow or cannulation difficulty in 56% and thrombosis in 10% of cases. 95% procedures involved a combination of angioplasty and coiling with only 5% patients having coiling of ADV alone. Forearm AVFs constituted the majority of the cases as opposed to upper arm AVFs (74% vs. 26% respectively). Primary patency rates at 3, 6, 12, 18 and 24 months were 90%, 87%, 76%, 70% and 55%, respectively. Successful dialysis was achieved in 10 of the 14 fistulae that had hitherto failed to mature. Coil migration was observed in 1 patient, which led to fistula occlusion.

Conclusion:

Coil embolisation of ADVs is an effective treatment option for dysfunctional fistulae that can be performed at the same time as angioplasty.

5.2 Article

5.2.1 Introduction

Haemodialysis (HD) is a lifesaving and life sustaining treatment. Effective HD requires a reliable, long-term and safe vascular access. Native arteriovenous fistulae (AVFs) are the preferred vascular access in view of the low complication rates and longevity.[27, 28, 139, 144, 145] AVFs also reduce patient morbidity and mortality.[2, 140, 141] AVFs are therefore recommended first choice HD access by most national and international guidelines.[4, 146, 147] The UK renal association recommends a target of 65% and 85% AVF use in incident and prevalent HD patients respectively. AVFs are however, plagued by high early failure rates. In some series, this has been reported to be as high as 30 - 40%.[131, 148] But once matured, they have a longer operational life and a lower complication rate, especially from infections, when compared to prosthetic grafts (AVGs) and dialysis catheters.

Fistula failure has been classified as early or late. Accessory draining veins (ADVs) may contribute to up to 40% of cases of early failure.[19, 149] Late failure usually results from reduction in flow across the fistula. The commonest cause of low flow is vein stenosis [19, 150] but it may also result from arterial disease or systemic factors such as hypotension or volume depletion. ADVs divert flow away from the target vein and can result in low flow. In a mature AVF, a hitherto clinically 'silent' ADV can become clinically relevant due to development of another lesion such as venous stenosis. Presence of a downstream stenosis may facilitate flow preferentially to the ADV. Correction of the stenosis may not always lead to resolution of the ADV in

such cases and if low flow persists, obliteration of the ADV may be helpful. Surgical ligation of AVFs has been shown to be effective.[151-154] Nassar et al have also reported successful outcomes of endovascular coiling in their series of endovascular treatment in failing to mature fistulae.[150] These reports have included other lesions or have small numbers. Moreover, all the previous reports deal almost exclusively with early AVF failure. In our series patients presented with low flow in their 'mature' AVFs. To our knowledge, this is the first series reporting outcomes of obliteration of ADVs in early as well as late failure. We report initial outcomes and follow-up of our series of 42 patients who underwent endovascular coiling of ADVs.

5.2.2 Material and methods

Design of the study and definitions

This retrospective study analyses the initial outcomes and the results of longer term follow-up of patients who underwent endovascular coiling of ADVs in AVFs from our centre in the period from 1st January 2007 to 31st December 2010. The analysis included all patients who underwent coiling regardless of indications. Early failure was defined as an AVF which never worked or failed within 3 months of initial use, a widely used definition of early failure.[19, 20] Late failure was defined as AVF failure occurring after this period.

Technical or anatomical success of PTA was defined as presence of less than 30% residual stenosis. Successful obliteration was defined angiographically, as lack of flow through the ADV. Patency was defined as successful dialysis using the study AVF with 2 needles for 1 month period with a minimum dialysis blood flow of 350

ml/min without recirculation. Primary patency was defined as AVF patency without the need for any intervention. Secondary patency was defined as AVF patency with the use of additional interventions to maintain patency. Re-interventions were defined as any surgical / radiological interventions on the AVFs during the follow-up period.

Patient selection

Patients are referred to our centre for imaging and treatment of dysfunctional dialysis access from all across the Greater Manchester area which serves a prevalent dialysis population of around 1000. Renal and haemodialysis services within Greater Manchester region are delivered in a 'hub and spoke' model with 2 main 'hub' centres. The satellite units initially refer patients with AVF problems back to their main centre for evaluation. Any endovascular or surgical interventions on AVFs are carried out only in these two centres with the majority of endovascular procedures performed in our centre comprising more than 200 interventions on arteriovenous dialysis access per year. We selected all patients who underwent coil embolisation of ADVs in the above period at our centre.

Interventional procedures (Figure 5-1)

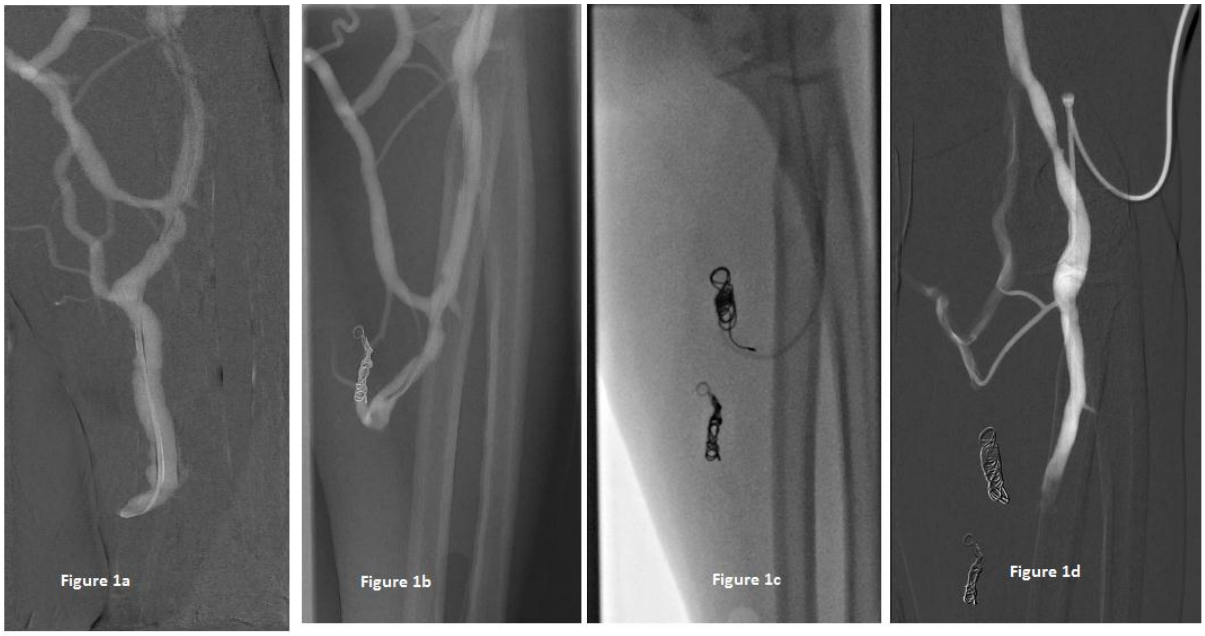

Figure 5-1: Serial images demonstrating the ADVs being coiled endovascularly. Fig 1a: Initial angiogram which reveals 2 ADVs. Fig 1b: The distal ADV being embolised with a coil. Fig 1c: The proximal ADV being embolised. Fig 1d: Post-coiling angiogram which reveals complete obliteration of the ADVs.

All procedures were performed or supervised by consultant vascular interventional radiologists. Informed consent was obtained prior to the procedure. Initial physical examination and ultrasound evaluation of the AVF was undertaken prior to any invasive intervention. The ultrasound evaluation included assessment of the feeding artery, the anastomosis, the main fistula vein and the drainage. Lesions such as stenosis and accessory veins were usually identified at this point. Ultrasound evaluation was followed by diagnostic angiography if indicated. Retrograde cannulation and angiography was used to define the feeding artery anatomy and exclude any arterial lesions. Any inflow stenosis in the main vein was initially treated with balloon dilatation (PTA). Patients presenting with clotted AVFs underwent balloon maceration or in a few cases Angiojet™ thrombectomy. In cases where despite anatomical success of PTA, the flow in the target vein remained poor

(as determined by the operator clinically and angiographically) *and* ADVs were seen to persist, the ADVs were deemed to be functionally significant. In these patients, decision to obliterate the ADV was made. In our centre, this is done endovascularly in majority of cases mainly because the procedure can be done at the same time as angiography and/or PTA. It also saves the patient's time; avoid repeat procedure (surgery) and visits. In these patients, the ADVs were selectively catheterised and embolised with stainless steel (Cook Medical, Bloomington, IN) or platinum (BALT Extrusion, France) coils. Coil size was determined by diameter of the target ADV as assessed by angiography. Our usual protocol was to choose coils which were 1 – 2 mm larger than the diameter of the target ADV. One or more coils were used until complete obliteration of flow, or near-stasis, as determined angiographically, was obtained.

Data collection and follow-up

Baseline clinical, demographic and radiological data were recorded at the time of procedure. Data on subsequent interventions were also recorded on and gathered from the same radiology information system. Information on any surgical interventions was gathered from electronic patient records. Data on AVF use were gathered by using electronic patient records and/or phone calls to individual patients or dialysis units. Statistical analyses were performed using SPSS version 19 (IBM Corporation, NY).

5.2.3 Results

In the study period, 42 patients underwent coil embolisation of ADVs. Coil embolisation accounted for around 5% of our total AV dialysis access interventional procedures. The mean age was 60±12 years with a range of 31 to 87 years. Males outnumbered females with a Male: Female ratio of 2:1. The majority (>80%) patients were of Caucasian origin. Radio-cephalic AVFs as opposed to brachiocephalic accounted for majority of the referrals (74% and 26% respectively). The proportion of radio-cephalic AVFs compared to brachio-cephalic AVFs was not found to be statistically significant when the prevalence of these AVF types was taken into account (p=0.127 using Fisher's exact test).

The most common indication for referral was early failure (34%), followed by needling difficulty (29%) and poor flow (27%). 4 patients (10%) presented with a clotted AVF.

The median time to referral from AVF creation was 8 months with a range between 2 months and 46 months. In the 14 patients with early failure, the median time of presentation from creation of AVF was 5.4 months as opposed to the 'late failures', where the median time was 11.9 months. 40 procedures involved PTA and coil embolisation with only 2 procedures involving coiling as the sole intervention. The 4 patients presenting with clotted AVFs, underwent balloon maceration. Two patients required repeat coil embolisation (in different ADVs).

11 (26%) of the patients were on home HD (HHD) experiencing cannulation difficulties, 2 (5%) were pre-dialysis and the rest of the patients (69%) were on in-centre HD. In our cohort, we observed a disproportionately higher number of HHD patients. In the study period, the prevalence of HHD, in our centre has been in the range of 10-12% of the total HD population. This finding is statistically significant ($p<0.01$ using Fisher's exact test).

Follow up (Table 5-1 and figure 5-2)

The minimum follow up duration was 4 months and the median follow-up was 28 months. Technique success was achieved 41 (98%) patients. Patients who were in the pre-dialysis stage (n=2) were excluded from the analysis. Initial clinical success at 1 month, as defined by successful dialysis, was 90% with failure rate of 10%. Longer term patency was calculated using Kaplan Meier survival method (censored for transplantation and death). The primary and secondary patency rate along with standard error and numbers at risk at each time interval are represented in the table below.

Time (months)	Primary Patency			Secondary Patency		
	Patency rate (%)	Numbers at risk	Standard error	Patency rate (%)	Numbers at risk	Standard error
3	90	36	0.049	90.2	38	0.046
6	87.2	33	0.054	90.2	35	0.046
12	76.1	27	0.07	87.2	29	0.054
18	69.5	21	0.078	83.6	23	0.063
24	55	15	0.089	83.6	17	0.063

Table 5-1: Primary and secondary patency rate at follow up period (obtained by Kaplan-Meier survival analysis) including numbers at risk and standard error for each time-point.

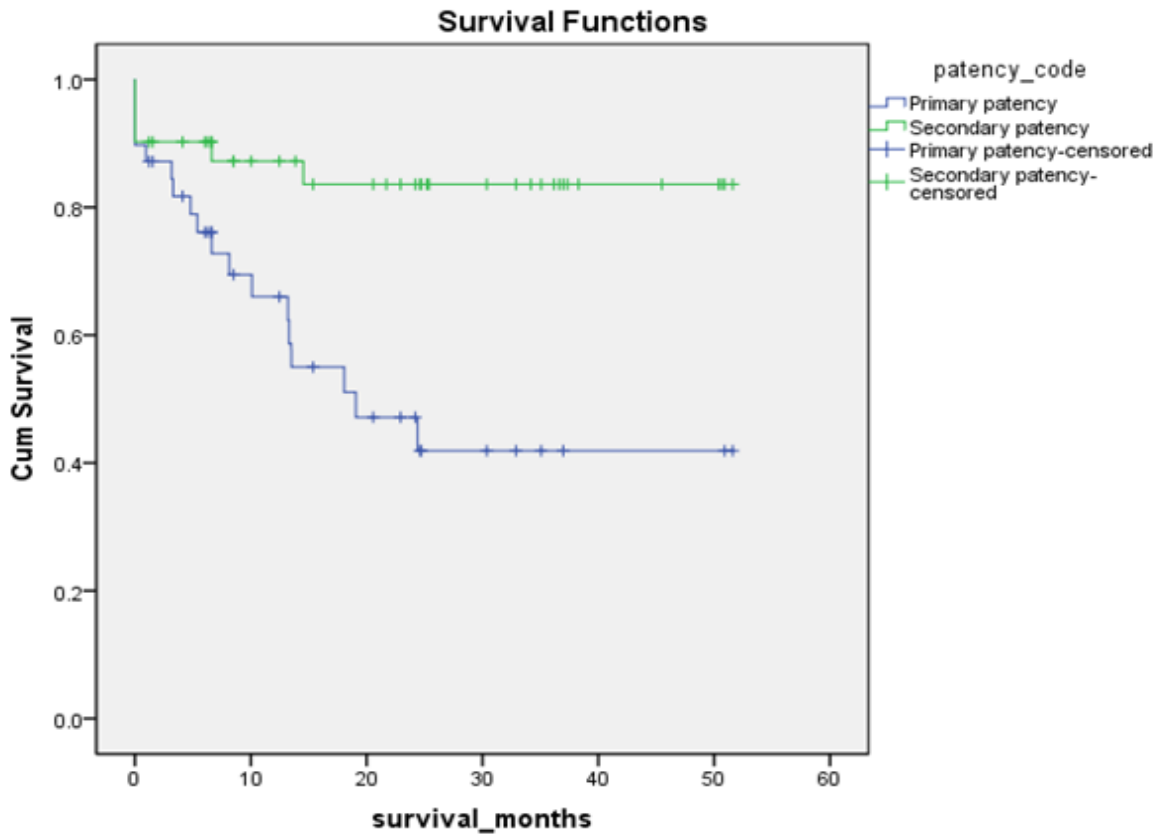

Table 5-2: Kaplan-Meier survival plot depicting primary and secondary patency rates following intervention, The X-axis represents survival time in months and Y-axis represents proportion of AVF surviving at a particular time-point.

34% (n=14) patients required repeat endovascular interventions on their AVFs during the study period. This yields a total AVF re-intervention rate of 0.14 per access-year (total follow-up 1176 patient-months). Re-stenosis in relation to the original stenotic lesion followed by development of new stenotic lesions were the dominant reasons for re-intervention.

Complications

A single major complication was observed in 1 patient. Initially a small coil was placed which dislodged and migrated to the pulmonary circulation with no adverse sequelae. In the same patient, another coil migrated into the main fistula vein leading to loss of the AVF. We believe, that this complication resulted from firstly, use of a coil that was too small and secondly, incorrect placement of a subsequent coil.

5.2.4 Discussion

ADVs may account for up to 40% cases of early AVF failure.[19] ADVs can be confused with collateral veins. Various terminologies have been used in the past leading to some confusion. Terms such as branch veins, accessory veins and collateral veins have all been used to refer to true ADVs. Recent attempts at standardising the terminology have attempted to simply this nomenclature.[155] ADVs are natural branches/tributaries of the target vein which may also undergo the process of enlargement on creation of an AVF. Collateral veins, on the other hand, develop as a result of downstream stenosis. However, distinction between a collateral and ADV

may not be always straightforward. A previously clinically insignificant accessory vein may enlarge in the presence of downstream stenosis. Following treatment of the stenotic lesion, this accessory vein may still continue 'stealing' blood away from the target vein and become clinically significant.

The significance of ADVs in late AVF failure has not been well studied or reported in the literature. In our case series, late failure accounted for a major proportion of referrals. This data may be skewed because although early failures are often referred for angiographic evaluation, the 'very early failures' occurring within 2 weeks of creation are not usually referred and are classed as abandoned. Furthermore, not all cases of early failure may be referred, particularly when likelihood of failure was anticipated as 'high' by the surgeon due to anatomical or patient specific factors.

It has been previously noted that ADVs are common in forearm AVFs as compared to elbow / upper arm AVFs due the higher number of naturally occurring branches of the forearm cephalic vein. In our series, majority of the AVFs were forearm. Whilst this may be interpreted to be in keeping with the previous observation, on adjusting for the prevalence of type of AVFs in our unit, this observation is not found be statistically significant.

A high number of patients require repeat interventions following their initial coiling. This is generally due to recurrence of stenosis or development of new stenotic lesions. Further coil embolisation was required in a very small proportion of patients and was performed on ADVs other than the ones previously coiled. It would appear

that coiling is very effective for obliteration of flow in the target ADV but upon coiling of an ADV other channels may enlarge and require intervention.

Migration of the coil into the pulmonary circulation is a rare adverse event but surprisingly often goes without major clinical consequence. The luminal diameter of the venous system increases from capillaries to the central circulation. Despite this, the risk of coil migration appears to be low. However, use of coils larger than the apparent size of the target ADV, as determined angiographically, is advisable to minimise this risk.

Although, coil embolisation as means of obliteration of ADVs has not been compared directly with surgical ligation, it appears to be effective. Moreover, it can be performed at the same time as angiography and angioplasty. The procedure has high initial technical and clinical success rates but primary patency drops rapidly with time. At 12 months, primary patency is just over 60%. Secondary patency rates at 12 months are acceptable at around 87%. These figures are in keeping with patency rates in AVFs not treated endovascularly[131, 156] and appear to be better than those who had PTA alone.[69, 157] This observation has also been made in previous studies by Beathard et al and Nassar et al.[19, 150] Our own data (unpublished) for patients undergoing non-coiling interventions (excluding thrombosed AVFs) is represented in table 5-3. In our centre, the primary patency of coiling +/- PTA is significantly superior to in the PTA alone group.

Time in months	Primary Patency (%)
6	60
12	39
18	38
24	38

Table 5-3: Primary patency of PTA-only AVF interventions over a consecutive 1 year period.

We noted a disproportionately higher representation of our HHD patients in those requiring coiling. The HHD cohort were a younger (mean age 50±7) compared to the rest of the cohort. Younger patients may have a more vein branches possibly related to level of physical activity. These patients also had a higher prevalence of radio-cephalic / forearm AVFs (72% vs. 60%), although this is not statistically significant. It has been noted in previous studies that forearm AVFs have a higher incidence of ADVs.[19, 152] However, this observation has not borne out in our own analysis.

A plausible explanation of the above finding is the higher need and dependency of HHD patients on optimal flow through the AVF for independent self-cannulation. Although they undergo significant training, they are likely to have problems with cannulation much earlier and more frequently than in-centre HD patients where cannulation is typically performed by HD nurses.

Study limitations

Our study evaluated the outcomes retrospectively and the numbers studied are relatively small. Blood flow on HD or solute clearance methods for dialysis

adequacy were not used to determine the patency rates. However, it is standard practice in our centre to perform monthly adequacy measurements and dialysis blood flow is measured on each session. Patients who are thought have poor solute clearance secondary to access problems and/or consistent poor flow on HD would be referred for evaluation of their AVF. The decision to embolise was made by the interventionist after balloon angioplasty depending on the angiographic appearances. This is a subjective judgement. The absence of a control group means that the added value of embolisation over balloon angioplasty alone is speculative. Future work should include objective measurement of flow volume in the main vein before and after ADV embolisation.

However, this study is unique in several ways – it is relatively large series, includes patients with late AVF failure and reports of clinically relevant outcome of dialysis use.

5.2.5 Conclusion

Coil embolisation is an effective procedure for obliteration of ADVs, with good technical success rates and acceptable secondary patency at 1 year. ADVs may play a more significant role in the failure of mature AVFs than previously thought. The additional value of embolisation of ADVs over balloon angioplasty alone merits further prospective evaluation. Care should be taken to carefully select coil size and target veins for embolisation to avoid inadvertent embolisation or coil migration.

Chapter 6: Vascular access outcomes in Home Haemodialysis

Vascular access in home haemodialysis: Trends and outcomes[§]

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[§] This study was presented as an oral abstract in the Renal Association / British Renal Society Annual Conference in 2011 and was awarded a scholarship prize for being 'one of the best abstracts'. More data has been collected since the presentation in order to allow multivariate analysis of patient survival.

6.1 Abstract

Background: Optimal vascular access (VA) is vital to all in-centre haemodialysis (IHD) patients, but plays an even more critical role in maintaining independence on Home Haemodialysis (HHD). We undertook this study to outline the trends of VA outcomes from one of the largest HHD programmes in the UK over a 5-year period.

Study design and methodology

VA information was analysed from the prospectively maintained HHD database for the period of 2005-2010 for the East Sector Greater Manchester Renal Network. Retrospective data on VA use practice patterns, including catheter complications were obtained from the community team. Vascular access outcome definitions were in accordance in international reporting standards.

Results

150 patients had undergone training for independent HD at Home. The prevalence of HHD increased from around 8% to 14% of all dialysis during this time. Of the incident HHD patients, 79% commenced training with an AVF; in prevalent HHD patients this had risen to 89% AVF prevalence at home (0.5% graft, 10.5% catheter use).

Primary patency for AVFs, at 3, 6, 12, 24, 36 and 60 months was 94%, 81%, 55%, 32%, 23% and 17% respectively. Secondary patency for the same time intervals was 100%, 99%, 98%, 97%, 97% and 87% respectively. During the 5-year period, for catheter use, 2 episodes of 'tunnel infections' and 7 exit site infections but no bacteraemia were reported. However there was a significant difference in patient survival

between the groups who commenced HD with catheter vs. AV access (log rank $p<0.001$).

Conclusion

In general VA outcomes are superior in HHD compared to IHD patients; however, there is trend to increased VA interventions. In this cohort, incident VA type was associated with patient survival and this effect needs further investigation in larger studies. Whilst outcomes of patients starting HHD with catheter are inferior, catheter outcomes when compared to IHD patients are still significantly better.

6.2 Manuscript

6.2.1 Introduction

Optimal vascular access (VA) is vital to all in-centre haemodialysis (IHD) patients, but plays an even more critical role in maintaining independence on Home Haemodialysis (HHD). All major steps in the HHD patient journey – from decision making; training; self-cannulation to long term HHD success are dependent on availability of good VA. Although technical failure is rare in HHD, access failure can precipitate IHD. Optimising VA outcomes is the stepping-stone to a successful outcome on HHD. Despite the importance of VA in HHD, there is a distinct lack of literature on this subject. In the recently published Frequent Hemodialysis Network Trial, significant benefit of more frequent HD was observed.[158] However, there was a trend towards higher need for VA procedures in the frequent HD group,[158] thus highlighting the importance of VA care in this cohort of patients.

