

## Current tools for prediction of arteriovenous fistula outcomes

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### Abstract

It remains challenging to accurately predict whether an individual arteriovenous fistula (AVF) will mature and be useable for haemodialysis vascular access. Current best practice involves the use of routine clinical assessment and ultrasonography complemented by selective venography and magnetic resonance imaging. The purpose of this literature review is to describe current practices in relation to pre-operative assessment prior to AVF formation and highlight potential areas for future research to improve the clinical prediction of AVF outcomes.

**Keywords:** arteriovenous fistula; clinical assessment; definitions; ultrasonography; venography

### Introduction

It remains challenging to accurately predict whether an individual arteriovenous fistula (AVF) will mature and be useable for haemodialysis vascular access. In part, this is due to the heterogeneity of end-stage renal disease (ESRD) populations studied as these have varied in terms of age structure, background ethnicity and the relative prevalence of different ESRD aetiologies. The natural history of AVF maturation is also confounded by multiple comorbid conditions, such as diabetes and peripheral vascular disease, which may be present in ESRD patients. The outcome (clinically usable AVF) is further impacted by variation in point-of-care management of AVFs, e.g. cannulation expertise. In order to study the effect any variable has on a given vascular access outcome, it is important to establish specific definitions. The fact that there are multiple definitions of vascular access outcomes (summarized in Table 1) makes it more difficult to compare published data from different centres and countries.

The Renal Association Vascular Access for Haemodialysis clinical practice guidelines [1] have encouraged the earlier formation of AVFs in an attempt to reduce the number of ESRD patients commencing haemodialysis using a central venous catheter (CVC). Furthermore, in the UK, National Health Service best practice tariffs for haemodialysis promote the use of AVFs as renal units providing haemodialysis receive higher annual payments for those ESRD patients using an AVF (compared with patients with a CVC). These financial incentives coupled with the persistently high failure rate of AVFs support renewed efforts to identify pre-operative predictors of AVF outcomes. The purpose of this literature review is to describe current practices in relation to pre-operative assessment prior to AVF formation as summarized in Figure 1 and

highlight potential areas for future research to improve the clinical prediction of AVF outcomes.

### How an AVF matures

Guidelines suggest attempting to create an AVF at the most appropriate distal arm site. In practice, this means choosing the more proximal radiocephalic site before considering a brachiocephalic AVF. If these sites are unsuitable then a brachiobasilic procedure or placement of an arteriovenous graft (AVG) may be most appropriate [1]. A useable AVF can offer the haemodialysis patient a durable vascular access option which, in comparison to prolonged CVC dependence, is associated with a lower risk of bloodstream infection and central venous stenosis [2]. The ideal AVF must achieve an adequate connection between the high-pressure arterial and low-pressure venous systems; bypassing the small capillary network of the palmar arch while maintaining arterial perfusion and venous drainage in the tissues distal from the site of creation [3]. As a result of the arteriovenous anastomosis, pressure within the vein increases, causing dilatation and 'arterialization' of the anastomosed vein. A reflex increase in cardiac output allows for this distal tissue perfusion and maturation of the fistula which is frequently complemented by retrograde arterial flow [4]. Where retrograde flow is excessive, steal syndrome may occur characterized by distal neuralgia and eventually peripheral limb ischaemia [5, 6].

Poiseuille's law [as shown in Equation (1)] describes essential determinants of blood flow which are related to perfusion pressure, blood vessel radius and length and the viscosity of blood. The maturation of an AVF is partly

**Table 1.** Definitions of fistula outcomes

Primary failure	Immediate failure of AVF within 72 h of surgery, early dialysis suitability failure or late dialysis suitability failure (NAVAC definition)
	Early dialysis suitability failure This is an AVF for which, despite interventions (radiologic or surgical), it was not possible to use the AVF successfully for haemodialysis by the third month following its creation (NAVAC definition)
	Late dialysis suitability failure This is an access for which, despite interventions (radiologic or surgical), it was not possible to use the AVF successfully for haemodialysis by the sixth month following its creation (NAVAC definition)
Primary patency	The interval from the time of access creation until the first access thrombosis or any intervention to maintain or restore blood flow (NAVAC and SVS definition)
Assisted primary patency (thrombosis-free access survival)	The interval from time of access placement to access thrombosis or time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to maintain the functionality of a patent access (not recommended by NAVAC or SVS)
Functional primary patency	The time from the first successful two-needle cannulation until the first intervention or access failure
Secondary (cumulative) patency	The time from access creation until access abandonment. Secondary patency was not terminated by surgical or interventional radiology procedures to maintain or restore patency (NAVAC and SVS definition)
Functional secondary patency	The interval from the first successful two-needle cannulation for haemodialysis treatment to access abandonment (NAVAC and SVS definition)