In this study we outline the trends of VA outcomes from one of the largest HHD programmes in the UK over a 5-year period. The aim is to determine incidence, prevalence, access patency rates, practice patterns of VA use and its complications.

6.2.2 Material and methods

Design of the study and subject selection

VA information was analysed from the prospectively maintained HHD database for the period of 2005-2010 for the East Sector Greater Manchester Renal Network. All patients who undertook HHD and were trained for HHD during this period were included in the study. Retrospective data on VA use practice patterns, including

catheter complications were obtained from the community team. Information on vascular access events and interventions was obtained using clinical case records and electronic case records. Greater Manchester prospective arteriovenous access salvage database was utilised to extract information on acute access dysfunction/failure.

Outcome definitions

Vascular access outcomes definitions were in accordance with Society of Vascular and Interventional Radiology (SVIR) reporting standards guidelines.[159] Primary patency was defined as AVF patency without the need for any interventions (excluding planned superficialisation and diagnostic studies). Secondary patency was defined as AVF patency with the use of additional interventions to maintain patency. Secondary patency allows any endovascular procedures including salvage procedure but stopped at all non-planned surgical interventions. Re-interventions were defined as any surgical / radiological interventions on the access during the follow-up period.

Statistical analysis

All statistical analyses were performed using SPSS version 20 (IBM Inc., USA) licensed to the University of Manchester. Chi square test and independent sample t test was used to detect difference between the groups in case of variables which were normally distributed. For variables with non-normal distribution, independent samples Mann-Whitney U test was used. Survival analysis was performed using the Kaplan Meier method with log rank testing to detect difference in survival between groups.

6.2.3 Results

During the study period, 150 patients had undergone training for independent HD at Home. The prevalence of HHD increased from around 8% to 14% of all dialysis during this time. 75% patients were on extended dialysis schedules and undertook frequent self cannulation. Of the incident HHD patients, 79% commenced training with an AVF; in prevalent HHD patients this had risen to 89% AVF prevalence at home (0.5% graft, 10.5% catheter use). Buttonhole needling was higher in patients commencing training (50%) but fell significantly (30%) at 1 year. Cannulation support time was required in about a third of the patients but the amount of support required each year was variable. Cannulation support requirement did not correlate with age or gender. The maximum support required for all patients was 189 hours/year, with a range between 2-62 hours/year for individual patients. Time to self-care, defined as time from start of training to self-care at home, had a small but statistically significant correlation with age ($r=0.28$, $p=0.006$). Access retraining episodes were necessary in cases of a new AV access formation, superficialisation surgery or non-dominant arm AVF.

Primary patency for AVFs, at 3, 6, 12, 24, 36 and 60 months was 94%, 81%, 55%, 32%, 23% and 17% respectively. Secondary patency for the same time intervals was 100%, 99%, 98%, 97%, 97% and 87% respectively. There was a tendency towards higher need for intervention. During the 5-year period, for catheter use, 2 episodes of 'tunnel infections' and 7 exit site infections but no bacteraemia were reported. However there was a significant difference in patient survival between the groups who commenced HD with catheter vs. AV access (figure 6-1).

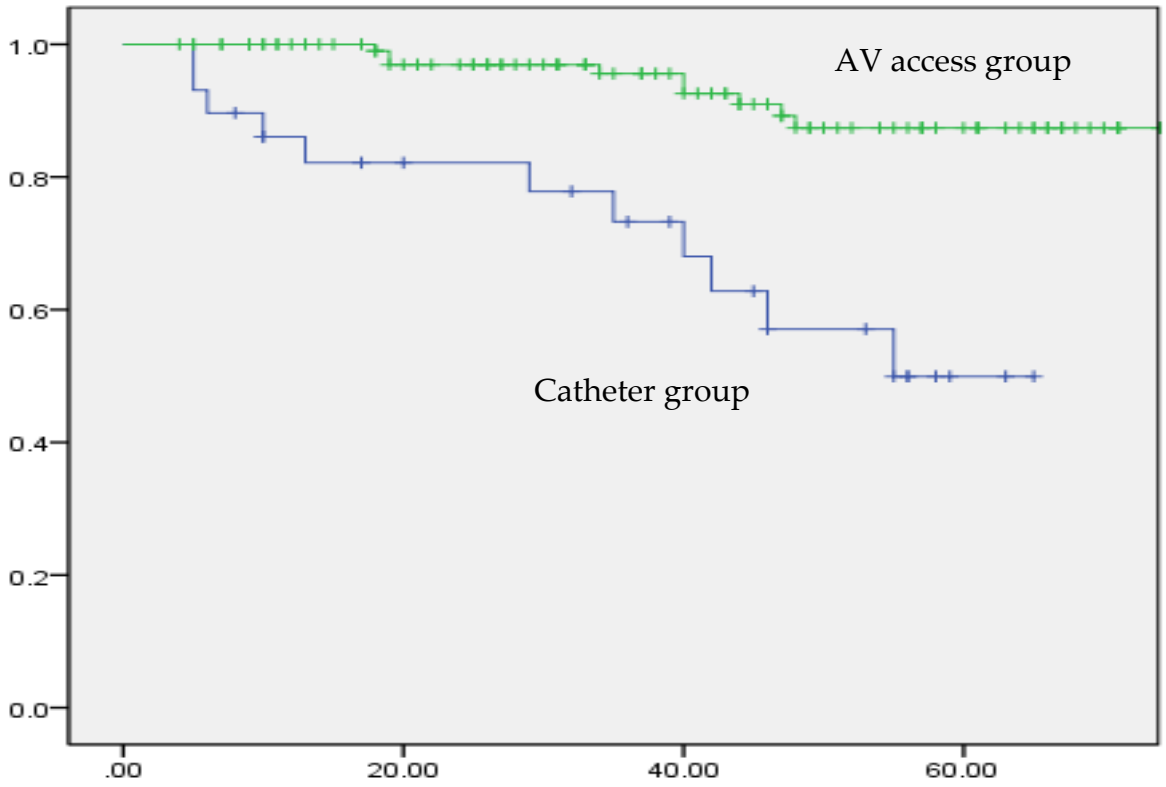

Figure 6-1: Kaplan-Meier survival graph comparing survival by incident access type.

6.2.4 Discussion

VA in HHD poses unique challenges. Overall access outcomes for HHD are superior compared to IHD for both AV access and catheter use. However suboptimal access may contribute significantly to technique failure, substantial additional community support time & loss of independence at home on this modality. Renal units keen on building and expanding their HHD programmes need to dedicate significant resource and attention towards VA. A third of our patients required cannulation support from HHD nurses – thus mounting to substantial demand on a scarce resource. Cannulation training for HHD patients and *HHD caregiving staff*, is an

important area of focus. Success rate for buttonhole cannulation was unfortunately low in our group and this is also most likely related to staff training.

Our data suggest survival advantage of starting HHD with an AV access. This observation persisted despite censoring for transplantation. The two cohorts were well matched for age and gender distribution. In view of observational nature of the study, selection bias cannot be reliably excluded. However it is noteworthy that in this cohort access type was not dependent on age. Moreover, over half of the patients with incident catheter group converted to having successful AV access suggesting that confounding error may not entirely explain this significant survival difference. The survival advantage of AV access has been noted before.[2, 160] Intensive HD schedules have been associated with improved survival with outcomes approaching those of cadaveric renal transplantation.[161] Majority of our patients had significantly higher weekly dialysis duration compared to standard thrice weekly HD. Thus, to observe the survival advantage of AV access in this group, with lower mortality, is indeed a striking observation and deserves further exploration.

Despite this data, it is quite clear that overall catheter outcomes are still superior in HHD compared to IHD. Complete absence of catheter related bacteraemia in this group is a very desirable outcome – and a very humbling one. This study suggests that patients with appropriate training may be better at vascular access care than healthcare staff.

6.2.5 Conclusion

The VA outcomes are superior in HHD patients, despite frequent access use, less rigorous monitoring and remote base. The trend towards higher VA interventions has also been highlighted in other studies and perhaps indicates need for greater care towards VA in this cohort. Improved patient survival associated with incident VA type also needs further investigation in larger studies.

Chapter 7: Acute vascular access failure

7.1 Prospective long term outcomes of endovascular salvage of acute arteriovenous access failure[**]

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[**] Results from this study have been presented as an abstract at the ASN meeting held in November 2012.

7.1.1 Abstract

We report results from a prospective study of endovascular salvage (EVS) of acutely failed fistulae and grafts.

Methods:

All patients presenting with acute fistula or graft failure, from 1st January 2008 to 31st December 2011 were included except those with primary failure. Altogether, 410 procedures were carried out in 232 patients.

Results

Fistulae (AVFs) accounted for 71% whilst 29% were grafts, despite a graft prevalence of <5%. Overall incidence of thrombosis was 12% per year for AVFs and 90% for grafts. Median age of access at the time of first thrombosis was 17 and 7 months in case of AVFs and grafts, respectively. Anatomical success rate for EVS was 94% for AVFs and 92% for grafts.

Primary patency rates for AVFs at 1, 6, 12, 24, and 36 months were 77%, 57%, 35%, 25% and 18% respectively, whereas secondary patency rates were 83%, 79%, 66%, 61% and 53% respectively. Primary patency rates for grafts at 1, 6 and 12 months were 49%, 13%, and 8% and respectively, whereas, secondary patency rates were 64%, 42%, and 36% respectively.

AVFs had superior primary and secondary patency compared to grafts (log rank p<0.001). Forearm AVFs had superior primary (p=0.04), but not secondary patency, compared to upper arm AVFs. Presence of thrombosis was associated with inferior secondary patency (p=0.008).

Balloon maceration (BM) is our preferred technique and the results are comparable to most published series with no incidence of symptomatic pulmonary embolism. Complications were observed in 6% of all procedures, with only 3 patients experiencing major complications.

Conclusion

EVS is effective but longer-term outcomes are poor especially for grafts. Presence of thrombosis in AVFs is associated with poorer fistula survival and efforts to reduce incidence of thrombosis need to be evaluated. BM is a safe and cost effective technique and outcomes compare favourably to other techniques.

7.1.2 Manuscript

7.1.2.1 Introduction

Vascular access (VA) is the Achilles' heel of haemodialysis therapy in end stage kidney failure. Arteriovenous access is the preferred mode of VA for HD, especially fistulae (AVFs). AVFs and grafts have several advantages over dialysis catheters – relatively lower infection rates and greater longevity.[162] The most common mechanism of AVF and graft failure is thrombosis, usually a result of restriction in flow due to an underlying stenotic lesion.

Annually, 14% of AVFs and between 50 – 80% grafts fail acutely.[62, 163] This often leads to a myriad undesirable consequences including disruption of dialysis schedules, hospitalisation with its related complications, the need for alternative access and associated increase in healthcare costs.

Salvage of AVFs and grafts can be reliably achieved by surgical or endovascular techniques. Endovascular salvage is preferred as it is effective, less invasive, logistically easier to organise and has low complication rates. Technical and immediate clinical success rates are high and average around 90% in most series. Whilst this is acceptable, longer-term patency rates, especially primary patency rates are poor.[69] Most studies, barring a few, report short-term patency rates and have low patient numbers. [21, 69, 164]

Effective treatment and prevention of acute AVF and graft failure remains a priority in order to reduce catheter use and improve dialysis outcomes. We therefore undertook a prospective longitudinal analysis of all patients referred with acute AVF

and graft failure restored by EVS in our regional centre with a prevalent HD population of around 1100 patients, over a period of 4 years. The aim of the study was to prospectively analyse immediate and long term outcomes after EVS.

7.1.2.2 Methods

Study protocol

A failed access salvage pathway had been established in our centre in January 2008 serving 12 dialysis units, around 1100 dialysis patients under supervision of 2 tertiary renal networks with a catchment population of 3.5 million populations. All patients with an episode of fistula or graft failure (defined clinically as inability to use the AVA by an experienced nurse to commence a dialysis session) who were referred for EVS were included in the study. Patients with primary or early fistula or graft failure were excluded from the study.

Clinical and radiological information such as baseline demographic information, procedural details, co-morbidity data, blood results (haemoglobin, haematocrit and C-reactive protein), medication use (antiplatelet agents, statins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and coumarin anticoagulants) were recorded in the database. Follow up information was obtained from electronic patient records, patient case notes and by liaison with dialysis units. Recorded co-morbid information included coronary artery disease (CAD), defined as history of angina or myocardial infarction, angiographic evidence of coronary arterial lesions, positive radionuclide stress test or history of coronary angioplasty or coronary artery bypass grafting surgery. Peripheral vascular disease (PVD) was

defined as history of claudication, evidence of peripheral arterial lesions on angiogram or non-invasive study, history of angioplasty or amputation due to PVD. Chronic heart failure (CHF) was defined as evidence of reduced left ventricular ejection fraction on echocardiogram or radionuclide imaging or left 'ventriculo-gram' performed during angiography. Information on diabetes mellitus (DM) status, primary renal disease, malignancy history, hypertension (HTN) status, dialysis vintage and AVA age was sought. Primary renal disease was classified in 5 categories – vascular, primary glomerulonephritides (GN), renal limited disease such as reflux nephropathy, multisystem disorders affecting the kidney such as myeloma or lupus and remaining diseases were classified as others.

Interventional procedures

All referred patients were evaluated by ultrasound following a clinical history and examination. The interventional technique subsequently chosen is dependent on the nature of the problem and discretion of the operator.

In cases of thrombosed access, the standard approach is as follows:

The fistula or graft is punctured in a retrograde and antegrade fashion using 19 gauge introducer needle. In difficult cases, a micro-puncture kit is used with or without ultrasound guidance. This is followed by insertion of 6-8 F vascular sheaths. Site of initial puncture is guided by clinical examination and / or ultrasound findings. Careful contrast injection through the initial sheath (or a catheter introduced through the sheath) is used to define the location and extent of thrombosis. The anastomosis is crossed using a catheter introduced through the retrograde sheath. In cases, where this is difficult, an arterial puncture is used.

Unfractionated heparin is used unless contraindicated at a usual dose of 3000 units. The preferred technique for de-clotting is balloon maceration (BM) in combination with angioplasty. Other techniques used are – Trerotola device or the Angiojet™ device, bolus and / or infusion of recombinant tissue plasminogen activator (tPA). These methods were used as second line where BM and PTA alone failed to obtain desirable thrombus clearance. Stenotic lesions with >50% lumen loss was considered for treatment.

Definition of outcomes

Outcome definitions used are consistent with the Society of Vascular and Interventional Radiology (SVIR) recommendations.[159]. Anatomical success was defined as <30% residual stenosis in case of stenotic lesions and recanalization with restoration of flow in the access. All reported patency rates comply with SVIR standards and include immediate failures.

Primary patency was defined as access survival without any endovascular or surgical procedures. Secondary patency was defined as AVA survival until access abandonment or surgery. For patency measurements, only patients having first salvage procedure were included.

Statistical methods

Parametric data are presented as mean ± standard deviation and non-parametric data as median [interquartile range]. Between groups, comparisons for categorical variables were made using Chi-squared test and ANOVA appropriate to the distribution of the data for continuous variables.

For access survival the end-point was defined as date of access failure, with patients censored for death, transplantation and change of modality to PD other than due to study access failure. Primary and secondary patency AVA survival rates were calculated using Kaplan-Meier survival method

All analyses were performed using SPSS 20 (IBM Inc., USA) under licence to the University of Manchester.

7.1.2.3 Results

Patient and VA demographics

A total of 445 episodes of access failure were referred in the study period and 410 endovascular salvage procedures were carried out. The mean follow up period was 29 months with minimum follow up of 6 months and maximum of 54 months.

Mean age (±SD) of the study cohort was 59 years (±15 years). Men accounted for 49% and females 51%, the latter over-represented in our cohort as women account for 38% of HD patients [165]. The rest of the baseline data in our cohort is presented in table 1.

AVFs accounted for 73% whilst the rest 27% were grafts, despite low graft prevalence across the region of less than 5%. In the AVF group, 53% were forearm AVFs and 47% upper arm AVFs. In the AVF group, 75% episodes were a result of thrombosis as opposed to the AVG group where 93% episodes were a result of thrombosis. Incidence of thrombosis was 12% per year and 90% per year in case of AVFs and grafts respectively. Time to first thrombosis was significantly longer in

fistulae [17.4 months (IQR 10 – 35.6)] as compared to grafts [7.3 months (IQR 3.1 – 20.1)] ($p<0.001$).

Thrombectomy techniques used and their frequencies are as per table 7-1 below. Balloon maceration was tried in all cases as the first line before moving on to other therapies.

Technique	Frequency
Balloon maceration in combination with PTA alone	59%
Mechanical methods (Trerotola device, Angiojet device)	15%
Pharmacological thrombolysis using tPA	16%
Mechanical methods + pharmacological thrombolysis	8%
Stents	2%

Table 7-1: Thrombectomy techniques employed and their respective frequencies

Findings on initial angiogram apart from thrombosis were classified as isolated lesions (69%) and combined (>1) lesions (31%). The types and nature of underlying lesion/s found on angiogram in AVFs are as listed in table 7-2 and in case of grafts in figure 7-2.

Access type	Thrombosed AVFs	Non-thrombosed AVFs
Anastomotic / JA stenosis	31%	42%
Multiple lesion	37%	25%
Proximal vein stenosis	27%	24%
Arterial stenosis	1%	
Non-stenotic lesions	2%	3%
Central vein stenosis	1%	6%
Thrombosis only	1%	NA

Table 7-2: Type and incidence of lesions in native fistulae

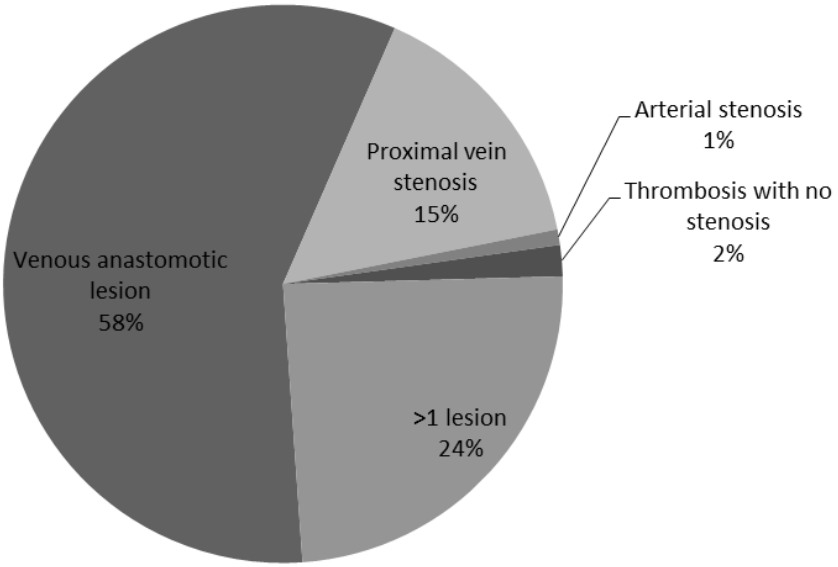

Figure 7-1: Type of lesions and their incidence in grafts

Following intervention, the overall anatomical success rate was 94% for AVFs and 92% for AVGs. Primary and secondary patency rates for fistulae and grafts were as listed in tables 7-3 and 7-4, respectively.

	Primary patency (n=134)			Secondary patency (n=122)		
Time in month/s	Patency (%)	Standard error	Numbers at risk	Patency (%)	Standard error	Numbers at risk
1	77	0.036	103	84	0.034	102
3	70	0.04	94	82	0.035	100
6	57	0.043	76	79	0.037	96
12	35	0.035	45	66	0.044	71
18	28	0.041	29	63	0.045	59
24	25	0.04	24	61	0.046	46
36	18	0.039	11	53	0.052	27

Table 7-3: Primary and secondary patency rate in AVF group

	Primary patency – AVGs n=39			Secondary Patency (AVGs) n=36		
Time in month/s	Primary patency (%)	Standard error	Numbers at risk	Secondary patency (%)	Standard error	Numbers at risk
1	49	0.08	19	64	0.08	24
3	36	0.077	14	53	0.083	19
6	13	0.054	5	42	0.082	15
12	8	0.043	3	36	0.081	14

Table 7-4: Primary and secondary patency of grafts

There was significant difference in primary but not secondary patency between forearm and upper arm AVFs (figure 7-5). Secondary patency was much lower in those presenting with thrombosed AVFs or grafts as compared to non-thrombosed ones (log rank p=0.008).

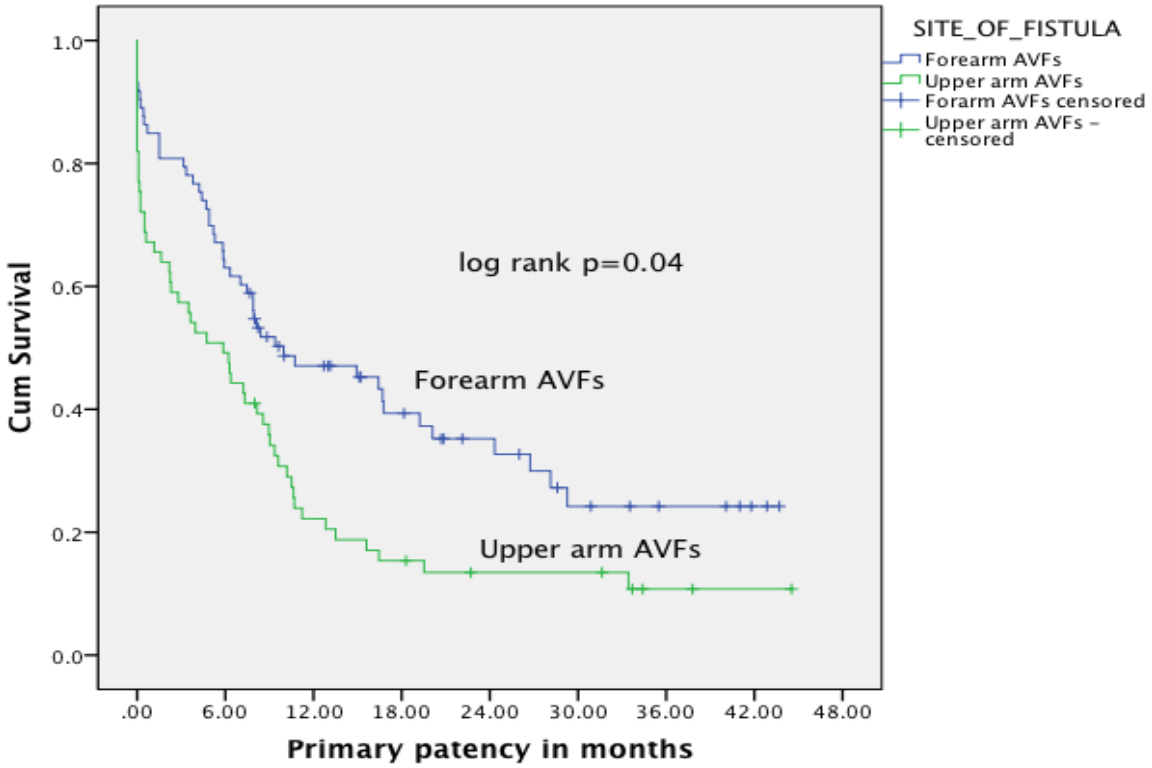

Table 7-5: Kaplan Mier survival graph of primary patency of AVFs by location

Complications

Six per cent patients undergoing endovascular procedures experienced complications. No deaths occurred as a direct result of the procedure. Significant complication leading to fistula loss occurred in 2 patients, due to vessel rupture in both cases. 1 patient experienced rigors after attempted declotting of her graft – this was presumed to be pre-existent infection of the graft. Vein rupture was the most

common complication observed in 3.3% cases. Arterial embolisation was observed in 1.2% cases. The former complication was initially managed conservatively (50% cases) or, if this failed, with stents (50%). 1 patient experienced severe bradycardia thought to be due to release of mediators such as adenosine associated with Angiojet™ thrombectomy. [166]

7.1.2.4 Discussion

Increasing AVF prevalence and its longevity remains a priority for haemodialysis patients. Whilst creating more AVFs is an important first step, maintenance of existing AVFs by preventing failure is equally important. Unfortunately access thrombosis remains a common event which causes inconvenience and harm to patients leading to significant morbidity and mortality. [13, 50]

Endovascular treatment has become standard practice in access salvage. Whilst immediate outcomes are typically satisfactory, patency rates drop very quickly with 1-year primary patency months under 30% and 20% for fistulae and grafts respectively. Secondary patency rate for AVFs are more acceptable but signify the need for repeated interventions, which is expensive and causes morbidity.

In the multivariate analysis using Cox proportional hazards model we observed that presence of thrombosis was associated with an almost 3-fold increase in loss of permanent fistula failure. In our series very few patients underwent surgical revisions of their access, hence loss of secondary patency equated to permanent fistula failure. Thus prevention of fistula thrombosis needs to be an important goal for all caring for haemodialysis patients. However, there are no proven strategies for

primary and secondary prevention of fistula thrombosis. Whilst most national and international guidelines recommend surveillance [64, 163, 167], opinion remains divided regarding the benefit of surveillance, especially in AVFs. Ultrasound monitoring, the most widely used method for access surveillance, was found to have no benefit in preventing thrombosis in AVGs and only small benefit in AVFs.[65] A recent review by Paulson et al concluded that in the light of current evidence, routine surveillance couldn't be recommended.[66] All the studies included in these reviews have not specifically targeted high-risk fistulae. Our results raise the issue of whether we should we be considering a different surveillance strategy. It is conceivable that surveillance directed at high-risk AVA such as those with a history of thrombosis, may be a more cost-effective strategy.

Upper arm AVFs were found to have inferior primary patency but not secondary patency when compared to forearm AVFs, thus indicating a need for more interventions. Turmel-Rodrigues et al found that forearm AVFs had higher primary patency rates as compared to upper arm AVFs but there was difference in secondary patency between these 2 groups in their study. [69]

In 2009, Littler et al reported superior outcomes by using Angiojet™ for treatment of thrombosed AVFs to standard techniques.[168]. In our centre BM is the first-line thrombectomy method and mechanical or pharmacological methods are only used if BM and PTA fail to achieve satisfactory clearance of thrombus. Our results compare favourably to those reported in the above case series and are approach is much more cost-effective.

BM has attracted criticism because of its potential to cause PE. In our study BM has been used in over 300 procedures with significant number of patients having repeated procedures. We have not observed a single case of symptomatic PE. None of our patients were been investigated for dyspnoea thought be secondary to PE in the peri-procedure period (1 month). None of the patients undergoing these procedures were investigated for pulmonary hypertension as a result of recurrent PE. It is likely that small amount of thrombus does embolise to the pulmonary circulation but this does not seem to be of any clinical significance.

Limitations of the study

This is an observational study but is one of the largest prospective studies. PE is a potential complication and whilst we did not have any patients presenting with symptomatic PE after the intervention, clinically silent PE cannot be excluded.

7.1.2.5 Conclusion

This study is one of largest prospectively analysed outcomes studies of EVS of arteriovenous HD access. Endovascular salvage of failed access is highly effective but long-term patency rates are unsatisfactory. Grafts and have significantly poorer long-term outcomes as compared to fistulae and require more interventions to maintain patency. Presence of thrombosis signifies poor long-term access survival and all interventions that can reduce thrombosis need to be evaluated. BM is a cheap, safe and equally effective technique that merits consideration by the vascular access community.

7.2 : Failed arteriovenous dialysis access and endovascular salvage: Factors determining long term patency and proposed risk equation to prognosticate long term outcomes

Failed arteriovenous dialysis access and endovascular salvage: Factors determining long term patency and proposed risk equation to prognosticate long term outcomes.

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Running title: Long term results of arteriovenous dialysis access salvage.

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7.2.1 Abstract

Failed AV access salvage is commonly performed using endovascular salvage techniques. Whilst initial results are acceptable, longer-term results of endovascular salvage are quite poor; hence understanding of factors affecting long term outcomes is essential. This study aimed to firstly, identify risk factors associated with long term access survival after endovascular salvage and secondly, develop and validate a risk scoring system to help prognosticate access survival.

Methods

Study subjects and basic statistical methods are as described in previous chapter. Univariate and multivariate analysis using Cox regression analysis was performed to evaluate impact of various risk factors affecting primary patency, secondary patency and patient survival (all-cause mortality). Using factors which were deemed significant, the proposed risk scoring was developed with a view to help in prognostication after an episode of VA thrombosis.

Results

Patency rates were as described in previous chapter. Native AVFs (HR 0.3, p<0.001), antiplatelet therapy (HR 0.67, 95% CI 0.45-0.9, p=0.04) and coumarin therapy (HR 0.49, p=0.004) were associated with longer primary patency whereas presence of thrombosis (HR 2, p=0.011) was associated with poorer outcomes. For secondary patency, coumarin therapy (HR 0.39, p=0.005), antiplatelet therapy (HR 0.59, p=0.062) and history of being non-smoker (HR 0.13, p=0.026) was associated with longer patency whereas treatment delay (HR 1.17, p=0.009), male gender (HR 1.59, p=0.01) and presence of thrombosis (HR 5.43, p=0.004) was associate with poorer

outcomes. For patient survival, age, CRP value, vascular disease score and history of malignancy were all associated with poor survival. Longer secondary patency (surrogate for overall AVF survival) was associated with improved patient survival (HR 0.93, $p<0.01$). Using the significant variables for secondary patency, a risk scoring model was developed and patients were stratified into low, moderate and high risk. Event rates in the low, moderate and high risk categories in per 100-patient-years were 7.5 (CI 3.9 – 14.4), 25.6 (CI 19.9-32.8) and 51 (37.3-69.8).

Conclusion

Endovascular salvage techniques are effective in restoring access patency but longer-term results are poor. Antiplatelet and coumarin therapy is associated with improved patency whereas presence of thrombosis portends poor long term patency. The clinical risk scoring system has been developed and if validated in other populations, could prove to useful simple tool to predict long term access survival after an episode of thrombosis.

7.2.2 Manuscript

7.2.2.1 Introduction

Vascular access is the Achilles' heel of haemodialysis therapy. The preferred modality is arteriovenous access is the preferred mode of VA for HD, especially AV fistulae (AVFs). AVAs have several advantages over dialysis catheters – relatively lower infection rates, longer life and reliability. Unfortunately, AVAs are prone to failure themselves. The most common mechanism of failure is thrombosis, usually a result of underlying stenotic lesion leading to reduction in flow.

Annually, 14% of AVFs and between 50 – 80% grafts fail acutely.[62, 163] This often leads to myriad undesirable consequences including disruption of dialysis schedules, hospitalisation with its related complications, and the need for alternative access. These factors have a direct relationship with increased healthcare costs.

Salvage of thrombosed AVFs and grafts can be reliably achieved by surgical or endovascular techniques. Endovascular salvage is preferred where available as it is effective, less invasive, logistically easier to organise and has low complication rates. Technical and immediate clinical success rates are high and average around 90% in most series. Whilst this is success rate is acceptable, longer-term patency rates, especially primary patency rates are poor.[69] Very little is known about what happens to AVAs in the long term after EVS. No effective therapies currently exist to prolong the life of AVAs following thrombosis. The benefit of antiplatelet agents in the setting of primary prevention of AVF failure is not proven.[5] Antiplatelet agents

however, do appear to be beneficial in the case of AVGs in reducing the risk of thrombosis.[169]

Effective treatment and prevention of thrombosis remains a priority in order to increase AVF prevalence. Various studies have reported outcomes of endovascular treatment but very few studies to date have reported long term outcomes after AVA failure and endovascular salvage. Moreover, little is known about the impact of demographic and clinical variables that affect outcomes.

Our study aimed to firstly, understand the impact of demographic, clinical and radiographic variables on long term outcomes of EVS and secondly, using these variables, develop a simple clinical risk scoring system that would help clinicians predict long term outcomes after access salvage.

7.2.2.2 Methods

Study protocol

A failed AVA salvage pathway was established in our centre in January 2008. All patients with an episode of failed AV access, defined as the inability to dialyse the patient using the index AVA, are referred for evaluation and urgent salvage therapy. The study database records details of all haemodialysis patients referred for emergency salvage procedures with a confirmed angiographic abnormality. Baseline demographic information and procedural details are recorded, with co-morbid data, blood results (haemoglobin, haematocrit and C-reactive protein), medication use (antiplatelet agents, statins, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers and coumarin anticoagulants) and

follow up information obtained from electronic patient records. Recorded co-morbid information included coronary artery disease (CAD), defined as history of angina or myocardial infarction, angiographic evidence of coronary arterial lesions, positive radionuclide stress test or history of coronary angioplasty or coronary artery bypass grafting surgery. Peripheral vascular disease (PVD) was defined as history of claudication, evidence of peripheral arterial lesions on angiogram or non-invasive study, history of angioplasty or amputation due to PVD. Chronic heart failure (CHF) was defined as evidence of reduced left ventricular ejection fraction on echocardiogram or radionuclide imaging or left 'ventriculo-gram' performed during angiography. Information on diabetes mellitus (DM) status, primary renal disease, malignancy history, hypertension (HTN) status, dialysis vintage and AVA age was sought. Primary renal disease was classified in 5 categories – vascular, primary glomerulonephritides (GN), renal limited disease such as reflux nephropathy, multisystem disorders affecting the kidney such as myeloma or lupus and remaining diseases were classified as others.

Vascular disease score: Presence of DM, HTN, CAD and PVD was allotted 1 point each and the total score was calculated for individual patients. Thus a patient could potentially have a score ranging from 0 – 4 depending on the risk factors present.

Definition of outcomes

Outcome definitions used are consistent with the Society of Vascular and Interventional Radiology (SVIR) recommendations.[159] Anatomical success was

defined as <30% residual stenosis in case of stenotic lesions, recanalization with restoration of flow in the AVA.

Primary patency was defined as AVA survival without any endovascular or surgical procedures. Primary assisted patency was defined as AVA survival including any endovascular procedures until the next episode of thrombosis or surgery on the study access. Secondary patency was defined as AVA survival until AVA abandonment or surgery.

Failed AVA was defined as an AVA that could not be used for dialysis (excluding primary / early failures).

Statistical methods

Parametric data are presented as mean ± standard deviation and non-parametric data as median [interquartile range]. Between groups, comparisons for categorical variables were made using Chi-squared test and ANOVA appropriate to the distribution of the data for continuous variables.

For survival analyses time zero was defined as the date of interventional procedure. For AVA survival the end-point was defined as date of AVA failure, with patients censored for death, transplantation and change of modality to PD other than due to study access failure. For patient survival the end-point was defined as date of death with surviving patients censored at date of last clinical follow-up. Primary and secondary patency AVA survival rates were calculated using Kaplan-Meier survival method. Associations of co-variates with risk for AVA failure were considered using Cox proportional hazards regression. Proportionality of variables was assessed

using cumulative Martingale residual plots with all baseline co-variates considered in univariate analysis. A multivariate model was then constructed using stepwise selection of variables with a plausible link to AVA failure (alpha value for inclusion <0.3, retention <0.2). Where variables were significantly correlated the most clinically relevant variable was selected for consideration in the multivariate model. The same analytical methodology was used to consider patient survival, with loss of primary and secondary patency considered as additional co-variates and patients with active malignancy excluded from analysis. Results are presented as hazard ratio [95% confidence interval]. Based on results of the multivariate analysis for AVA failure, an ordinal scoring system - weighted by the results of the multivariate model, was generated. This was applied to the patient population with further classification into low, moderate and high risk-groups applied. The utility of this system was considered using Cox regression and Kaplan Meier survival plots (log-rank test). Unless otherwise specified, statistical significance was defined as an alpha value of <0.05 and all interventional procedures were considered on an intention to treat basis.

All analyses were performed using SAS version 9.2 (SAS Institute Cary, NC) and SPSS 20 (IBM Inc., USA) under licence to the University of Manchester.

7.2.2.3 Results

Risk factor analysis and ordinal scoring system

Results of univariate analysis in relation to loss of primary patency, secondary patency and death are presented in supplementary table 7-10. Results of the

multivariate analyses are presented in table 7-6. Based on these results an ordinal scoring system for risk stratification model was generated (table 7-7).

	HAZARD RATIO	p
	Loss of primary patency	
Diabetes mellitus	0.66 (0.41-1.06)	0.087
Antiplatelet therapy	0.67 (0.45-0.99)	0.042
Warfarin	0.49 (0.31-0.8)	0.004
Smoking history	0.5 (0.24-1.03)	0.06
Native graft	0.3 (0.2-0.45)	<0.001
Thrombosis	2.04 (1.18-3.54)	0.011
	Loss of secondary patency	
Age	0.99 (0.97-1.01)	0.171
Delay in treatment	1.17 (1.04-1.31)	0.009
Male gender	1.59 (0.9-2.81)	0.017
ESA use	0.65 (0.39-1.1)	0.107
Antiplatelet	0.59 (0.34-1.03)	0.062
Warfarin	0.39 (0.2-0.75)	0.005
Smoker	0.13 (0.02-0.79)	0.026
Native graft	0.2 (0.11-0.38)	<0.001
Thrombosis	5.43 (1.73-17.02)	0.004
	Death	
Time to failure of secondary patency	0.93 (0.9-0.96)	<0.001
Age	1.05 (1.02-1.08)	0.001
CRP*	1.32 (1.04-1.68)	0.023
Vascular risk score	2.74 (1.21-6.19)	0.016
Cancer	5.13 (2.83-9.28)	<0.001

Table 7-6: Results of multivariate analysis for loss of primary patency, secondary patency and death. CRP = C-reactive protein (hazard ratio is for log-transformed data).

	LOSS OF SECONDARY PATENCY
Male gender	1
No anti-platelet use	1
No warfarin use	1
Graft	2
Thrombosis on angiogram	5
No smoking history	2
Time to intervention	0 if intervention within 48 hours 1 if intervention within 48-96 hours 2 if intervention delayed >96 hours
MAXIMUM SCORE	*13*

Table 7-7: Proposed risk scoring system for predicting risk of access loss

GROUP	RISK SCORE	HAZARD RATIO (95% CI)	EVENT RATE (per 100 patient years)	p
Low risk	0 to 5 (n=80)	Referent	7.5 (3.9-14.4)	-
Moderate risk	5 to 8 (n=214)	3.53 (1.9-6.5)	25.6 (19.9-32.8)	<0.001
High risk	>= 9 (n=111)	6.68 (3.5-12.7)	51.0 (37.3-69.8)	<0.001

Table 7-8: Risk for loss of secondary patency by high and low risk scores. Referent group is low risk patients.

Assessment of scoring system

For loss of secondary patency, the potential range of scores was from 0-9. Patients were therefore assigned to three groups; low-risk (score 0-5, n=80), moderate risk (score 5-8, n=214), and high-risk (score >=9, n=111). Compared to low risk patients,

both higher risk groups were associated with increased risk for loss of secondary patency (moderate risk HR 3.53 [1.9-6.5], p<0.001; high risk HR 6.68 [3.5-12.7], p<0.001). The increased risks corresponded to greater event rates (table 7-8 and figure 7-2). Distribution of patients within risk categories and corresponding - proportions of patients with loss of AVA patency are presented in table 7-9.

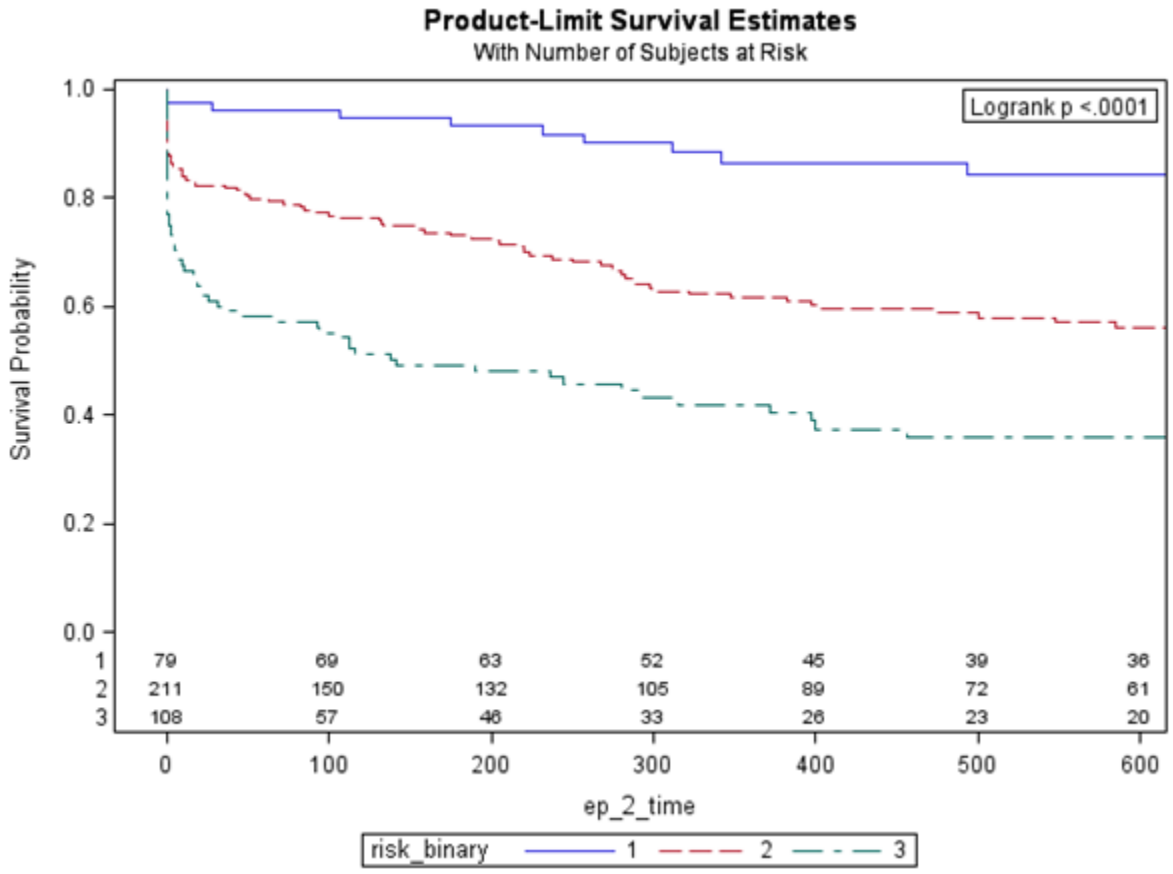

Figure 7-2: Kaplan Meier survival curve for loss of secondary patency by risk group

SCORE	LOSS OF SECONDARY PATENCY
0	0 (0%)
1	4 (1.0%)
2	25 (6.2%)
3	34 (8.4%)
4	14 (3.5%)
5	3 (0.7%)
6	21 (5.1%)
7	93 (22.9%)
8	100 (24.7%)
9	64 (15.8%)
10	37 (9.1%)
11	8 (2.0%)
12	1 (0.25%)
13	1 (0.25%)

Table 7-9: Distribution of risk scores within population

7.2.2.4 Discussion

Increasing AVF prevalence remains a priority for all HD services. Whilst creating more AVFs is an important first step, maintenance of existing AVFs and preventing failure is at least as important. Unfortunately access thrombosis remains a common event and these episodes cause inconvenience to patients and also lead to significant morbidity.

Endovascular treatment of AVA thrombosis has become standard practice across most regions. Whilst immediate outcomes are typically satisfactory, these data

demonstrate that patency rates drop very quickly. In our study, primary patency at six months for thrombosed AVFs was 50% and 15% for AVGs. Poor primary patency rates signify the need for repeated interventions, which is expensive and increases risk of procedural morbidity. Though values for secondary patency may initially appear more acceptable at 74% and 47% respectively, almost 50% of thrombosed AVFs are lost by 3 years. This implies a significant rate of on-going AVA complications. This data also suggest that an episode of failure should perhaps prompt consideration and / or planning of alternative access for the patient in view of high risk of failure.

There are no proven strategies for secondary prevention of thrombosis and failure of AVAs after an episode of thrombosis. Whilst most national and international guidelines recommend surveillance [163] [167] [64], opinion remains divided regarding the benefit of surveillance, especially in AVFs. Ultrasound monitoring, the most widely used method for access surveillance, was found to have no benefit in preventing thrombosis in AVGs and only small benefit in AVFs.[65] A recent review by Paulson et al concluded that in the light of current evidence, routine surveillance cannot be recommended. [66]. All the studies included in these reviews have not specifically targeted high-risk AVFs and grafts. Our results raise the issue of whether we should be considering a different surveillance strategy. Although external validation of our proposed risk scoring system is required, it is conceivable that the greatest benefit from surveillance and / or pre-emptive intervention may be achieved in the highest risk AVF – a cohort that our data suggest may be identified using routinely

measured clinical variables. It is conceivable that surveillance directed at high-risk fistulae and grafts such as those with a history of thrombosis, may therefore be a more cost-effective strategy. Given the beneficial impact of having a patent fistula on survival, both described here and in previous studies[170-172], this may be an important avenue for further study.

Multivariate analysis in this study has revealed several interesting findings. Antiplatelet therapy was associated with better access survival. In the DAC trial, clopidogrel was not found to be effective in the improving primary failure rate of AVFs.[5] In the context of secondary prevention, these drugs may be effective as the therapy is targeted to a much higher risk population. Warfarin therapy was also associated with better AVA survival.

Limitations of the study

This is an observational study and hence associations of risk factors with endpoints by no means imply causality and these observations need to be confirmed in randomised controlled trials. Due to the observational nature of this study we are unable to report significant bleeding complications or other medication related adverse events, another important consideration.

7.2.2.5 Conclusion

In this large prospective series of interventions in failed arteriovenous access, we have reported long term outcomes post-thrombectomy and also analysed factors associated with AVF survival. Beneficial effect of anti-platelet agents and anti-coagulants in secondary prevention is attractive and needs further investigations.

Closer monitoring of AVAs with history of thrombosis is an alternative strategy which may be more cost-effective and further studies are required to evaluate its utility in secondary prevention. We also propose a risk stratification model, which if validated in other studies, could serve as a useful and simple clinical tool to predict loss of VA.

Supplementary tables

	LOSS OF PRIMARY PATENCY			LOSS OF SECONDARY PATENCY		
	n	**Hazard ratio (95% CI)**	**p**	**n**	**Hazard ratio (95% CI)**	**p**
Age (years)	391	0.99(1-1)	0.252	391	0.99(1-1)	0.221
Haemoglobin (g/dL)	361	1.01(0.9-1.1)	0.815	361	1.04(0.9-1.1)	0.472
Haematocrit	361	2.81(0.3-28.4)	0.381	361	5.57(0.2-163)	0.319
C-reactive protein*	253	1.12(1-1.3)	0.032	253	1.12(1-1.3)	0.172
Erythropoietin dose	242	1(1-1)	0.385	242	1(1-1)	0.616
Dialysis vintage (years)**	362	1(1-1)	0.221	362	1(1-1)	0.556
Fistula age (years)	364	1(1-1)	0.223	365	0.99(1-1)	0.038
Delay in intervention (days)	396	1.04(1-1.1)	0.226	396	1.03(0.9-1.1)	0.515
Male	398	0.62(0.5-0.8)	0.001	398	0.68(0.4-1.1)	0.099
Diabetes	398	0.69(0.5-1)	0.023	398	0.62(0.4-1)	0.07
Coronary artery disease	398	0.67(0.5-0.9)	0.023	398	0.81(0.5-1.4)	0.426
Stroke	398	0.66(0.3-1.3)	0.203	398	0.35(0.1-1.2)	0.086
Congestive heart failure	398	1.03(0.7-1.4)	0.869	398	1.24(0.8-2)	0.378
Peripheral vascular disease	398	1(0.7-1.5)	0.997	398	1.03(0.6-1.9)	0.925
Hypertension	398	0.97(0.7-1.3)	0.799	398	1.07(0.7-1.7)	0.774
Cancer	398	0.7(0.4-1.3)	0.265	398	0.71(0.3-1.9)	0.494
Erythropoietin use	398	0.82(0.6-1.1)	0.201	398	0.71(0.5-1.1)	0.133
Statin	398	0.85(0.6-1.1)	0.237	398	0.79(0.5-1.2)	0.277
Antiplatelet use	398	0.81(0.6-1.1)	0.113	398	0.88(0.6-1.3)	0.548
Warfarin	398	1.29(0.9-1.8)	0.133	398	1.18(0.7-2)	0.557

Angiotensin blockade	398	1.1(0.8-1.5)	0.499	398	1.13(0.7-1.8)	0.599
Caucasian	398	0.9(0.6-1.3)	0.549	398	0.89(0.5-1.6)	0.678
Forearm fistula	398	0.76(0.6-1)	0.04	398	1.16(0.7-1.8)	0.501
Smoking history	398	1.27(0.9-1.9)	0.202	398	0.26(0.1-1.2)	0.082
Native fistula	398	0.4(0.3-0.5)	<0.001	398	0.33(0.2-0.5)	<0.001
Thrombosis	398	1.72(1.3-2.3)	<0.001	398	4.48(2.5-8)	<0.001
PTA vs. mechanical	351	1.29(0.9-1.8)	0.144	352	1.19(0.8-1.8)	0.442
PTA vs. thrombolysis	351	1.48(1-2.1)	0.027	352	1.65(1.1-2.6)	0.029

Table 7-10: Univariate association of baseline characteristics with loss of primary and secondary patency. Data are presented as hazard ratio (95% CI). n represents number of patients with data point available. * indicates log transformation of continuous variable. ** indicates square transformation of continuous variable. Delay in intervention calculated as time from referral to procedure. PTA – angioplasty +/- balloon maceration only

	DEATH (ALL-CAUSE)		
	n	Hazard ratio (95% CI)	p
Age (years)	398	1.07(1-1.1)	<0.001
Haemoglobin (g/dL)	366	0.86(0.7-1)	0.057
Haematocrit	366	0.01(0-1.1)	0.053
C-reactive protein*	255	1.39(1.1-1.7)	0.005
Dialysis vintage (years)**	366	1(1-1)	0.603
Male	405	1.41(0.7-2.7)	0.298
Diabetes	405	1.26(0.7-2.4)	0.475
Coronary artery disease	405	2.97(1.6-5.5)	<0.001
Stroke	405	4.14(1.8-9.5)	0.001
Congestive heart failure	405	1.59(0.8-3.2)	0.189
Peripheral vascular disease	405	1.98(0.9-4.2)	0.078
Hypertension	405	1.08(0.6-2)	0.798
Cancer	405	5.2(2.7-9.9)	<0.001
Smoking history	405	0.88(0.2-3.7)	0.863

Table 7-11: Univariate association of baseline characteristics with all-cause mortality. Data are presented as hazard ratio (95% CI). n represents number of patients with data point available. * indicates log transformation of continuous variables, ** indicates square transformation of continuous variables.

Chapter 8: Discussion and Conclusions

Discussion and conclusions

The primary aim of this thesis was to design studies that further our knowledge of HD vascular access outcomes with focus on AVFs – studies that investigate the outcomes and interventions at the various time points in the natural history of AVFs. This section is aimed at drawing together the various outcomes of the work into a coherent synthesis with directions for future work.

The MANVAS study

This project was designed in order to understand the natural history of AVFs and evaluate interventions that could improve AVF outcomes. It is the largest study of its kind to be conducted in the UK. The MANVAS study will not only provide epidemiological data but also be a rich source of clinical and biological datasets that can define the natural history of AVF lifecycle. These findings will help define the clinical base and its heterogeneity in vascular access creation. There are several other anticipated utilities from this study.

Firstly, it will provide an opportunity to identify factors associated with AVF outcomes. Secondly, the study provides biological samples to be used for testing various hypotheses. The biological samples obtained from the MANVAS study are already being used for various nested case controlled studies – examine histological aspects, influence of genetic markers such as microRNAs and serum biomarkers. These studies will be unique in having validated clinical endpoints and will provide an excellent link between clinical and basic science research. Thirdly, the role of US,

especially the early 2 week scan and role of serial monitoring, can be evaluated. Fourthly, the study will also provide insights into a poorly studied domain of cannulation practice. Lastly, from a more holistic perspective, the study will provide insights into the vascular access care pathway/s that our HD patients undergo. This understanding is important to elucidate pathways that can provide safe, reliable and long term VA to improve outcomes and patient experience on HD.

The results of interim analysis presented in this thesis show that maturation rates of AVF (<60%) remain poor and will be a significant impediment for renal units trying to improve their AVF prevalence. Due to paucity of reliable clinical predictors of AVFs outcomes, we need to rely on other techniques such as ultrasound. Even though these techniques are widely available, there are a lot of unanswered questions – what is the best time to perform these scans, what is the role of performing serial scans, which reliable and easily reproducible ultrasound measures are associated with outcomes? This initial analysis suggests that brachial artery flow on US scan performed at 2 weeks may be reliable predictor of AVF outcomes. Measurement of volume flow in the AVF itself is less reliable due to significant inter- and intra-operator variability. Moreover, quality and capability of the ultrasound equipment also plays an important role. However, arterial volume flow measurements are more reliable and more reproducible. These findings need further validation in the larger MANVAS cohort and also in other populations. But if validated, this can serve as simple tool in predicting AVF outcomes at an early stage and planning timely interventions.

The MANVAS study findings reported in this thesis are limited to the initial cohort dataset that were available and therefore lack full interpretation. However, the design and its implementation of MANVAS has been a unique personal research experience and has given me the grounding in developing research questions and robust protocols in complex areas such as vascular access research. The successful implementation of MANVAS has enabled road testing the protocol and the study procedures. The preliminary report in this thesis bears promise of high quality research output that I wish to pursue on completion of the MANVAS study in the near future.

The OPEN study

The aim of the OPEN study was evaluating the Optiflow device which was designed to address the most common cause of early AVF failure – juxta-anastomotic stenosis secondary to neo-intimal hyperplasia. In the context of heterogeneity in clinical practice of vascular access creation, the influence of surgical skill mix in AVF failure due to juxtanastomotic stenosis must be considered. Against this clinical landscape, the Optiflow™ device may be an effective intervention to standardise practice of creation of AVFs. This is increasingly relevant where highly experienced and skilled surgical services are not readily accessible. By shielding the peri-anastomotic area from effects of shear stress, the device may also influence the biological processes that culminate into development of juxta-anastomotic stenosis and high primary AVF failure.

Our study is the first study to have investigated use of this device in systematically conducted trial setting. The OPEN study results indicate that the Optiflow™ device may play a role in enhancing AVF maturation. If these results are replicated in a larger analysis, this device would certainly form a part of the therapeutic armamentarium of clinicians and could potentially augment the surgical skill base required in creation of AVF and improve maturation.

This study also showed that outcomes of the 3mm device were inferior to the 4mm device – this finding has led to reconfiguration of the device design by the manufacturer. The findings from this study have also served as the basis for Food and Drug Administration, USA approval application and planning a larger study.

The study was a prospective controlled but non-randomised as it was designed to be a pilot study to assess the clinical safety profile and efficacy of the device.

This study raises some interesting research questions. Long term outcomes studies of 'AVFs with in-situ devices' are not available. Currently published work indicates that use of stents in AVFs is associated with poor outcomes, but these are limited to studies evaluating stents originally designed for treating arterial lesions. Clinical applicability of using these stents in AVFs which are arterialised veins has never been proven in RCTs. The design of venous stents deserves further investigation and especially in the research of arteriovenous fistula. To improve outcomes of stents and vascular in-situ devices in AVFs, other approaches may need to be considered. Bio-absorbable and coated stents for use in venous stenosis and other clinical settings in AVF complications in the long term may be particularly relevant and

could be developed further. The results from the OPEN study could act as a pathfinder in the developmental and clinical research of venous stents to minimise AVF complications.

The coil embolisation study

The second most common cause of early AVF failure is accessory draining veins. Despite this, the role of accessory draining veins has been a matter of debate. This study was designed to review the practice of ADV obliteration – is it appropriate and is it effective? The study findings attest to the biological significance of these anatomical variations in the functional development of AVF. The study also provides further evidence of the beneficial effect of endovascular coiling for salvaging failing and non-maturing AVFs. Moreover, this procedure can be performed at the same time as diagnostic angiography ± angioplasty.

Understanding the clinical significance of branch veins is important, as is distinguishing a large collateral vein from a large ADV and also insignificant branches. Collateral veins develop as a result of downstream stenosis and provide a haemodynamically significant conduit to divert the blood flow. Obliterating these can lead to thrombosis of the AVF. Differential volume flow measurements across the ADVs, using US may help in determining the blood flow into the branch and compare it to the blood flow within the main fistula vein. This can be helpful to identify clinically insignificant branches, which ought to be left alone. Yet, it does not reliably distinguish between a collateral vein and true ADV. Currently; angiography remains the only method where this judgment can be made. There are no

prospective controlled or randomised studies in this area and such studies are unlikely to be conducted in the near future.

This was a retrospective study and did not have a control group and therefore does not provide conclusive evidence of benefit. Comparison with the PTA alone group within the same centre revealed superior outcomes of coiling ± PTA. Whilst, direct comparison may be difficult due to possible clinical heterogeneity between these groups, resulting in selection bias, these findings serve as a guide to clinicians who are faced with failing AVFs which have ADVs.

VA in Home HD

AVFs undergo repeated cannulation with large bore needles at least thrice weekly in in-centre dialysis patients and more frequently in patients on extended dialysis schedules. Despite this, very few studies have reviewed the practice of AVF cannulation and its impact on AVFs.

HHD remains the best form of dialysis in the long term with outcomes approaching those of cadaveric transplantation. Despite the importance of such research, to date there are very few clinical studies looking into this important area. Typically AVF cannulation is practised by staff with variable experience and skill mix which makes cannulation studies difficult to undertake. The practice of self cannulation removes this inter-operator variability and provides a naturally controlled setting to examine hypothesis and questions.

In view of lack of literature on this topic, the above study was undertaken to gain insight into AVF use in the HHD cohort. The study was set up with specific

objectives – 1) outline the trends and outcomes of VA in this cohort and 2) study the impact of more frequent AVF use in unmonitored non-healthcare setting.

Over three-quarters of the HHD patients were on extended dialysis schedules, thus subjecting their AVFs to more frequent cannulation. Access outcomes including AVF prevalence were superior in the HHD group than in-centre group. Selection bias, at least, partially is the likely explanation for this observation.

It is also apparent that despite better longer term AVF survival, significant support was required for cannulation which puts pressure on already stretched NHS resources. Association of patient survival with incident access type is an interesting finding and needs further exploration in larger populations. This effect was observed despite more than 50% of the catheter group going on to have successful AVF creation.

Does catheter use incite biological processes that give rise to poor outcomes? Catheter use has been previously shown to be associated with poor survival in large registry studies, so this finding is not entirely surprising. What is striking though is that even short duration of catheter use seems to be associated with poor outcomes. HHD patients have better morbidity and mortality outcomes compared to in-centre patients and yet, we observed this difference in survival. Incident access type may potentially have more significant effects on in-centre HD populations where mortality is higher. Further studies perhaps extended to a national cohort or linked to the registry dataset are warranted for validation of this observation. If this effect is observed in larger populations, investigation into the putative mechanisms will be

warranted and these investigations will provide rare insights into effects of devices on vascular health.

Acute vascular access failure study

The study investigates a terminal or pre-terminal phase of an AVF lifecycle, and is one of the largest series reporting outcomes of clotted/failed AVA and the results of endovascular salvage. To our knowledge, this is the only study reporting relatively longer-term results and has also helped identify factors associated with outcomes. The study has provided epidemiological data on acute VA failure, which has been lacking in view of shorter duration of follow up in previously reported studies.

The balloon maceration technique has been criticised by some authors due to a few reports of pulmonary embolism. This technique is commonly and safely practised in many large centres in the UK. However, in view of lack of safety data, some centres have favoured more expensive techniques over this long-established, simple and cost effective one. This study not only highlights the safety of the BM technique but also shows that the outcomes are comparable. In the days of ever increasing health-care costs and finite resources, cost-effectiveness is an important consideration.

Moreover, the long noted association of AVF use with lower mortality has also been replicated in this unique setting. It is a reassuring message to health care planners and clinicians that all the efforts invested in keeping AVFs patent do pay their dividends.

Using this data, a clinical risk scoring system has been developed which could prove to be a useful tool to predict long term access survival after an episode of thrombosis. This requires validation in a larger population base.

Finally, this study has allowed us to evaluate the care pathways for patients presenting with acute VA failure. The study was made possible due to a standardised service delivery model that preceded the data collection. On the other hand, prospectively analysing outcomes from this service delivery model has helped to further streamline the care process, identification and rectification of any issues with the service model. Lack of availability of such service delivery model is an important challenge in designing prospective studies to evaluate outcomes of acute VA failure. The findings strongly argue for a dedicated standardised salvage pathway to reap the full benefits of prompt interventions in prolonging the life of an AVF. Economic modelling could also be undertaken for such a provision within different health care settings. Furthermore the model provides an ideal platform to undertake more robust interventional trials to reduce the incidence of fistula failure.

This study also serves as a good example of how research and clinical service improvement can be incorporated together using a multidisciplinary approach. A multidisciplinary research team support with access to a large population base is an essential prerequisite to undertaking comprehensive research in vascular access.

The meta-analysis demonstrates that there is an unmet need for more head to head comparative studies for VA interventions in practice. The meta-analysis provides

further evidence to the equivalence of EVS compared to surgery for management of thrombosed grafts.

Summary

This MD project involved clinical studies that were designed to evaluate the entire AVF pathway – starting from the pre-creation phase to maturation and finally clinical use and failure. These studies have contributed to increasing our understanding of current problems and evaluate interventions addressed at solving those. The studies have also contributed to our knowledge from a variety of approaches –improving clinical knowledge, evaluating care delivery models and will serve as a platform to design basic science research to elucidate biological mechanisms underlying AVF maturation and outcomes.

This MD project has been a unique research experience of conceiving, designing and conducting multipronged research into the area of vascular access. It has also provided me a great deal of clinical insights into all aspects of vascular access care and research. The research experience and knowledge gained in this project would serve as an excellent foundation to develop clinical care, care pathways and clinically relevant research studies.

Appendices

A META-ANALYSIS OF RANDOMIZED TRIALS COMPARING SURGERY VERSUS ENDOVASCULAR THERAPY FOR THROMBOSED ARTERIOVENOUS FISTULAS AND GRAFTS IN HEMODIALYSIS ††

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9.1.1 Abstract

Purpose

To carry out a systematic review of randomized trials comparing surgery vs. endovascular therapy for occluded fistulas and grafts.

Methods

All randomised trials which compared surgery and endovascular therapy for occluded fistulas and grafts were retrieved from 1990 onwards. The following search terms were used- "haemodialysis", "thrombosis", "arteriovenous fistula", "arteriovenous shunt", "end stage renal failure" on MEDLINE and PubMed. The results of the pooled data was analysed using a fixed-effect model.

Results

There were no randomized trials comparing surgery versus endovascular therapy for native fistulas and vein grafts. There were 6 randomised studies on 573 occluded grafts. Technical success, need for access line and primary patency at 30 days were similar between the two groups (OR 1.40 (95% CI 0.91, 2.14), 0.77 (95% CI 0.44, 1.34) and 1.15 (95% CI 0.79, 1.68)) respectively. There was no significant difference in morbidity at 30 days between groups OR 1.12 (95% CI 0.67, 1.86). Surgery had a better 1 year primary patency rate although it was not statistically significant OR 2.08 (95% CI 0.97, 4.45). Primary assisted patency at 1 year was better with surgery OR 3.03 (1.12, 8.18) in a single study.

Conclusions

Comparable short term results to surgery have been achieved with endovascular techniques for occluded prosthetic grafts for dialysis access. Long term data comparing the two groups is lacking. Further trials designed to encompass variation in methods is warranted in order to obtain the best available evidence.

9.1.2 Article

Introduction

The incidence of patients requiring dialysis with end stage renal failure is likely to increase in future. Vascular access for haemodialysis (HD) can be in the form of arteriovenous fistulas (AVF), prosthetic grafts (AVG) or catheters. AVF are considered to be the gold standard for long term dialysis access. Catheters are best avoided due to infective and thrombotic complications. However, thrombotic occlusion of fistulas and grafts is increasingly a common complication facing access providers, resulting in multiple hospital admissions, complex interventions and morbidity.[3] The methods used for thrombectomy of occluded AV access can be broadly categorized into surgery or endovascular therapy.

The most efficacious method for access salvage is not known. Consequently there is a wide variation in methods employed for thrombectomy among access providers. Meta-analysis carried out in 2002 supports surgical thrombectomy for occluded prosthetic grafts.[173] There are several case series involving various devices reporting success rate of 76 to 90% with endovascular therapy.[174] A recent review identified lack of good quality evidence in the form of randomized trials.[175] KDOQI guidelines highlight the importance of meta-analysis and further trials in this especially for AVFs.[176] The aim of the study was to carry out a systematic review of randomized trials comparing surgery and endovascular therapy for occluded AVF and AVG in order to ascertain the available evidence, and inform best practice

Materials and Methods

Eligibility criteria

The objectives, methodology of the systematic review and analysis, and the inclusion criteria for study enrollment were pre-specified and documented in a protocol. Randomized studies from 1990 onwards comparing the outcomes of surgery and endovascular therapy were eligible. Males and females of any age with an occluded AVF or AVG were included. Early as well as late occlusions were included. Studies which combined surgery and endovascular therapy were excluded. Eligibility assessment of studies for inclusion in this review was performed independently in a blinded standardized manner by two reviewers. Disagreements between reviewers were arbitrated by discussion.

Definitions and endpoints

Endovascular therapy was defined by a procedure requiring percutaneous puncture of a graft or fistula and the use of percutaneous devices under X-ray control for thrombectomy. The underlying stenosis should be treated with angioplasty or stent. Surgery was defined as procedure requiring a skin incision to access graft or fistula and the use of Fogarty thrombectomy catheter combined with retrograde digital expression of thrombus. The underlying stenosis should be treated with surgery (patch-plasty, revision or interposition graft).

Primary outcome was primary patency at 30 days and at 1 year. Secondary outcomes were technical success, primary assisted patency, secondary patency, need for access line and morbidity. Primary patency was defined as graft or fistula free of

stenosis greater than 50% or complete occlusion at a fixed time period on Duplex scan or an angiogram. Primary assisted patency was defined as graft or fistula free of occlusion at a fixed time period. Secondary patency was defined as graft or fistula free of occlusion after intervention for occlusion in a defined period.[159] Technical success was defined as restoration of adequate flow to dialyze.

Information sources and search methods

An electronic search of the literature was undertaken. The search was applied to MEDLINE (database provider PubMed, from 1966 to 2012), EMBASE (database provider Ovid, from 1980 to 2012) and Cochrane Central Register of Controlled Trials (2012). A second-level of search included a manual screen of the reference lists of selected articles identified through the electronic search. No language constraints existed. Expanded Medical Subject Headings (MeSH) and keywords searches for "haemodialysis", "thrombosis", "arteriovenous fistula", "shunt" and "end stage renal failure" was done.

Data collection and analysis

A data extraction sheet was developed and pilot-tested on three randomly selected included articles. Data were independently extracted and verified by two authors. The collected variables were divided in three broad categories: 1) baseline clinical/demographic data and procedure-related characteristics, 2) primary early and late outcome data, and 3) secondary outcome data. The methodological quality of the included studies was assessed using Jadad score.[177]

The above outcome measures were organized in a two-by-two table to permit calculation of events for surgery and endovascular group. Dichotomous outcome variables were used for fixed time period when patency rates were mentioned in percentages. Data were extracted from the text, life tables or graphs. Study effects were presented using the odds ratio (OR) and the 95% confidence interval (CI). The OR and 95% CI for combined studies were calculated using the fixed effects model of meta-analysis. The Cochran's Q-test was applied to estimate between study heterogeneity, and p-values < 0.05 were considered significant for heterogeneity. Publication bias was assessed visually by evaluating the symmetry of such funnel plots. Review manager version 5.1 was used for all the analysis.

Results

There were no randomized trials comparing surgery and endovascular therapy for native fistulas and vein grafts. Seven studies met our inclusion criteria and, after adjusting for duplicate publications, six papers reporting on a total of 573 occluded prosthetic grafts were available for analysis (figure 7-3).[68, 76, 164, 178-180] The mean Jadad score was 2.5.

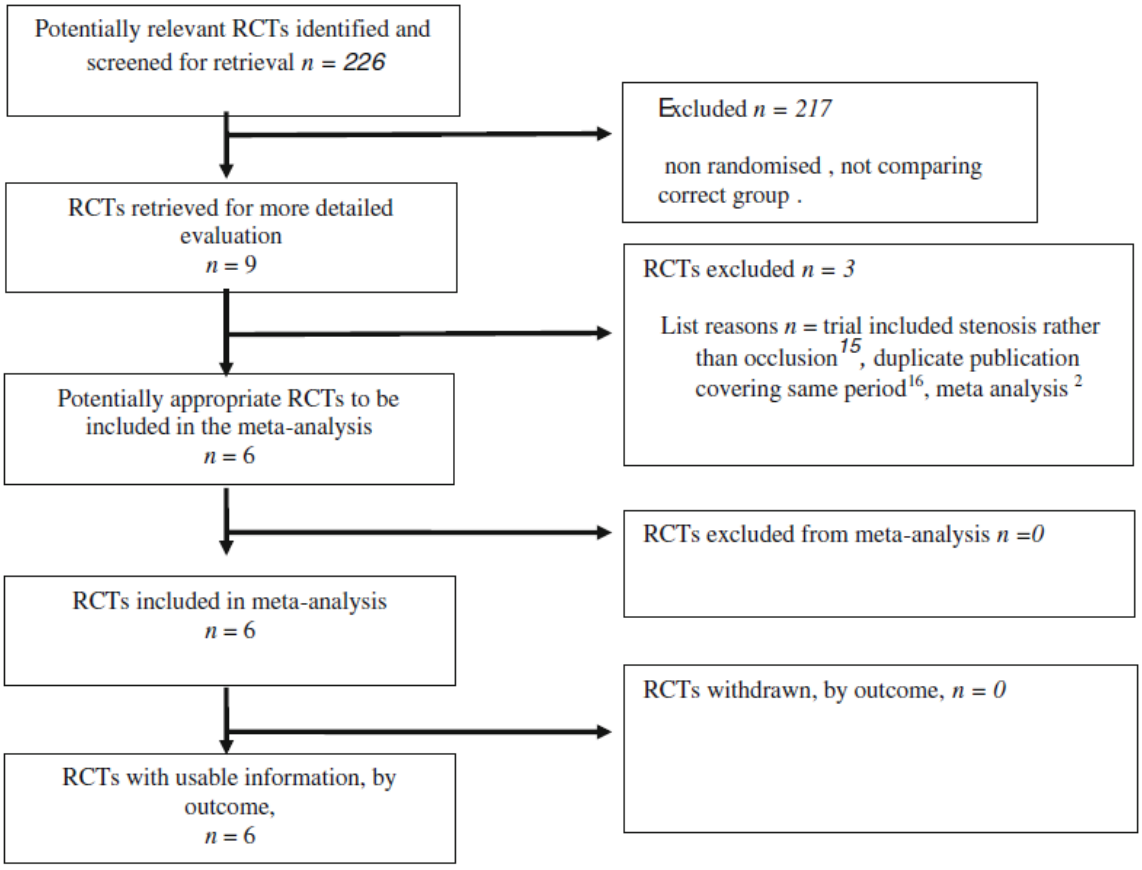


Figure 0-1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram for the study

Technical success: Five studies reported technical success rates.[68, 76, 164] Technical success rate was 74.5% and 80.3% in the endovascular and surgical groups respectively (OR = 1.40, 95% CI 0.91-2.14; p = 0.13) (figure 7-4). No significant heterogeneity between the studies was found (I^2=0%, p = 0.42).

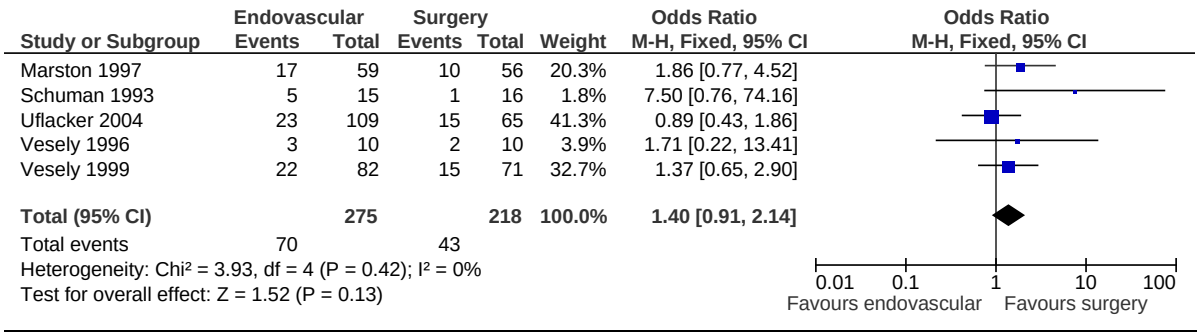


Figure 0-2: Forest plot for technical success

Primary patency at 30 days: Six studies reported primary patency at 30 days.[68, 76, 164, 178-180] Primary patency rate was 64.6% and 66.8% in the endovascular and surgical groups respectively. (OR = 1.15, 95% CI 0.79-1.68; p = 0.46). No significant heterogeneity between the studies was found (I^2=14%, p = 0.33) (figure 7-5).

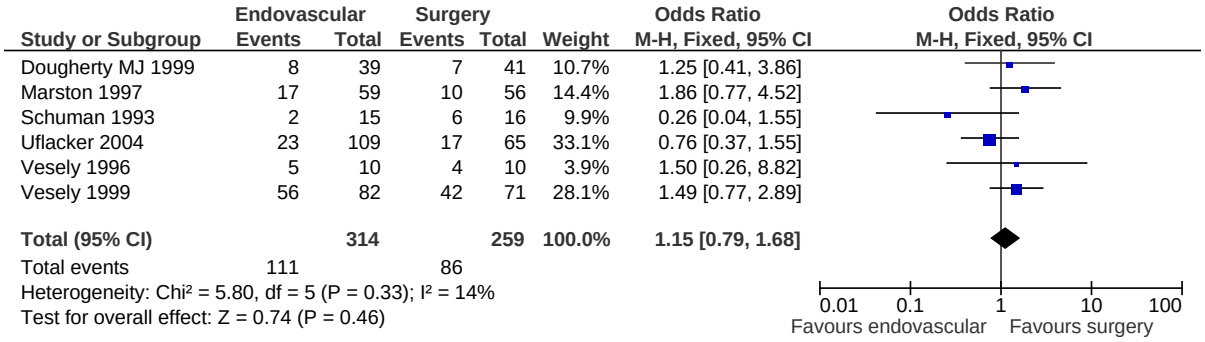


Figure 0-3: Forest plot for primary patency at 30 days

Primary patency at 1 year: Three studies reported 1 year primary patency rates.[76, 179, 180] The patency rates were 14.2% and 23.9% for endovascular and surgical group respectively. (OR=2.08, 95% CI 0.97-4.45; p=0.06). No significant heterogeneity was found between studies (I^2=0%, p=0.83) (figure 7-6).

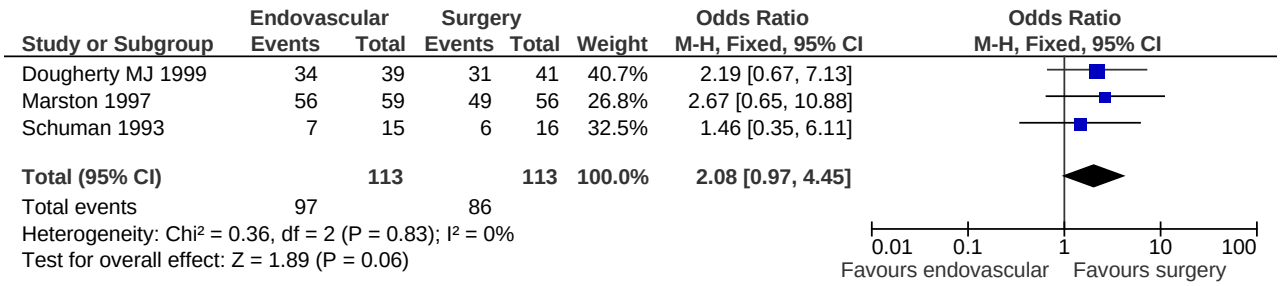


Figure 0-4: Forest plot for primary patency at 1 year

Primary assisted patency at 1 year: Only 1 study reported this outcome.[180] The patency rate was 20.5% and 43.9% for endovascular and surgical groups (OR=3.03, 95% CI 1.12-8.18, p=0.03).

Secondary patency rate at 1 year: Only one study reported this outcome.[179] The patency rate was 86.7% and 62.5% for endovascular and surgical groups (OR=0.26, 95% CI 0.04-1.55, p=0.14).

Need for access line: Three studies reported this outcome.[68, 76, 179] The need for a line was 19.6% and 25.6% for endovascular and surgical group (OR=0.77, 95% CI 0.44-1.34, p= 0.35). There was no significant heterogeneity among the studies (I^2= 37%, p=0.21) (figure 7-7).

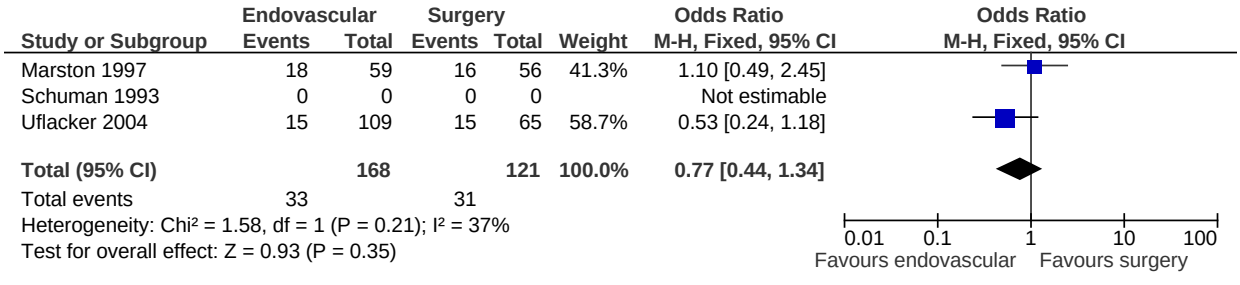


Figure 0-5: Forest plot for need for catheter

Morbidity at 30 days: Six studies reported this outcome.[68{Vesely, 1996 #236, 76, 178-180}] Overall morbidity at 30 days was 15% and 11.6% for endovascular and surgical groups (OR=1.12, 95% CI 0.67, 1.86, p=0.67). There were no significant heterogeneity among the studies (I^2=0%, p=0.56) (figure 7-8).

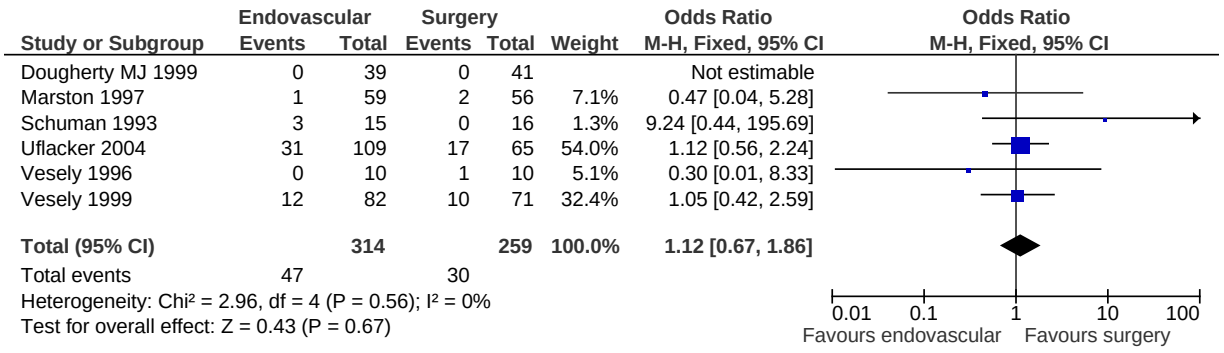


Figure 0-6: Forest plot for morbidity at 30 days

Funnel plots did not show any significant publication bias on visual inspection (figures 7-9 and 7-10).

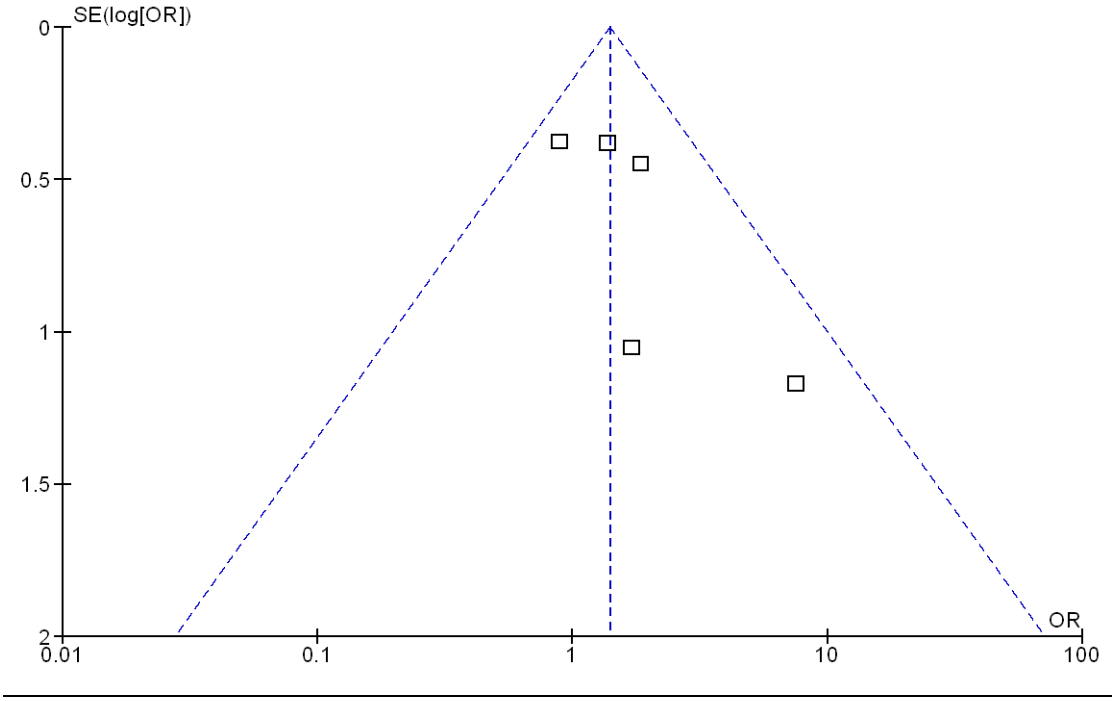


Figure 0-7: Funnel plot for technical success

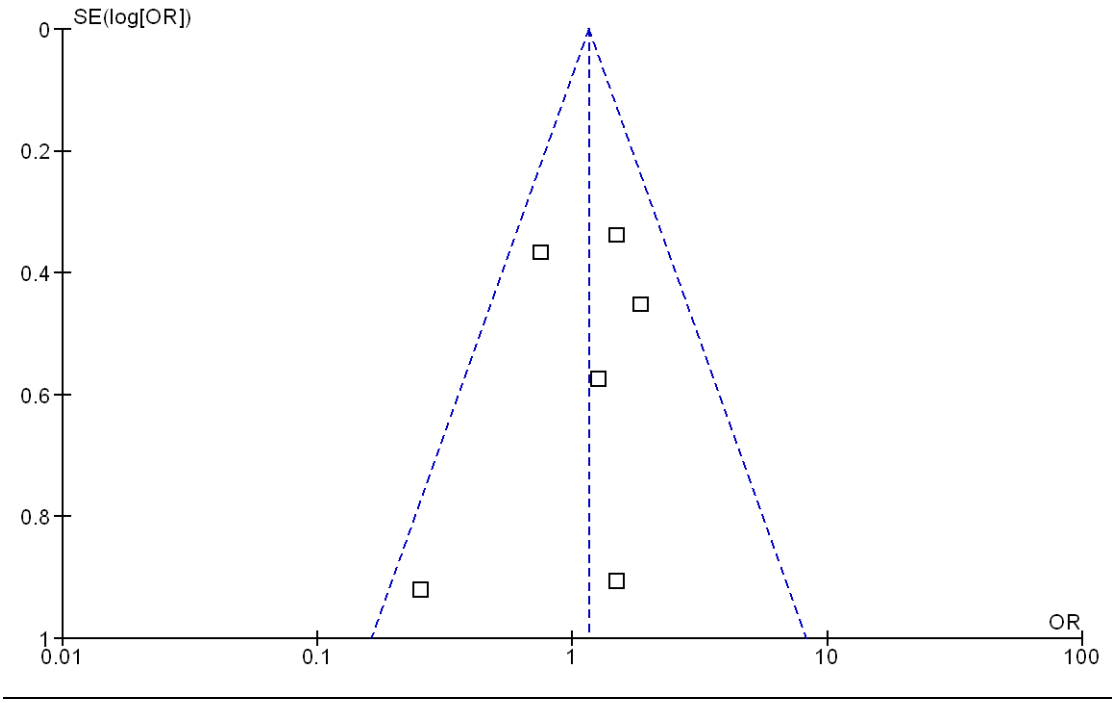


Figure 0-8: Funnel plot for primary patency at 30 days

Discussion

Surgical thrombectomy has been the traditional means of treatment for occluded access grafts and fistulas. Endovascular therapy is an attractive alternative and has gradually become the mainstay for thrombectomy as interventional radiology has become embedded in clinical medicine. Implementation of the recent guidelines has resulted in access provision with native fistulas and vein grafts rather than prosthetic grafts.[3] The results of the current systematic review show that there were no randomized trials comparing surgery and endovascular therapy for gold standard vascular access i.e. native fistulas and vein grafts. It is clear from the present review that further studies are needed in order obtain the best available evidence in this area.[175] A meta-analysis carried out in 2002 concluded superiority of surgery for prosthetic grafts patency.[173] In the current review technical success, need

for access line and primary patency at 30 days were similar between the two groups (OR 1.40 (95% CI 0.91, 2.14), 0.77 (95% CI 0.44, 1.34) and 1.15 (95% CI 0.79, 1.68) Long term results suggest surgery had a better 1 year primary patency rate although it was not statistically significant (OR 2.08, 95% CI 0.97, 4.45) (figure 3). Primary assisted patency at 1 year was better with surgery OR 3.03 (1.12, 8.18). Only one study reported primary assisted patency rate and 3 studies reported primary patency rate at 1 year. The need for long term outcome data is lacking in the literature. Previous meta-analysis in 2002 suggested technical success in favour of surgery.[173] The current review concludes comparable technical success to surgery for prosthetic grafts. The improved patency rate with endovascular therapy might be attributed to the improvement in technical success. Technical improvements and operator experience with various endovascular devices is likely to account for the improved success with endovascular salvage procedures.

There were several methodological limitations in the current review. The studies included in the review were predominantly before 2000. There has been improvement in the technique and increase in experience with endovascular therapy since 2000. There is also variation in methods used in endovascular therapy. Balloon thrombectomy, aspiration, Angiojet and Amplatz device were the endovascular methods used for thrombus removal. There are currently several other newer devices for thrombectomy which have not been used in these trials.[77] Balloon angioplasty was the only technique used for treating underlying stenosis. Drug eluting balloons, bare metal stents and stent grafts were not used. Balloon

angioplasty with stent graft has a better patency rate compared to balloon angioplasty alone for venous stenosis related to AVF in a recent randomised trial.[181] The inclusion and the exclusion criteria varied among the trials. Three of the studies failed to disclose the method of randomisation.[76, 179, 180] None of the studies were blinded which is an inevitable consequence of surgical trials.

There are several methods of thrombectomy with endovascular therapy for occluded access. Similarly there are several methods for the treatment of underlying stenosis. A study designed to encompass all different methods is needed to identify the best available method. Cost effectiveness of various methods needs to be assessed. In conclusion comparable short term results to surgery have been achieved with endovascular techniques for occluded prosthetic grafts for dialysis access. Long term data comparing the two groups is lacking.

The nephrology community, worldwide, is challenged with increasing the prevalence of AVF in patients on HD. This is dependent on both increased surgical creation of new AVFs and maintenance of higher patency rates of established AVFs. This review highlights a distinct lack of literature comparing surgical vs endovascular salvage in management of thrombosed AVFs. Future trials designed to encompass variations in methods used for thrombectomy and treatment of underlying stenosis is warranted. There is an urgent need for further studies in this area to help inform the best methods of improving longevity of AVFs – the gold standard in vascular access. The available evidence can then deliver manifold

benefits, to inform the design of optimal dialysis access care provision, standardise clinical practice in renal units and improve patient outcomes.

MANVAS study patient information sheet

Central Manchester University Hospitals NHS
NHS Foundation Trust

REC Ref: 11/H1016/3

Renal Patient Information Sheet

Title: Manchester Vascular Access Study (MANVAS)

A study to understand how a dialysis fistula matures (becomes usable) and to identify factors which influence this process

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you do take part you will be given a copy of this information sheet and a signed consent form to keep.

What is the purpose of this study?

Haemodialysis is a life sustaining treatment that requires good access to the blood stream, called vascular access. Maintaining a good vascular access is the foundation for ideal haemodialysis treatment. This study aims at understanding the maturation process of dialysis arteriovenous fistula (AVF) and we aim to identify factors that may influence outcomes of AVFs.

If we can identify factors that matter, we may be able to improve the performance of AVFs so that they work when they are required to be used by patients and also, patients will avoid having to have repeat procedures. This may also allow planning in advance for procedures that are more likely to succeed. Finally some of these factors that we discover may be manipulated by using various treatments to see if in future studies, we can further improve outcomes of AVFs.

Why have I been chosen?

We are asking all patients who are undergoing access formation in the Greater Manchester region.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If

you decide to take part you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

We would like to invite you to take part in this study which consists

1. Extra Doppler ultrasound scans – patients normally have a scan done pre-surgery and again at 6 weeks. So you would have 2 extra scans (at 2 weeks and 3 months post-surgery) compared to usual practice. These scans are painless and do not have any side effects as no radiation is involved (unlike an X-ray).
2. Patients from Salford renal unit may need to attend for the pre-surgery scan at Manchester Royal Infirmary or Wythenshawe Hospital Vascular Lab for their scan. This may lead to an extra visit (total 3 extra visits) but every effort will be made to minimise the total number of visits.
3. You may an extra blood sample before, during and after surgery (about 40ml) along with your usual blood tests. We do not anticipate that there will be any side effects from you giving a small extra blood as the sample would be taken at the same time as other routine clinic blood samples are taken. Your blood samples will allow us to test for any factors that may influence success or failure of your dialysis access.
4. During the surgery that creates the AVF; small pieces of excess blood vessel tissue are removed and discarded. Should you have any surplus tissue (usually the thickness of a 5p coin) removed during access surgery for any reason, we would ask you to gift that tissue to the research project. No extra tissue will be taken during your surgery.

The research plan will have been authorised by the local ethics committee. Taking part in this study will not affect the type of medicine you are prescribed or any aspect of your clinical care.

What are the possible benefits of taking part?

Taking part in the study will allow us to do more frequent monitoring of your access which may lead to earlier detection of problems that are developing with it.

What are the possible disadvantages of taking part?

You will be having extra visits to the hospital and this would include extra scans and blood tests. Rarely, some patients can experience fainting as a result of blood being taken.

Will my taking part in this study be kept confidential?

Your clinical information will be confidential and will not be released to anyone outside the hospital. When the results of the study are reported and published, your

name will not be released and it will be impossible to identify your results or any other individual patient's results. However, it may be necessary for the CMFT hospital regulatory authorities to review this study to confirm that the research has been conducted properly. We would also like to inform your General Practitioner about the study and will send him/her a letter to explain the research project.

There may be an extra member (researcher) present during your surgery who would take detailed notes of the operation. They are not normally present during the operation. They would not participate in the actual procedure itself.

With your permission, we would like to keep your GP and / or kidney doctor informed of your participation in the study.

What will happen to the results of the study?

This is part of a long term study. We expect to do an initial analysis and publish the results in medical journals. You will not be identified in any of these publications.

What happens if something goes wrong / you notice any problems?

This study does not involve any medical procedure that could cause problems. However should things go wrong, you could contact your GP, renal team or nearest A&E, depending on the nature of the problem. Your doctor can get in touch with the transplant surgical doctor on-call at the Manchester Royal Infirmary if any additional specialist input is required.

What will happen to the samples that I donate for research?

We are asking you to gift for this project your blood and any tissue samples only for research into vascular access and kidney disease. These samples will be stored in the Renal Labs at Manchester Royal Infirmary during this project.

The Renal Research Labs has already established the MINT Biobank for Kidney Research (under a separate ethics authority Reference 06/Q1406/38) which stores blood, DNA, tissue and urine on kidney patients from previous and current research studies. We are asking you to consent for storage in the MINT BioBank of any remaining samples left over from this current study for future studies on kidney disease. In this event, your samples will be coded by disease type only so nobody will be able to trace them back to the patient that donated them.

Research often benefits from national and international collaborative projects. We also ask you to consent for your samples and clinical data (coded so that your identity is protected) to be used in any national/international study on vascular access and kidney disease that is ethically approved and that we participate in.

Who is funding the research?

The study is being funded initially from the UHSM and CMFT Charitable Endowment Funds. We have also received some industrial sponsorship from Bioconnect Inc., USA. We will seek further funding from medical research charities and industry sponsors in future.

Who has reviewed this study?

This research study has been given a favourable ethical opinion for conduct in the NHS by the North West - Preston Ethics Committee. CMFT R&D Department monitor research projects to ensure that it has been conducted properly, according to the best practice in research.

Contact for further information

If you wish to know more about the study please contact any of the investigators listed here.

Dr Milind Nikam	tel: 0161 276 4436; email: milind.nikam@cmft.nhs.uk
Professor Paul Brenchley	tel:0161 276 6323; email paul.brenchley@manchester.ac.uk
Dr Sandip Mitra	tel: 0161 276 6509; email sandip.mitra@cmft.nhs.uk.

If you have any concerns and/or complaints about this study and wish to contact someone independent of the research team, please contact the Patient Advisory Liaison Service (PALS) on 0161 276 4261

MANVAS study consent form

PATIENT CONSENT FORM FOR RESEARCH STUDY

Centre Number: Study Number:

Patient Identification Number for this trial:

Title of Project: **Manchester Vascular Access Study (MANVAS)**

Name of Researcher: Please initial box

1. I confirm that I have read and understand the information sheet dated 15/2/2011 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. Do you agree to take part by donating (gifting) blood (DNA and serum) and urine samples (where possible) for medical research to be held in the MINT Biobank? ☐

5. Do you agree to take part by donating (gifting) any existing excised vascular tissue or future excised vascular tissue that is surplus to routine clinical management? ☐

6. I agree that my anonymised clinical data can be used by the Renal Research team in other ethically approved national/international studies on vascular access and kidney disease. ☐

7. I agree to my GP being informed of my participation in the study. ☐

8. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

OPEN study patient information sheet

REC Ref: 11/H1308/10

Renal Patient Information Sheet

Study title: **OptiflowTM Patency and maturation (OPEN) study**

Invitation to participate in the above study:

You are being invited to take part in a research study. Before you decide whether you want to take part, it is important that you understand why the research is being done and what it will involve. This sheet may contain words you may not understand. Please ask the study doctor or the staff to explain any words or facts that you do not understand.

Why have I been chosen?

Patients with advanced kidney failure who have not received a functional kidney transplant are dependent upon dialysis for survival. Your doctor has determined that treatment of your illness requires a fistula creation. You have been chosen because you need a new fistula in your arm for haemodialysis access. A total of 40 volunteers will be recruited in this study from Manchester Royal Infirmary, Salford Royal Hospitals and St George's Hospital, London.

Fistula creation operation involves connecting an artery and vein. The vein usually takes four weeks to six months after surgical connection to be ready for use because it needs to go through a process of expansion (getting bigger) and having increased blood flow as it changes and becomes more like an artery. The process is described as the vein 'maturing' for use as a fistula. This process of fistula maturation should begin naturally in your body immediately after the surgical connection and in about 50% of patients, it happens well enough to be used when it is needed. Some patients require further operations to help maturation happen and in some patients the process doesn't happen for reasons that we can't always explain.

When the fistula matures, blood can be removed by needles. The blood will then be processed and returned to your body through the vein.

The Optiflow connector is put surgically at the time of your fistula operation. The device is made by a company called Bioconnect Systems in Philadelphia, North America, USA. It is hoped that this device makes it easier for the surgeons to make these connections, reduces variability between surgeons, reduces scarring and creates a better blood flow profile in the fistula. Rather than relying on the natural process of AVF maturation, we think that the use of this connector will mean that

more patients will be able to dialyse using their fistula when they need to and that the fistula will work better for longer.

Part 1

What is the purpose of the study?

You are being asked to be in this preliminary study to evaluate the effectiveness of the OptiflowTM device when used to create an arteriovenous fistulae (referred to as fistula from hereon).This study has two specific aims, which are:

1. To observe the history of OptiflowTM created maturation and success rates
2. To collect information which may be compared to the success and maturation rates of other methods for creation of fistulae.

Do I have to take part?

No; your participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you decide not to take part you do not have to give a reason. There will be other treatment options available for you and your doctor will discuss these with you. Any decision not to take part will not affect:

- your eligibility for other treatment
- your relationship with your doctor and other clinical staff.

If you decide to take part, you will be asked to sign and date the consent form to show that you understand. Nothing will happen until you give your consent. You will be given a copy of this information sheet and consent form to keep.

Even if you decide to take part in the study you still have the right to withdraw at any time and without giving a reason. Should you decide to withdraw from the study the decision will not affect your future medical care by your doctor. Please tell your doctor if you want to withdraw at any time.

What will happen to me if I take part?

Your involvement in the study will start as soon as you have signed the consent form. To summarise:

- You will have the fistula created using the OptiflowTM device usually within 60 days of giving your consent.
- You will need to come to hospital for a number of visits (explained below). Overall participation in this study will last as long as 90 days after fistula creation.

Visit 1: Before your surgery

Your doctor will determine if you are able to take part in the study within 30 days before your surgery. This will involve:

- coming to appointment at Manchester Royal Infirmary to have an ultrasound scan of your arms to determine the site of potential fistula creation and the size of vessels to be used to create a fistula
- being asked about your medical history and medication
- having an assessment of the arm where your doctor plans to create a fistula
- having blood taken: about 20-30ml (about 4 teaspoons full) for laboratory testing to monitor your health
- measuring your height and weight

If you decide to join the study, you will be asked to sign the informed consent form.

Visit 2: The day of surgery

During the operation the study doctor will do an assessment of blood vessel diameter and condition to confirm the blood vessel is of the correct size required for you to be included in the study

You will be given an antibiotic during the surgery to minimise any risk of infection.

After the operation, examination of the site will be performed by the study doctor and their staff before you leave the hospital to go home.

Visit 3: Two weeks after surgery

The arm where the fistula was created will be examined and the stitches will be removed from the wound. You will have scan of your fistula arm and fistula to check how well your fistula is maturing.

Visit 4: First time the fistula is used for haemodialysis (a minimum of 42 days after surgery)

The fistula arm and fistula will be examined. You will have scan of your fistula arm and fistula.

Haemodialysis (if you are not already on haemodialysis) will be started using the fistula, which will be tested to make sure it is properly / normally functioning.

Final Visit: 90 days after surgery or the last visit of your participation in the study

The following procedures will be performed at your last final visit:

The fistula arm and fistula will be examined. You will have scan of your fistula arm and fistula. Haemodialysis (if you are not already on haemodialysis) will be started using the fistula, which will be tested to make sure it is properly / normally. The same procedures will be performed should you withdraw from the study

prematurely. Your study doctor may decide that it is in your best interest to stop the study at any time if:

- you do not follow all study procedures and do not attend study visits
- the study shows any signs of causing you major harm
- if any required tests pose a substantial risk to you
- if an intervention is performed that precludes the follow up visits required by the study.

If this happens, the Optiflow device may be removed. If you are asked to leave the study, the reasons will be discussed with you. The study sponsor may decide to end study at any time.

Would I receive payment towards my travel expenses?

Any reasonable costs incurred due to your participation (such as travel expenses from extra hospital visits) will be reimbursed. You will not be paid for taking part in this study.

What do I have to do?

- You will be required to attend all scheduled visits as detailed above.
- You will need to make a note of all medication you have taken as you will be asked about this at your visits.
- You will need to be willing to have your general health examined.
- You will need to be willing to have your arm examined and scanned by ultrasound.
- You will not be able to participate in another clinical trial which may interfere with the results/analysis of either study.
- If you are a female of childbearing age, you should not get pregnant during this study or after the Optiflow fistula has been created in your arm.

Why might I not be able to take part?

- If it is discovered in the operating room that your blood vessels' size and diameter are not meeting the minimum measurements required for you to have an Optiflow fistula creation.
- If you do not attend study appointments.
- If you are enrolled in another study within 30 days before being included in this study, which may interfere with the results/analysis of either studies.
- If you received an investigational drug during this study time.
- If you participate in another clinical trial whilst on study.

Please tell your doctor if any of these are relevant to you.

What are the alternatives for diagnosis or treatment?

If you choose not to participate in this study, your doctor will recommend another treatment and discuss the potential benefits and risks of this with you. There are other things that your doctor can use for dialysis including a conventional AV fistula surgery without the use of OptiflowTM device and usual other options of dialysis access.

What are the side effects and potential disadvantages of taking part?

During this study you will be observed for any adverse side-effects (any bad or harmful effects). The study doctor will decide if it is safe for you to continue in the study. Potential risks and complications that may occur with any surgical procedure involving a fistula creation include, but not limited to the following:

- Procedure or device-related infection
- Abnormal Swelling
- Bleeding
- further surgery
- narrowing of a vein or artery
- fistula stealing too much blood than expected causing cold hand, pain during haemodialysis
- a bulge in a blood vessel
- lack of maturation causing inability of the fistula to be ready for use
- blockage in the blood vessel
- damage to vessel
- death.
- This being a newer device some, yet unknown, complications may arise.

Harm to unborn child

There are unknown risks regarding the use of this study product during conception, pregnancy or while breast-feeding in humans. It is important that you are aware of this and avoid becoming pregnant during this study. During this study, you must tell the study doctor immediately if you think might be pregnant or trying to conceive. Your doctor will take this account along with your other medical details and may advice you to enrol in the study.

What are the possible benefits of taking part?

If you decide to be in this study, the Optiflow anastomotic connector should help you as much as the other ways for creating fistulae used for dialysis. The Optiflow anastomotic connector may increase the chances of having a successful fistula which may last longer. The preliminary results show that patients having fistula using the

device have 90% chance of success as opposed to usual surgery where success rate is around 70%.

Your doctor does not know if anything good will happen to you just because you decide to be in this study. You may or may not receive any benefit from being in the study. It is possible that you may get better, stay the same, or get worse. If the Optiflow anastomosis connector is effective, you may benefit having a longer term working fistula for haemodialysis, however this cannot be guaranteed. Your participation may provide additional scientific information/data for future patients.

What happens when the research study stops?

If the Optiflow fistula created remains intact in your arm, this may be used as an access point for haemodialysis for future standard treatment.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the device that is being studied. If this happens your doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide to carry on your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also on receiving new information your research doctor might consider it to be in your best interest to withdraw you from the study.

What will happen if I don't want to carry on with this study?

You may refuse to join or leave this study at any time with no loss of benefits to you. You may withdraw or take away your permission to use and disclose your health information at any time; you do this by sending written notice to the study doctor.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable. if you choose not to join this study or not to be part of the study anymore, your doctor and staff will keep on taking care of you.

Harm:

In the event that something goes wrong and you are harmed during this research and this is due to someone's negligence then you may have grounds for legal action. This would be for compensation against Central Manchester Foundation Trust, but you may have to pay your legal costs. The normal NHS complaints mechanism will still be available to you.

The co-sponsors will pay compensation where the injury probably resulted from:

- An investigational product being tested or administered as part of the trial protocol
- Any test or procedure you received as part of the trial
- Any payment will be without admission of liability.

The co-sponsors would not be bound by these guidelines to pay compensation where:

- The injury resulted from a drug or procedure outside the trial protocol
- The protocol was not followed.

Will my taking part in this study be kept confidential?

Your identity will be kept confidential at all times except to those professionals who need to check study data. For the purpose of scientific research, the following people will have direct access to your medical records:

- representatives (only those involved in the study) of CMFT NHS Trust
- auditors / inspectors within CMFT and of national and/or foreign regulatory health care authorities.

Access to your medical records by the above could mean that you will be identified in order to verify (check):

- the accuracy
- Completeness of the data collected.

Access to your medical records is only possible if permitted by the national laws and regulations on data privacy protection (UK Data Protection Act 1998).

Data and biological samples collected for the purpose of the study may be processed, reported and transferred to associated researchers in other countries. As laws in other countries might not protect your privacy to the same extent as the law in the UK, CMFT Trust will take all reasonable steps to protect your privacy. Any data leaving the research site will be coded so that your data will only be identified by a study number.

The results of this research may be published in scientific journals or presented at the medical meetings, but your identity will not be disclosed. If you withdraw from the study, study data collected before this may still be processed along with other data collected as part of the clinical study. By signing this form you specifically authorise your medical information to be checked, transferred and processed as above.

Under the UK Data Protection Act of 1998, you have the right to control the use of your medical information. You can request access to all information processed about you and have any wrong data about yourself corrected. You can do this through your study doctor.

What will happen to any samples I give?

Any blood samples obtained will be used for research purpose for this study only.

Involvement of the general practitioner (GP)/family doctor

Your GP, and other medical practitioners not involved in the study who may be treating you, may be notified of your participation in the trial with your consent.

What will happen to the results of the research study?

The results of this research may be published in scientific journals or presented at the medical meetings, but your identity will not be disclosed. When results become available you would be able to request a summary of the results of the study. You may access your medical information as allowed by national law and your personal results may be accessible to you after the data have analysed.

Who is organising the funding of the research?

The study is being directly funded by Bioconnect Systems Inc., USA who make the device and indirect support is available from the UHSM and CMFT Charitable Endowment Funds. None of the doctors or other staff have any financial interest in the manufacturer of the study device.

Who has reviewed the study?

This research was given a favourable ethical opinion for conduct in the NHS by …….. Research Ethics Committee.

What if there is a problem?

Contact for further information

If you wish to know more about the study please contact any of the investigators listed here.

Dr Milind Nikam tel: 0161 276 4436; email: milind.nikam@cmft.nhs.uk

Professor Paul Brenchley tel:0161 276 6323; email paul.brenchley@manchester.ac.uk
Dr Sandip Mitra tel: 0161 276 6509; email sandip.mitra@cmft.nhs.uk.

Complaints:

If you have any concerns and/or complaints about this study and wish to contact someone independent of the research team, please contact the Patient Advisory Liason Service (PALS) on 0161 276 4261

If you participate in this study - thank you. You will be given a copy of patient information sheet and consent form to take home with you and keep for future reference.

OPEN study consent form

(Copy to be retained by participant)

PATIENT CONSENT FORM FOR RESEARCH STUDY

Centre Number: Study Number:

Patient Identification Number for this trial:

Title of Project: **OPEN study**

Name of Researcher: Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version ....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Thank you for taking part in the study

Thrombus Innovation award entry form‡‡

Entry form

Entry criteria

Entries should demonstrate innovation and excellence that have improved the delivery of services to patients with venous/arterial thrombosis.

Each section of the entry form is designed to help the judging panel assess the most effective innovation, using the following criteria each being marked out of five:

The importance of the innovation to management of venous/arterial thrombosis

The multidisciplinary nature of the entry

The potential benefit to patients and thrombosis services

Evidence that the project is of sufficient scale to produce transferable results

The potential to impact on thrombosis medicine in the UK.

The closing date for entries is 31 July 2012

‡‡ The content is from the original application made to the Thrombus Award. Formatting has been changed to ensure compatibility with the rest of the thesis but the submitted content has not been modified.

Thrombus Innovation in Venous Thromboembolism Management Awards

Entry form

The project and its team

Please provide details of the project, including the lead clinician and project team.

Title of project:	Rapid Access Thrombosed Arteriovenous Fistula Salvage Pathway (**F**ailed **A**ccess **S**alvage pa**T**hway) FAST

Name and address of institution:	Dept of Renal Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL

Title and name of lead clinician:	Dr Sandip Mitra, Consultant Nephrologist

Qualification(s) and appointment(s) held:	Consultant Nephrologist , Central Manchester University Hospitals and Senior Lecturer, University of Manchester Qualifications: MD, FRCP

Address (if different from above)**:**	Central Manchester Foundation Trust Oxford Road, Manchester M13 9WL

Telephone:	01612766509	**email:**	**Sandip.mitra@cmft.nhs.uk**

Team members (title/name/qualifications/ job title/address, if different from above, and contact details)**:**	Dr Milind Nikam – MRCP (Neph), Senior Research Fellow Sr Helen Hurst PhD, Senior Nurse lead Renal Day Care for FAST pathway Sr Lorrie Wright RN, Lead Coordinator for salvage and thrombolysis, pre and post thrombectomy care Sr Ann Connolly – Senior Radiographer for Angio-suite Dr Nicholas Chalmers Interventional Radiologist FRCR Dr Aladdin Shurrab Consultant Nephrologist SRFT Dr Sandip Mitra Consultant Nephrologist CMFT (Lead)

Entries should demonstrate innovation and excellence that has improved the delivery of venous thromboembolism services to patients. The following sections are designed to help the judging panel assess the most effective innovation, using the following criteria:

- The importance of the innovation to management of venous/arterial thrombosis
- The multidisciplinary nature of the entry
- The potential benefit to patients and thrombosis services
- Evidence that the project is of sufficient scale to produce transferable results
- The potential to impact on thrombosis medicine in the UK.

Explain the objectives of your project **(in no more than one page).**

⇒ Please provide a brief overview of your innovation, confirming the objectives.

Background

Haemodialysis (HD) is a life-saving and life-sustaining treatment for patients with endstage kidney failure. A functioning (patent) native arteriovenous fistula (AVF) typically in the arm provides access to the blood stream and is considered the gold standard for providing safe and sustainable dialysis access for the best patient outcomes[1,3]. AVFs or synthetic grafts (AVG) have several advantages over dialysis catheters – i.e. lower infection rates, longer life and reliability. Unfortunately, AVAs are prone to failure themselves. The most common mechanism of failure is thrombosis. Annually, 14% fistulae & 50-80% grafts fail acutely. This often leads to a myriad of undesirable consequences i.e. disruption of dialysis schedules, hospitalisation with its related complications, need for alternative access, and increased healthcare costs. Salvage of AVAs can be reliably achieved using surgical or endovascular techniques, the latter preferred as it effective, less invasive, logistically easier to organise and has lower complication rates. Although the immediate technical success rate is high, it is dependent on urgency of the restoration of patency and its care. Very little is known about longer-term results of endovascular salvage and natural history of salvaged AVFs.

Greater Manchester Kidney Network is one of the largest UK kidney networks Manchester Royal Infirmary (MRI) & Salford Royal Foundation Trust (SRFT), serving a catchment population of 3.5 million, with approx. 1000 patients treated by

HD, supervised by 2 large renal centres across 10 satellite dialysis units delivering HD care, across the conurbation.

Pre-2008 era

Patients with thrombosed AVFs were typically admitted pending intervention. No referral pathway was defined and patients were dealt in an ad hoc manner and referred to either surgeons or radiologists after admission & assessment by the primary physician. Surgeons would typically then refer the patient to the radiology department for declotting. There were inherent delays at each step (Fig 1) leading to unacceptable time to intervention. Meanwhile the patient would often need hospitalisation & temporary dialysis access in the form of a catheter - both outcomes significantly adding to patient morbidity and cost. Majority of patients failed to be treated promptly (average wait 7-10 days) & dialysis was performed with a tunnelled catheter indefinitely until creation of AVF that typically took 6-9 months to mature for use. The key challenges of the project were:

1. Assuming thrombosis rate around 15 %, expected thrombosed or failed access events around 100-150 episodes per year (unpredictable& emergency referrals)
2. Highly skilled resource required (operator dependent techniques for salvage)
3. Timing of intervention (Ideal window 48 hrs. – referral to intervention time)
4. Delivering the best outcomes through efficient use of existing resources

2008 onwards (Innovative service model)

We designed an innovative care model focussed on a lean management approach to deliver the goals of prompt intervention and efficiency through redesign of patient pathways. The model objectives were to implement an outpatient day care regional thrombosed AVF salvage service aimed at :

1. Urgent restoration of thrombosed access patency (within 48 hrs. referral)
2. Minimise use of dialysis catheters (catheter last approach)
3. Restore dialysis schedules to avoid treatment disruption
4. Prospectively evaluate and improve overall patient outcomes
5. Efficiency through lean management – optimize flow, reduce waste & hospitalisation
6. Multidisciplinary setup : Coordinated and delivered by a team of staff from different specialities – renal teams at SRFT & MRI, Access link nurses at dialysis units, renal surgeons, dialysis & renal day care nursing team, and the interventional radiology department (nursing and clinical staff) at MRI.

Describe the innovation

⇒ Please outline how you embarked on this innovation.
⇒ What was the evidence base for the innovation, how did this influence your methodology, what population was involved and what timescale did you set?

The lead clinician undertook a series of stakeholder meetings and gained support from the Clinical directors (Dr A Hutchison & Dr D Lewis) for Manchester & Salford renal centres. Consensus was drawn on deliverable goals, pathways and protocols based on available evidence. The evidence was drawn from the consensus amongst

the key stakeholders guidelines and recommendations. The model and pathway was re-designed along these 6 principles

1. Based at a single center (to access MRI Renal Day care and Radiology)
2. Comprehensive Regional model – 2 renal centers (SRFT & MRI, 3.5 million pop)
3. Offer service 7 days a week (7am – 9pm)
4. Specified referral pathways and interventions
5. Establish close liaison between radiology, surgical and renal multidisciplinary teams (scheduling , pre and post care responsibilities defined)
6. Adopt a Lean management pathway

Essential first steps

- A Thrombosed fistula referral pathway was defined and agreed with measures of performance and audit that were clearly defined. A patient and staff awareness program of the importance of AVF was drawn up.
- To advertise the model of service delivery, and raise awareness (especially in dialysis centres and amongst frontline staff) about the importance of prompt referral to the new service delivery model for all patients presenting to any dialysis unit within the conurbation anytime during the week with failed/thrombosed AVFs
- A prospective data collection was set up on a rolling basis designed to capture the whole patient pathway (initial referral information, patient historical data, and intervention and outcomes data over a 12 month period of time). An

evaluation was planned at 2 and 4 yr. interval with full analysis of patient outcomes, experience and cost efficiency. Dr Nikam with an interest in vascular access was assigned to the project.

- PDSA cycles: We captured patient experience through surveys conducted at 6 month and 12 month of the service. There was clear feedback regarding the pain management during the declotting procedure. This was used as PDSA cycle by introduction of an anaesthetic (inhaled) set up in the angio-suite with clear improvements in patient feedback. Such an iterative process helped refine the model alongside.

Salvage techniques (combined radiological thrombectomy and thrombolysis)

All patients referred were scheduled through this fast track pathway. Detailed history (proforma based), clinical examination followed by ultrasound evaluation of the access, with subsequent scheduling for radiological thrombectomy in cases of thrombosed or occluded AVAs, using techniques of balloon maceration in combination with angioplasty. If the former was ineffective, Trerotola device, Angiojet device was used followed by bolus and / infusion of TPA thrombolysis.

Results achieved

⇒ Please comment on the results of your innovation, outlining the benefits for patients and any implications for health economics.

Service delivery /output

All patients referred with failed AV access (defined as an inability to dialyse using the AVF access) Jan 1st 2008 – Dec 31st 2011 were included. A total of 445 episodes of failed AVAs were referred & 406 procedures were carried out. Majority of the failure episodes were secondary to thrombosis and loss of blood flow in the AVF. The mean & median delay (referral to intervention) was 2 days – significant improvement from past performance and within the defined window of intervention. The immediate clinical success rate has been 85 – 90%, thus restoring patient's valuable dialysis life-line. Majority (60%) cases have been treated as an outpatient thus reducing morbidity and inconvenience to patients and also reducing cost burden on the NHS. 20% treated with minimal stay reducing bed days. Importantly the service has brought about increased liaison and cohesion between the 2 centres & motivation amongst the multidisciplinary staff involved in the vascular access care.

Reduction in use of vascular catheter devices for dialysis

Temporary catheters bring morbidity in the form of hospital stay, infections such as MRSA bacteraemia and in the longer-term damage to a patient's valuable vasculature. This service has had a significant reduction on temporary catheter usage. All OP treatments in > 60% were catheter free events. Temporary catheter use was used only occasionally to optimise patient biochemistry for radiological procedure.

Restoration of fistula flow/ patency

Primary patency rates for AVFs at 3, 6, 12, 24, and 36 months were 68%, 45%, 37%, 26% and 21%, respectively whereas secondary patency rates were 83%, 79%, 64%, 60% and 60% respectively. Primary patency rates for AVGs at 3, 6, 12 and 24 months were 37%, 15%, 9%, and 6% respectively, whereas, secondary patency rates were 57%, 47%, 37%, and 24% respectively. Significant difference existed in primary and secondary patency rates between AVFs and AVGs and also between occluded and non-occluded access.

Risk analysis (Cox regression)

Role for antiplatelet agents in prolonging AVF life after a clotting event (HR 0.46, $p<0.05$, CI 0.274 – 0.791). Adverse effect of higher Erythropoietin dose (HR 1.011, $p<0.019$, CI 1.009 – 1.020). Longer AVF patency post salvage (restored patency after functional loss) associated with improved patient survival (HR 0.998, $p<0.001$, CI 0.997 – 0.999).

Cost Effectiveness

60% patients treated as outpatient (OP) (n =0.6 x 445 = 267), approx. bed-days saved = 5 x 267 = 1335 bed-days. Cost saving = £250 x 1335 = £ 333,750 **(£0.33m cost avoidance**). Catheter days saved is difficult to estimate, but safe to assume at least all OP were catheter free.

PbR tariff for hemodialysis @ £161 for dialysis performed via AVF and @£128 for dialysis performed via catheter set the benchmark for evaluating cost savings following interventions. Restoration of AVF patency is a potential avoidance of catheter based dialysis for at least 6 months (until maturation of a new AVF),

equivalent to a loss of £33*350 AVF*72 dialysis**= £ 831600 (potential loss of income)** avoided for renal centres. **The total cost benefit (**reducing loss & cost avoidance**) is estimated at £1,165350 (£ 1.16 million) over a period of 4 yrs. in addition to clinical benefit.**

Sustainability

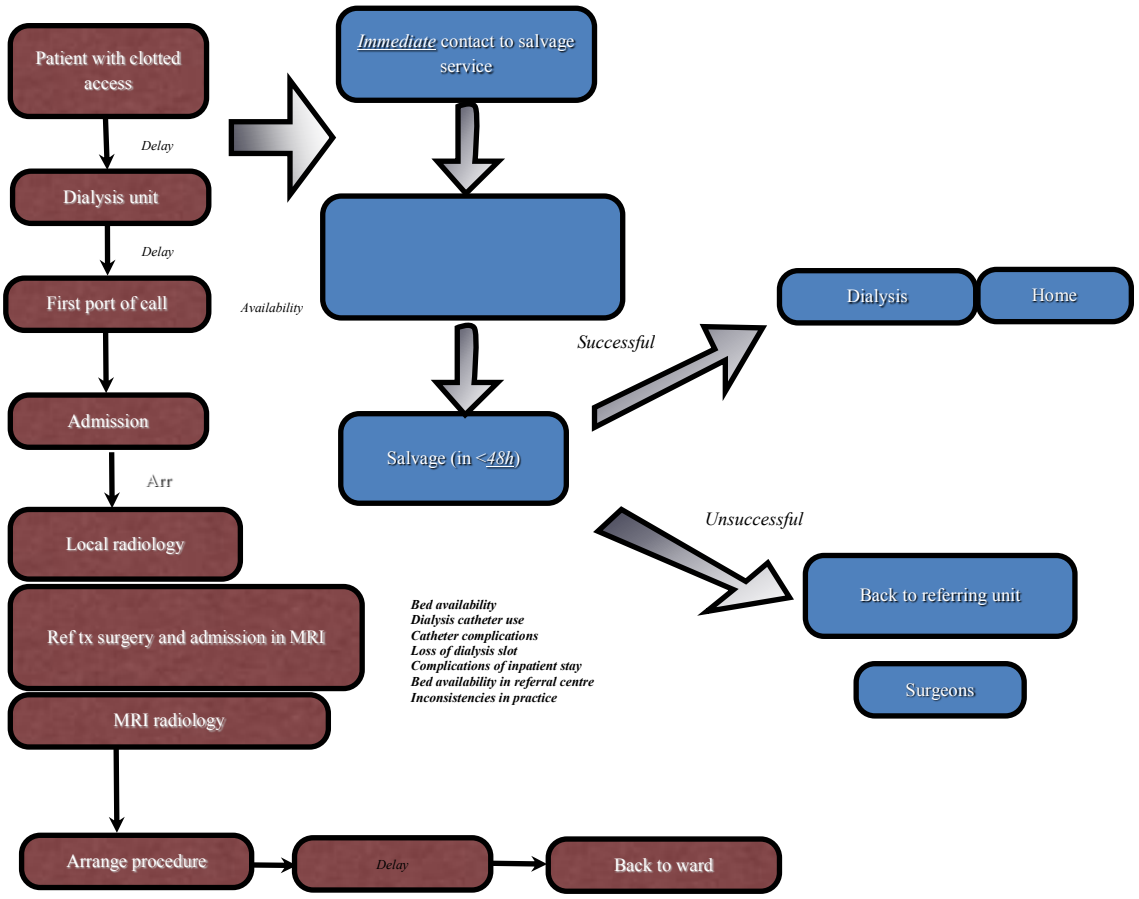
⇒ Explain how the project is of sufficient scale to produce transferable results.

The project was designed to serve a 3.5 million catchment population, 1000 HD patients served by two large tertiary renal centres in one of the largest kidney network and treatment delivered through the whole spectrum of HD settings in UK (hospital, community and home based dialysis) by two foundation trusts. The integration of services to overcome the barrier and deliver high quality outcome through cost efficiency is in line with safe and sustainable health care driven purely by innovation of existing resources and skill sets. The 3 principles (defined below) underline the model and are in line with the QIPP agenda.

1. Principle of lean management (efficiency driven) and superior performance (outcomes driven)
2. Regional delivery of service (numbers) refined through iterative process and revaluation (validation)
3. Model applicable to a larger proportion of renal units across the country (transferability)

The clinical problem of sustaining functioning AVFs is of high priority in the NHS[2, 3] and its successful delivery will benefit dialysis kidney patients uniformly across the NHS. The patient benefit is clear and is supported by patient experience within the model. The reduction of hospital admissions and minimal disruption to dialysis routine means a lot to patients on lifelong dialysis. The set of staff utilised and the pathways and procedures implemented are not unique to Manchester and can be made available in all regions. The care model defines a validated approach to integrating teams and resources to deliver results. The potential cost benefit is attractive to commissioners, renal units and policy makers alike especially as it drives better results at a lower cost.

We therefore do not foresee any clinical, administrative or commissioning barriers to its implementation. The need for a clinical lead & a motivated multidisciplinary team will be the key to its successful adoption for wider NHS. The success of the model represents a major advance in tackling AVF thrombosis management and it's planning in UK for Nephrology, Renal Surgery, Radiology and Haematology services.



Schematic comparison of Pre 2008 (brown) and New (blue) Innovative care model for thrombosed AVF

Additional comments

⇒ Please include any additional information that you feel is relevant to your entry to the *Thrombus* Innovation Awards.

We have developed a transformational model of care of restoring patency in thrombosed AVF in regional dialysis units in a safe and sustainable manner, the results potentially transferable to other regions in UK.

Dissemination

The innovative model of AVF care has been presented at 2 national meetings in UK (Renal Association Annual Conference 2010, Vascular Access Society of Britain and Ireland – Sept 2010 and 2 regional events Clinical audit and risk management showcase event at CMFT. The output from the project is at the final stages of publication.

Future work

We wish to undertake a national survey of practices across UK centres for thrombosed AVF and seek support of the Renal Association UK, and subsequently inform policymakers through NICE and other events of the potential gain from such an innovative care model in delivering optimal outcomes. This innovation is at the core of safe and sustainable care in AVF thrombosis and is being written into the service specifications for Greater Manchester Kidney Care Network Strategy for the next 5 yrs.

The innovative care model has given us a unique opportunity to analyse outcomes of AVF thrombosis and its salvage. This ongoing project forms the largest cohort analysis of this clinical problem and its solution through an innovative care model designed on the principles of lean approach and efficiency achieved through pathway redesign and validated using data capture in real time using existing resources. The care model also sets the platform to investigate means of improving longevity of dialysis access through trialling new interventions and strategies.

References

1. Huijbregts HJT, Bots ML, Wittens CHA, Schrama YC, Moll FL, Blankestijn PJ, et al. Hemodialysis Arteriovenous Fistula Patency Revisited: Results of a Prospective, Multicenter Initiative. Clinical Journal of the American Society of Nephrology. 2008; **3**(3): 714-9.
2. Clinical Practice Guidelines for Vascular Access. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2006; 48: S176-S247.
3. Fluck R, Kumwenda M. Renal Association Clinical Practice Guideline on Vascular Access for Haemodialysis. Nephron Clinical Practice. 2011; 118(1):c225-c40.

Please ensure that you complete the official entry form for your submission in full and return it by email to: thrombus@hayward.co.uk

or by post to:

Thrombus Innovation Awards,

Hayward Medical Communications, The Pines, Fordham Road,

NEWMARKET CB8 7LG

The closing date for entries is 31 July 2012

Thrombus innovation award intimation

20th September 2012

Dept of Renal Medicine
Manchester Royal Infirmary
Oxford Road
M13 9WL, Manchester

Dear Dr Sandip Mitra,

The Thrombus Innovation Awards 2012

Thank you for submitting your entry: 'Rapid Access Thrombosed Arteriovenous Fistula Salvage Pathway (**F**ailed **A**ccess **S**alvage pa**T**hway) FAST' to the 2012 Thrombus Innovation Awards.

The *Thrombus* Editorial board have commented on the high standard of entries this year and I am delighted to advise you that your entry has been shortlisted for an award.

I am pleased to invite you to the Awards Ceremony, which will be held over lunch on **Tuesday 20th November** at Chandos House, 2 Queen Anne Street, London, W1G 9LQ.
There will be a reception from 12.15pm with lunch starting at around 1.30pm after a presentation from an invited speaker.

I hope you can attend the event and bring other members of your team. A total of 5 places have been reserved for your institution. I would be grateful if you could let me know the names and roles/job titles of those who will be attending the ceremony, as soon as you are able. In addition, please, let us know if you or your colleagues attending the ceremony have any dietary requirements.

Finally, I would also be grateful if you can email any photographs of the hospital/ward/team to me, to be used as part of the awards presentation.

Many congratulations on being short-listed and I look forward to meeting you in November.

Yours sincerely,

Andrea Bucceri
Publications Manager
Hayward Medical Communications

Publications related to this thesis

Published papers

Nikam, M., R. K. Popuri, A. Inaba, U. Taylor, F. Farquharson, S. Mitra and N. Chalmers (2012). "Arteriovenous fistula failure: Is there a role for accessory draining vein embolization?" J Vasc Access 13(4): 498-503

Kuhan, G., G. A. Antoniou, M. Nikam, S. Mitra, F. Farquharson, J. Brittenden and N. Chalmers (2013). "A meta-analysis of randomized trials comparing surgery versus endovascular therapy for thrombosed arteriovenous fistulas and grafts in hemodialysis." Cardiovasc Intervent Radiol 36(3): 699-705.

Jayanti A, Nikam M, Ebah L, Dutton G, Morris J, Mitra S. Technique survival in home haemodialysis: a composite success rate and its risk predictors in a prospective longitudinal cohort from a tertiary renal network programme. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2013; 28(10): 2612-20

Abstracts

1. Vascular access in home haemodialysis: trends and outcomes
    a. European Renal Association / European Dialysis and Transplant Association Annual conference May 2012, Paris, France. Poster presentation. Published in NDT supplement.
    b. UK Renal Association Conference June 2011. Awarded as 'One of the best abstracts'. Oral abstract presentation.

2. Optiflow™ device – a novel technology for creation of arteriovenous fistulae for haemodialysis: early clinical experience, safety and efficacy - poster presentation at ERA/EDTA conference May 2012, Paris, France. Published in NDT supplement.
3. Endovascular Salvage of Failed Arteriovenous Dialysis Access: Long Term Results and Factors Predicting Access Survival. Poster presentation at the American Society of Nephrology annual conference in November 2012, Philadelphia, USA. Published as ASN conference abstracts.
4. Optiflow™ Anastomotic Connector – Safety and Efficacy: Results from the OPEN Study - accepted for poster presentation at ASN due in November 2012
5. Failed arteriovenous dialysis access – results of endovascular salvage and factors determining long term patency. Presented as a poster at the American Society of Diagnostic and Interventional Nephrology Conference in February 2013, Washington DC, USA. Candidate awarded 'Partial Fellow Scholarship'.

BIBLIOGRAPHY

1. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: Problems and solutions. *Kidney Int* 2002; **62**(4).

2. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. *Journal of the American Society of Nephrology* 2004; **15**(2).

3. Navuluri R, Regalado S. The KDOQI 2006 vascular access update and fistula first program synopsis. Seminars in interventional radiology; 2009: Thieme Medical Publishers; 2009. p. 122.

4. Fluck R, Kumvenda M. Vascular Access for Haemodialysis, 2010.

5. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA* 2008; **299**(18).

6. Julie Gilg CC, Damian Fogarty. Chapter 1 UK RRT Incidence in 2010: national and centre-specific analyses: UK Renal Registy, 2011.

7. Julie Gilg CC, Damian Fogarty. Chapter 2 UK RRT Prevalence in 2010: national and centre-specific analyses. In: Registry UR, editor.; 2011.

8. USRDS. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010, 2010.

9. Dr David Ansell DCC, Professor John Feehally, Dr Damian Fogarty, Dr Daniel Ford, Dr Carol Inward, Dr Charles Tomson, Dr Graham Warwick, Dr Lynsey Webb, Dr Andrew W. Renal Registry Report, 2009.

10. Rayner HC, Pisoni RL, Bommer J, et al. Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis

Outcomes and Practice Patterns Study (DOPPS). *Nephrology Dialysis Transplantation* 2004; **19**(1).

11. Lee H, Manns B, Taub K, et al. Cost analysis of ongoing care of patients with end-stage renal disease: The impact of dialysis modality and dialysis access* 1. *American Journal of Kidney Diseases* 2002; **40**(3).

12. Tentori F, Mapes DL. Opinion: Health-Related Quality of Life and Depression among Participants in the DOPPS: Predictors and Associations with Clinical Outcomes. *Seminars in Dialysis* 2010; **23**(1).

13. Feldman HI, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. *Journal of the American Society of Nephrology* 1996; **7**(4): 523-35.

14. Konner K. History of vascular access for haemodialysis. *Nephrology Dialysis Transplantation* 2005; **20**(12).

15. Hannan K, Conlon PJ. Introduction. In: Conlon PJ, Schwab SJ, Nicholson ML, eds.: Oxford University Press; 2000.

16. Brescia MJ, Cimino JE, Appell K, Hurwich BJ, Scribner BH. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. 1966. *J Am Soc Nephrol* 1999; **10**(1).

17. Ethier J, Mendelssohn DC, Elder SJ, et al. Vascular access use and outcomes: an international perspective from the dialysis outcomes and practice patterns study. *Nephrology Dialysis Transplantation* 2008; **23**(10).

18. Weijmer MC, Vervloet MG, ter Wee PM. Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. *Nephrology Dialysis Transplantation* 2004; **19**(3): 670-7.

19. Beathard GA, Arnold P, Jackson J, Litchfield T. Aggressive treatment of early fistula failure. *Kidney Int* 2003; **64**(4): 1487-94.

20. Turmel - Rodrigues L, Mouton A, Birmelé B, et al. Salvage of immature forearm fistulas for haemodialysis by interventional radiology. *Nephrology Dialysis Transplantation* 2001; **16**(12): 2365-71.

21. Romero A, Polo JR, Garcia ME, Garcia SJL, Quintans A, Ferreiroa JP. Salvage of angioaccess after late thrombosis of radiocephalic fistulas for hemodialysis. *International surgery*; **71**(2).

22. Roy-Chaudhury P, Spergel LM, Besarab A, Asif A, Ravani P. Biology of arteriovenous fistula failure. *Journal of nephrology* 2007; **20**(B).

23. Dunn J, Nylander W, Richie R. Central venous dialysis access: experience with a dual-lumen, silicone rubber catheter. *Surgery* 1987; **102**(5).

24. Oliver MJ. Chronic hemodialysis vascular access: Types and placement. 2010.

25. Rodriguez JA, Armadans L, Ferrer E, et al. The function of permanent vascular access. *Nephrology Dialysis Transplantation* 2000; **15**(3).

26. Munda R. Polytetrafluoroethylene graft survival in hemodialysis. *JAMA* 1983; **249**(2).

27. Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. *Journal of Vascular Surgery* 2003; **38**(5).

28. Perera GB, Mueller MP, Kubaska SM, Wilson SE, Lawrence PF, Fujitani RM. Superiority of autogenous arteriovenous hemodialysis access: Maintenance of function with fewer secondary interventions. *Annals of vascular surgery* 2004; **18**(1).

29. Kamalakannan D, Pai RM, Johnson LB, Gardin JM, Saravolatz LD. Epidemiology and clinical outcomes of infective endocarditis in hemodialysis patients. *The Annals of thoracic surgery* 2007; **83**(6): 2081-6.

30. Doulton T, Sabharwal N, Cairns HS, et al. Infective endocarditis in dialysis patients: new challenges and old. *Kidney international* 2003; **64**(2): 720-7.

31. Stewart PS, William Costerton J. Antibiotic resistance of bacteria in biofilms. *The Lancet* 2001; **358**(9276): 135-8.

32. Dixon B. Why don't fistulas mature? *Kidney international* 2006; **70**(8): 1413-22.

33. Papasavas PK, Reifsnyder T, Birdas TJ, Caushaj PF, Leers S. Prediction of arteriovenous access steal syndrome utilizing digital pressure measurements. *Vascular and endovascular surgery* 2003; **37**(3).

34. Lazarides MK, Staramos DN, Kopadis G, Maltezos C, Tzilalis VD, Georgiadis GS. Onset of arterial'steal'following proximal angioaccess: immediate and delayed types. *Nephrology Dialysis Transplantation* 2003; **18**(11).

35. Konner K, Nonnast-Daniel B, Ritz E. The arteriovenous fistula. *Journal of the American Society of Nephrology* 2003; **14**(6): 1669-80.

36. Clark TWI, Abraham RJ. Thrombin injection for treatment of brachial artery pseudoaneurysm at the site of a hemodialysis fistula: report of two patients. *Cardiovascular and interventional radiology* 2000; **23**(5).

37. MacRae JM, Ahmed A, Johnson N, Levin A, Kiaii M. Central vein stenosis: a common problem in patients on hemodialysis. *ASAIO journal* 2005; **51**(1).

38. Taal MW, Chesterton LJ, McIntyre CW. Venography at insertion of tunnelled internal jugular vein dialysis catheters reveals significant occult stenosis. *Nephrology Dialysis Transplantation* 2004; **19**(6).

39. Kundu S. Review of Central Venous Disease in Hemodialysis Patients. *Journal of Vascular and Interventional Radiology* 2010.

40. Agarwal AK, Patel BM, Haddad NJ. Central vein stenosis: a nephrologist's perspective. John Wiley & Sons.

41. Green D, Roberts PR, New DI, Kalra PA. Sudden Cardiac Death in Hemodialysis Patients: An In-Depth Review. *American Journal of Kidney Diseases* 2011; **57**(6): 921-9.

42. Drew DA, Meyer KB, Weiner DE. Transvenous cardiac device wires and vascular access in hemodialysis patients. *American Journal of Kidney Diseases* 2011; **58**(3): 494-6.

43. Saad TF, Hentschel DM, Koplan B, et al. Cardiovascular Implantable Electronic Device Leads in CKD and ESRD Patients: Review and Recommendations for Practice. *Seminars in Dialysis* 2012: no-no.

44. Haghjoo M, Nikoo MH, Fazelifar AF, Alizadeh A, Emkanjoo Z, Sadr-Ameli MA. Predictors of venous obstruction following pacemaker or implantable cardioverter-defibrillator implantation: a contrast venographic study on 100 patients admitted for generator change, lead revision, or device upgrade. *Europace* 2007; **9**(5): 328-32.

45. Do Carmo Da Costa SS, Neto AS, Costa R, Caldas JG, Filho MM. Incidence and Risk Factors of Upper Extremity Deep Vein Lesions After Permanent Transvenous Pacemaker Implant: A 6-Month Follow-Up Prospective Study. *Pacing and Clinical Electrophysiology* 2002; **25**(9): 1301-6.

46. Teruya TH, Abou-Zamzam AM, Limm W, Wong L. Symptomatic subclavian vein stenosis and occlusion in hemodialysis patients with transvenous pacemakers. *Annals of vascular surgery* 2003; **17**(5): 526-9.

47. Hernandez D, Diaz F, Rufino M, et al. Subclavian vascular access stenosis in dialysis patients: natural history and risk factors. *Journal of the American Society of Nephrology* 1998; **9**(8).

48. Haimov M, Baez A, Neff M, Slifkin R. COmplications of arteriovenous fistulas for hemodialysis. *Archives of Surgery* 1975; **110**(6): 708-12.

49. Quality AfHRa. Chapter 2. Methods: Health Care Efficiency Measures: Identification, Categorization, and Evaluation. 2008. http://www.ahrq.gov/research/findings/final-reports/efficiency/hcemch2.html.

50. Feldman HI, Held PJ, Hutchinson JT, Stoiber E, Hartigan MF, Berlin JA. Hemodialysis vascular access morbidity in the United States. *Kidney Int* 1993; **43**(5).

51. Manns B, Tonelli M, Yilmaz S, et al. Establishment and maintenance of vascular access in incident hemodialysis patients: a prospective cost analysis. *Journal of the American Society of Nephrology* 2005; **16**(1).

52. Miller PE, Tolwani A, Luscy CP, et al. Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 1999; **56**(1): 275-80.

53. Corpataux JM, Haesler E, Silacci P, Ris HB, Hayoz D. Low-pressure environment and remodelling of the forearm vein in Brescia-Cimino haemodialysis access. *Nephrol Dial Transplant* 2002; **17**(6): 1057-62.

54. Sivanesan S, How TV, Bakran A. Characterizing flow distributions in AV fistulae for haemodialysis access. *Nephrol Dial Transplant* 1998; **13**(12): 3108-10.

55. Ben Driss A, Benessiano J, Poitevin P, Levy BI, Michel JB. Arterial expansive remodeling induced by high flow rates. *American Journal of Physiology- Heart and Circulatory Physiology* 1997; **272**(2).

56. Tronc F, Mallat Z, Lehoux S, Wassef M, Esposito B, Tedgui A. Role of matrix metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. *Arteriosclerosis, thrombosis, and vascular biology* 2000; **20**(12): e120.

57. Yevzlin AS, Chan MR, Becker YT, Roy-Chaudhury P, Lee T, Becker BN. "Venopathy" at work: recasting neointimal hyperplasia in a new light. *Transl Res* 2010; **156**(4): 216-25.

58. Zhang L, Hagen P-O, Kisslo J, Peppel K, Freedman NJ. Neointimal hyperplasia rapidly reaches steady state in a novel murine vein graft model. *Journal of vascular surgery* 2002; **36**(4): 824-32.

59. Motwani JG, Topol EJ. Aortocoronary Saphenous Vein Graft Disease: Pathogenesis, Predisposition, and Prevention. *Circulation* 1998; **97**(9): 916-31.

60. Schachner T. Pharmacologic inhibition of vein graft neointimal hyperplasia. *The Journal of Thoracic and Cardiovascular Surgery* 2006; **131**(5).

61. Lee T, Chauhan V, Krishnamoorthy M, et al. Severe venous neointimal hyperplasia prior to dialysis access surgery. *Nephrology Dialysis Transplantation* 2011.

62. Huijbregts HJT, Bots ML, Wittens CHA, et al. Hemodialysis Arteriovenous Fistula Patency Revisited: Results of a Prospective, Multicenter Initiative. *Clinical Journal of the American Society of Nephrology* 2008; **3**(3): 714-9.

63. Knoll GA, Wells PS, Young D, et al. Thrombophilia and the risk for hemodialysis vascular access thrombosis. *Journal of the American Society of Nephrology* 2005; **16**(4).

64. Fluck R, Kumwenda M. Renal Association Clinical Practice Guideline on Vascular Access for Haemodialysis. *Nephron Clinical Practice* 2011; **118**(1): c225-c40.

65. Tonelli M, James M, Wiebe N, Jindal K, Hemmelgarn B. Ultrasound monitoring to detect access stenosis in hemodialysis patients: a systematic review. *American Journal of Kidney Diseases* 2008; **51**(4): 630-40.

66. Paulson WD, Moist L, Lok CE. Vascular access surveillance: an ongoing controversy. *Kidney Int* 2012; **81**(2): 132-42.

67. Bent CL, Sahni VA, Matson MB. The radiological management of the thrombosed arteriovenous dialysis fistula. *Clinical Radiology*; **66**(1): 1-12.

68. Uflacker R, Rajagopalan P, Selby JB, Hannegan C. Thrombosed dialysis access grafts: randomized comparison of the Amplatz thrombectomy device and surgical thromboembolectomy. *European radiology* 2004; **14**(11): 2009-14.

69. Turmel-Rodrigues L, Pengloan J, Baudin S, et al. Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrology Dialysis Transplantation* 2000; **15**(12): 2029-.

70. Beathard GA, Litchfield T. Effectiveness and safety of dialysis vascular access procedures performed by interventional nephrologists. *Kidney international* 2004; **66**(4): 1622-32.

71. Asif A, Byers P, Vieira CF, Preston RA, Roth D. Diagnostic and interventional nephrology. *American journal of therapeutics* 2002; **9**(6): 530-6.

72. Matuszkiewicz-Rowińska J, Billip-Tomecka Z, Rowiński W, Siciński A. Systemic streptokinase infusion for declotting of hemodialysis arteriovenous fistulas. *Nephron* 1994; **66**(1): 67-70.

73. Minar E, Zazgornik J, Marosi L. Local low-dose streptokinase thrombolysis of a thrombosed arteriovenous fistula. *American journal of nephrology* 1984; **4**(1): 66-7.

74. Mangiarotti G, Canavese C, Thea A, et al. Urokinase treatment for arteriovenous fistulae declotting in dialyzed patients. *Nephron* 1984; **36**(1): 60-4.

75. Tseke P, Kalyveza E, Politis E, et al. Thrombolysis With Alteplase: A Non-Invasive Treatment for Occluded Arteriovenous Fistulas and Grafts. *Artificial Organs* 2011; **35**(1): 58-62.

76. Marston WA, Criado E, Jaques PF, Mauro MA, Burnham SJ, Keagy BA. Prospective randomized comparison of surgical versus endovascular management of thrombosed dialysis access grafts. *Journal of vascular surgery* 1997; **26**(3): 373-81.

77. Bent CL, Sahni VA, Matson MB. The radiological management of the thrombosed arteriovenous dialysis fistula. *Clinical Radiology* 2011; **66**(1): 1-12.

78. Lok CE, Allon M, Moist L, Oliver MJ, Shah H, Zimmerman D. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). *Journal of the American Society of Nephrology* 2006; **17**(11).

79. Feldman HI, Joffe M, Rosas SE, Burns JE, Knauss J, Brayman K. Predictors of successful arteriovenous fistula maturation. *Am J Kidney Dis* 2003; **42**(5): 1000-12.

80. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A. Factors associated with early failure of arteriovenous fistulae for haemodialysis access. *European Journal of Vascular and Endovascular Surgery* 1996; **12**(2).

81. Reilly DT, Wood RFM, Bell PRF. Prospective study of dialysis fistulas: Problem patients and their treatment. *British Journal of Surgery* 1982; **69**(9).

82. Thomsen MB, Deurell SI, Elfstr"m J, Alm A. What causes the failures in surgically constructed arteriovenous fistulas? *Acta chirurgica Scandinavica* 1983; **149**(4).

83. Paszkowiak JJ, Dardik A. Arterial wall shear stress: observations from the bench to the bedside. *Vascular and endovascular surgery* 2003; **37**(1).

84. Haga M, Yamashita A, Paszkowiak J, Sumpio BE, Dardik A. Oscillatory shear stress increases smooth muscle cell proliferation and Akt phosphorylation. *Journal of Vascular Surgery* 2003; **37**(6).

85. Dobrin PB, Littooy FN, Golan J, Blakeman B, Fareed J. Mechanical and histologic changes in canine vein grafts. *Journal of Surgical Research* 1988; **44**(3).

86. Morris STW, McMurray JJV, Rodger RSC, Jardine AG. Impaired endothelium dependent vasodilatation in uraemia. *Nephrology Dialysis Transplantation* 2000; **15**(8): 1194.

87. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney international* 2002; **62**(5).

88. Mezzano D, Pais EO, Aranda E, et al. Inflammation, not hyperhomocysteinemia, is related to oxidative stress and hemostatic and endothelial dysfunction in uremia. *Kidney international* 2001; **60**(5).

89. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 2003; **107**(1).

90. Kielstein JT, Bode-Boger SM, Hesse G, et al. Asymmetrical dimethylarginine in idiopathic pulmonary arterial hypertension. *Arterioscler Thromb Vasc Biol* 2005; **25**(7): 1414-8.

91. Kokubo T, Ishikawa N, Uchida H, et al. CKD accelerates development of neointimal hyperplasia in arteriovenous fistulas. *Journal of the American Society of Nephrology* 2009; **20**(6).

92. Unnikrishnan S, Huynh TN, Brott BC, et al. Turbulent flow evaluation of the venous needle during hemodialysis. *Journal of biomechanical engineering* 2005; **127**.

93. Steele PM, Chesebro JH, Stanson AW, et al. Balloon angioplasty. Natural history of the pathophysiological response to injury in a pig model. *Circulation Research* 1985; **57**(1): 105-12.

94. Chang CJ, Ko PJ, Hsu LA, et al. Highly increased cell proliferation activity in the restenotic hemodialysis vascular access after percutaneous transluminal angioplasty: implication in prevention of restenosis. *Am J Kidney Dis* 2004; **43**(1): 74-84.

95. Davies PF, Remuzzi A, Gordon EJ, Dewey CF, Gimbrone MA. Turbulent fluid shear stress induces vascular endothelial cell turnover in vitro. *Proceedings of the National Academy of Sciences of the United States of America* 1986; **83**(7).

96. Krishnamoorthy MK, Banerjee RK, Wang Y, et al. Hemodynamic wall shear stress profiles influence the magnitude and pattern of stenosis in a pig AV fistula. *Kidney Int* 2008; **74**(11).

97. Hristov M, Weber C. Endothelial progenitor cells in vascular repair and remodeling. *Pharmacological Research* 2008; **58**(2).

98. Rabelink TJ, de Boer HC, de Koning EJP, van Zonneveld AJ. Endothelial progenitor cells: more than an inflammatory response? *Arteriosclerosis, thrombosis, and vascular biology* 2004; **24**(5).

99. Kirton JP, Xu Q. Endothelial precursors in vascular repair. *Microvasc Res* 2010; **79**(3): 193-9.

100. Lamping K. Endothelial progenitor cells: sowing the seeds for vascular repair. *Circ Res* 2007; **100**(9): 1243-5.

101. de Groot K, Bahlmann FH, Bahlmann E, Menne J, Haller H, Fliser D. Kidney graft function determines endothelial progenitor cell number in renal transplant recipients. *Transplantation* 2005; **79**(8).

102. Goligorsky MS, Yasuda K, Ratliff B. Dysfunctional endothelial progenitor cells in chronic kidney disease. *J Am Soc Nephrol* 2010; **21**(6): 911-9.

103. Awolesi MA, Sessa WC, Sumpio BE. Cyclic strain upregulates nitric oxide synthase in cultured bovine aortic endothelial cells. *Journal of Clinical Investigation* 1995; **96**(3).

104. Lal BK, Choi HM, Silva MB, Hobson RW, Pappas PJ, Dur n WN. Creation of Arteriovenous Fistulas Upregulates Venous eNOS. *Vascular and endovascular surgery* 2007; **40**(6).

105. Castier Y, Brandes RP, Leseche G, Tedgui A, Lehoux S. p47phox-dependent NADPH oxidase regulates flow-induced vascular remodeling. *Circulation research* 2005; **97**(6).

106. Arese M, Strasly M, Ruva C, et al. Regulation of nitric oxide synthesis in uraemia. *Nephrology Dialysis Transplantation* 1995; **10**(8).

107. Rotmans JI, Velema E, Verhagen HJM, et al. Matrix metalloproteinase inhibition reduces intimal hyperplasia in a porcine arteriovenous-graft model. *Journal of Vascular Surgery* 2004; **39**(2).

108. Misra S, Fu AA, Puggioni A, et al. Increased shear stress with upregulation of VEGF-A and its receptors and MMP-2, MMP-9, and TIMP-1 in venous stenosis of hemodialysis grafts. *American Journal of Physiology- Heart and Circulatory Physiology* 2008; **294**(5).

109. Nath KA. Heme oxygenase-1: a provenance for cytoprotective pathways in the kidney and other tissues. *Kidney international* 2006; **70**(3).

110. Juncos JP, Tracz MJ, Croatt AJ, et al. Genetic deficiency of heme oxygenase-1 impairs functionality and form of an arteriovenous fistula in the mouse. *Kidney Int* 2008; **74**(1): 47-51.

111. Lin CC, Yang WC, Lin SJ, et al. Length polymorphism in heme oxygenase-1 is associated with arteriovenous fistula patency in hemodialysis patients. *Kidney international* 2006; **69**(1).

112. Gosling J, Slaymaker S, Gu L, et al. MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B. *Journal of Clinical Investigation* 1999; **103**(6).

113. Juncos JP, Grande JP, Kang L, et al. MCP-1 Contributes to Arteriovenous Fistula Failure. *Journal of the American Society of Nephrology* 2011; **22**(1).

114. Stracke S, Konner K, Kostlin I, et al. Increased expression of TGF-[bgr]1 and IGF-I in inflammatory stenotic lesions of hemodialysis fistulas. *Kidney Int* 2002; **61**(3).

115. Heine GH, Ulrich C, Sester U, Sester M, Kohler H, Girndt M. Transforming growth factor [bgr]1 genotype polymorphisms determine AV fistula patency in hemodialysis patients. *Kidney Int* 2003; **64**(3).

116. Wolf YG, Rasmussen LM, Ruoslahti E. Antibodies against transforming growth factor-beta 1 suppress intimal hyperplasia in a rat model. *Journal of Clinical Investigation* 1994; **93**(3).

117. Verrecchia F, Mauviel A. Transforming Growth Factor-&bgr; Signaling Through the Smad Pathway: Role in Extracellular Matrix Gene Expression and Regulation. *Journal of Investigative Dermatology* 2002; **118**(2).

118. Ruiz-Ortega M, Rodr¡guez-Vita J, Sanchez-Lopez E, Carvajal G, Egido J. TGF-signaling in vascular fibrosis. *Cardiovascular Research* 2007; **74**(2).

119. Wasse H, Rivera AA, Huang R, et al. Increased Plasma Chymase Concentration and Mast Cell Chymase Expression in Venous Neointimal Lesions of Patients with CKD and ESRD. *Seminars in Dialysis* 2011; **24**(6): 688-93.

120. Jin D, Ueda H, Takai S, et al. Effect of Chymase Inhibition on the Arteriovenous Fistula Stenosis in Dogs. *Journal of the American Society of Nephrology* 2005; **16**(4): 1024-34.

121. Lok CE. Fistula First Initiative: Advantages and Pitfalls. *Clinical Journal of the American Society of Nephrology* 2007; **2**(5): 1043-53.

122. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney international* 2002; **61**(6): 2235-9.

123. Jassal S, Devins G, Chan C, Bozanovic R, Rourke S. Improvements in cognition in patients converting from thrice weekly hemodialysis to nocturnal hemodialysis: a longitudinal pilot study. *Kidney international* 2006; **70**(5): 956-62.

124. Mowatt G, Vale L, Perez J, et al. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure. 2003.

125. Walsh M, Culleton B, Tonelli M, Manns B. A systematic review of the effect of nocturnal hemodialysis on blood pressure, left ventricular hypertrophy, anemia, mineral metabolism, and health-related quality of life. *Kidney international* 2005; **67**(4): 1500-8.

126. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. *The New England journal of medicine* 2010; **363**(24): 2287.

127. Suri RS, Larive B, Sherer S, et al. Risk of vascular access complications with frequent hemodialysis. *Journal of the American Society of Nephrology* 2013; **24**(3): 498-505.

128. Schinstock CA, Albright RC, Williams AW, et al. Outcomes of arteriovenous fistula creation after the fistula first initiative. *Clinical Journal of the American Society of Nephrology* 2011; **6**(8): 1996-2002.

129. Lacson E, Lazarus JM, Himmelfarb J, Ikizler TA, Hakim RM. Balancing fistula first with catheters last. *American Journal of Kidney Diseases* 2007; **50**(3): 379-95.

130. Robbin ML, Chamberlain NE, Lockhart ME, et al. Hemodialysis arteriovenous fistula maturity: US evaluation. *Radiology* 2002; **225**(1): 59-64.

131. Dixon BS, Novak L, Fangman J. Hemodialysis vascular access survival: upper-arm native arteriovenous fistula. *Am J Kidney Dis* 2002; **39**(1): 92-101.

132. Huijbregts HJ, Bots ML, Moll FL, Blankestijn PJ. Hospital specific aspects predominantly determine primary failure of hemodialysis arteriovenous fistulas. *J Vasc Surg* 2007; **45**(5): 962-7.

133. Fassiadis N, Morsy M, Siva M, Marsh JE, Makanjuola AD, Chemla ES. Does the surgeon's experience impact on radiocephalic fistula patency rates? *Semin Dial* 2007; **20**(5): 455-7.

134. Prischl FC, Kirchgatterer A, Brandstatter E, et al. Parameters of prognostic relevance to the patency of vascular access in hemodialysis patients. *J Am Soc Nephrol* 1995; **6**(6): 1613-8.

135. Lynch TG, Plumb TJ. Invited commentary. *Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter* 2008; **47**(2): 421.

136. O'Hare AM, Dudley RA, Hynes DM, et al. Impact of surgeon and surgical center characteristics on choice of permanent vascular access. *Kidney Int* 2003; **64**(2): 681-9.

137. Konner K. Interventional Nephrology and Dialysis: The Initial Creation of Native Arteriovenous Fistulas: Surgical Aspects and Their Impact on the Practice of Nephrology. *Seminars in Dialysis* 2003; **16**(4): 291-8.

138. Nassar GM, Ayus JC. Infectious complications of the hemodialysis access. *Kidney Int* 2001; **60**(1): 1-13.

139. Pisoni RL. Vascular access use and outcomes: results from the DOPPS. *Contrib Nephrol* 2002; (137): 13-9.

140. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. *Kidney Int* 2001; **60**(4): 1443-51.

141. Woods JD, Port FK. The impact of vascular access for haemodialysis on patient morbidity and mortality. *Nephrol Dial Transplant* 1997; **12**(4): 657-9.

142. Rohl L, Franz HE, Mohring K, et al. Direct arteriovenous fistula for hemodialysis. *Scand J Urol Nephrol* 1968; **2**(3): 191-5.

143. Beathard GA, Settle SM, Shields MW. Salvage of the nonfunctioning arteriovenous fistula. *American journal of kidney diseases* 1999; **33**(5): 910-6.

144. Mehta S. Statistical summary of clinical results of vascular access procedures for hemodialysis. *Vascular Access for Hemodialysis-II (ed 2) Chicago, IL, Gore* 1991: 145–57.

145. Nassar GM, Ayus JC. Infectious complications of the hemodialysis access. *Kidney international* 2001; **60**(1): 1-13.

146. Clinical practice guidelines for vascular access. *Am J Kidney Dis* 2006; **48 Suppl 1**: S248-73.

147. Tordoir J, Canaud B, Haage P, et al. EBPG on Vascular Access. *Nephrology Dialysis Transplantation* 2007; **22**(suppl 2): ii88-ii117.

148. Allon M, Robbin ML. Increasing arteriovenous fistulas in hemodialysis patients: problems and solutions. *Kidney international* 2002; **62**(4).

149. Singh P, Robbin ML, Lockhart ME, Allon M. Clinically immature arteriovenous hemodialysis fistulas: effect of US on salvage. *Radiology* 2008; **246**(1): 299-305.

150. Nassar GM, Nguyen B, Rhee E, Achkar K. Endovascular treatment of the "failing to mature" arteriovenous fistula. *Clin J Am Soc Nephrol* 2006; **1**(2): 275-80.

151. Beathard GA, Settle SM, Shields MW. Salvage of the nonfunctioning arteriovenous fistula. *Am J Kidney Dis* 1999; **33**(5): 910-6.

152. Faiyaz R, Abreo K, Zaman F, Pervez A, Zibari G, Work J. Salvage of poorly developed arteriovenous fistulae with percutaneous ligation of accessory veins. *Am J Kidney Dis* 2002; **39**(4): 824-7.

153. Falk A. Maintenance and salvage of arteriovenous fistulas. *J Vasc Interv Radiol* 2006; **17**(5): 807-13.

154. Planken RN, Duijm LE, Kessels AG, et al. Accessory veins and radial-cephalic arteriovenous fistula non-maturation: a prospective analysis using contrast-enhanced magnetic resonance angiography. *J Vasc Access* 2007; **8**(4): 281-6.

155. Mishler RE. Selected short papers from the 5th Annual Controversies in Dialysis Access. October 20-21, 2008. Washington, DC, USA. *The journal of vascular access* 2008; **9**(3): 171-227.

156. Golledge J, Smith CJ, Emery J, Farrington K, Thompson HH. Outcome of primary radiocephalic fistula for haemodialysis. *Br J Surg* 1999; **86**(2): 211-6.

157. Rajan DK, Bunston S, Misra S, Pinto R, Lok CE. Dysfunctional autogenous hemodialysis fistulas: outcomes after angioplasty--are there clinical predictors of patency? *Radiology* 2004; **232**(2): 508-15.

158. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010; **363**(24): 2287-300.

159. Gray RJ, Sacks D, Martin LG, Trerotola SO. Reporting Standards for Percutaneous Interventions in Dialysis Access. *Journal of Vascular and Interventional Radiology* 1999; **10**(10): 1405-15.

160. Pisoni RL, Arrington CJ, Albert JM, et al. Facility Hemodialysis Vascular Access Use and Mortality in Countries Participating in DOPPS: An Instrumental Variable Analysis. *American Journal of Kidney Diseases*; **53**(3): 475-91.

161. Tennankore KK, Kim SJ, Baer HJ, Chan CT. Survival and Hospitalization for Intensive Home Hemodialysis Compared with Kidney Transplantation. *Journal of the American Society of Nephrology* 2014.

162. Clinical Practice Guidelines for Vascular Access. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2006; **48**: S176-S247.

163. NKF NKF. Clinical Practice Guidelines for Vascular Access. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2006; **48**: S176-S247.

164. Vesely TM, Idso MC, Audrain J, Windus DW, Lowell JA. Thrombolysis versus surgical thrombectomy for the treatment of dialysis graft thrombosis: pilot study comparing costs. *Journal of Vascular and Interventional Radiology* 1996; **7**(4): 507-12.

165. Health ARCf. 2010 Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data 1999-2008. Ann Arbor: Arbor Research Collaborative for Health, 2010.

166. Zhu DW. The potential mechanisms of bradyarrhythmias associated with AngioJet thrombectomy. *The Journal of invasive cardiology* 2008; **20**(8 Suppl A): 2A-4A.

167. Tordoir J, Canaud B, Haage P, et al. EBPG on vascular access. *Nephrology Dialysis Transplantation* 2007; **22**(suppl 2): ii88-ii117.

168. Littler P, Cullen N, Gould D, Bakran A, Powell S. AngioJet thrombectomy for occluded dialysis fistulae: outcome data. *Cardiovascular and interventional radiology* 2009; **32**(2): 265-70.

169. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *New England Journal of Medicine* 2009; **360**(21): 2191-201.

170. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. *Journal of the American Society of Nephrology : JASN* 2004; **15**(2): 477-86.

171. Perl J, Wald R, McFarlane P, et al. Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol* 2011; **22**(6): 1113-21.

172. Rayner HC, Pisoni RL. Opinion: The Increasing Use of Hemodialysis Catheters: Evidence from the DOPPS on Its Significance and Ways to Reverse It. 2010: Wiley Online Library; 2010. p. 6-10.

173. Green LD, Lee DS, Kucey DS. A metaanalysis comparing surgical thrombectomy, mechanical thrombectomy, and pharmacomechanical thrombolysis for thrombosed dialysis grafts. *Journal of vascular surgery* 2002; **36**(5): 939-45.

174. Turmel-Rodrigues L. Application of percutaneous mechanical thrombectomy in autogenous fistulae. *Techniques in vascular and interventional radiology* 2003; **6**(1): 42-8.

175. Tordoir JH, Bode AS, Peppelenbosch N, van der Sande FM, de Haan MW. Surgical or endovascular repair of thrombosed dialysis vascular access: Is there any evidence? *Journal of Vascular Surgery* 2009; **50**(4): 953-6.

176. Besarab A, Dinwiddie L. Changes noted to KDOQI guidelines for vascular access. *Nephrology news & issues* 2006; **20**(9): 36.

177. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled clinical trials* 1996; **17**(1): 1-12.

178. Vesely TM, Williams D, Weiss M, et al. Comparison of the AngioJet rheolytic catheter to surgical thrombectomy for the treatment of thrombosed hemodialysis grafts. *Journal of vascular and interventional radiology* 1999; **10**(9): 1195-205.

179. Schuman E, Quinn S, Standage B, Gross G. Thrombolysis versus thrombectomy for occluded hemodyalisis grafts. *The American journal of surgery* 1994; **167**(5): 473-6.

180. Dougherty MJ, Calligaro KD, Schindler N, Raviola CA, Ntoso A. Endovascular versus surgical treatment for thrombosed hemodialysis grafts: a prospective, randomized study. *Journal of vascular surgery* 1999; **30**(6): 1016-23.

181. Haskal ZJ, Trerotola S, Dolmatch B, et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. *New England Journal of Medicine* 2010; **362**(6): 494-503.