AVF, arteriovenous fistula; NAVAC, North American Vascular Access Consortium; SVS, Society for Vascular Surgery.

governed by these parameters.

$$\text{Volume flow rate} = \frac{\text{Pressure difference} \times \text{Radius}^4}{(8/\pi) \times \text{Viscosity} \times \text{Length}} \quad (1)$$

Normal brachial arterial blood flow is 50 mL/min with radial blood flow rates of 25 mL/min [7]. This blood flow rate has been shown to increase 3- to 5-fold during exercise or following reactive hyperaemia; however, according to Poiseuille's law, radial artery flow must increase 20-fold in order to deliver >500 mL/min of blood flow and achieve radiocephalic AVF maturation. The actual measured increase in blood flow is only 40–50% of this prediction and therefore other mechanisms must be operating [8]. The increase in blood flow is achieved through increased antegrade arterial blood flow in addition to retrograde blood flow from the palmar arterial arch in ~75% of AVFs [4], decreased blood viscosity associated with the increase in flow rate and therefore reduction in wall shear stress and friction [8]. This occurs in combination with maintained antegrade flow throughout the cardiac cycle as opposed to retrograde flow seen in diastole in a normal artery [9].

Other processes are involved in AVF maturation as shown in Figure 2. Arterial disease in the form of arteriosclerosis and pre-existing neointimal thickening associated with conditions such as diabetes, hypertension and ESRD itself may contribute to the development of neointimal hyperplasia after AVF formation [10]. Endothelial dysfunction can also impair the arterial response to increased wall shear stress, therefore inhibiting the dilatation and increased flow rates required for AVF maturation [3]. Venous trauma and fibrosis caused by previous cannulation, venepuncture and the surgical creation of an AVF can lead to inability of venous distension preventing flow-induced remodelling [11]. Pre-existing arterial or venous disease and the surgical procedure itself are important components of the success or failure of an AVF.

The effect of coagulation disorders (high factor VIII:C, homocysteine, fibrinogen, d-dimer; presence of antiphospholipid antibodies and short thrombin time) and thrombophilia (factor V Lieden and prothrombin G20210A mutations; protein C and antithrombin activities; and protein S) on maturation is unknown, although female sex and thrombophilia are independent risk factors for loss of primary patency [12]. A recent Cochrane systematic review on the use of

antiplatelet agents in chronic kidney disease found that while there was an associated reduction in early thrombosis rates of AVF, this had no effect on suitability for dialysis supporting other underlying reasons [13]. For the purposes of pre-operative evaluation, the presence of such factors may be important but are generally not modifiable or useful in individuals to plan access.

## Pre-operative assessment

### Clinical assessment

Clinical assessment of an ESRD patient's suitability for AVF creation involves detailed history taking and appropriate physical examination as summarized in Table 2. The use of clinical assessment alone may provide sufficient assessment in selected cases. Wells *et al.* [14] discuss the selective use of ultrasonographic vascular mapping in the evaluation of patients prior to the start of haemodialysis. They indicate that for some patients, ultrasound vascular mapping is unnecessary and allows patients to avoid any time delay associated with an extra clinic appointment for ultrasonography and also reduces overall costs associated with preoperative assessment. They suggest that this facilitates the development of a 'one stop shop' whereby patients undergo clinical assessment and surgery on the same day. It could also be argued that training of vascular access surgeons in the use of ultrasonographic techniques specific to vascular access would also reduce the costs incurred and time delays.

### Patient and fistula selection

Age and gender are often natural discriminators. As with many conditions, the average age of the population with ESRD is increasing annually. Hod *et al.* [15] highlighted that the important risk factors for AVF failure in those older than 67 years of age are increasing age, female gender, black race, diabetes, cardiac failure and a shorter period of pre-ESRD nephrology care. Similarly, Miller *et al.* [16] have shown a lower AVF adequacy in women compared with men which was unexplained by pre-operative blood vessel diameters. Ng *et al.* [17] found from their analysis of 2920 patients that AVGs, female gender, diabetes and advanced age were all associated with significantly shorter primary AVF patency.

<b>Clinical assessment</b>	
<b>Advantages</b>	
Readily available	
Cheap	
Quick	
No significant training outside of surgical training	
<b>Disadvantages</b>	
May fail to identify vessels suitable for radiocephalic	
Cannot identify central venous stenosis	
<b>Doppler ultrasound</b>	
<b>Advantages</b>	
Readily available	
Relatively cheap	
Improves uptake of distal vessels	
Useful in preoperative and post operative setting	
Can assess endothelial response to reactive hyperaemia	
Can assess venous distensibility	
Lends itself to computational modelling	
<b>Disadvantages</b>	
Requires additional training	
Can add to delay in proceeding to fistula formation	
<b>Venography</b>	
<b>Advantages</b>	
Identifies central venous stenosis	
DSA gold standard	
MRV available for pre-dialysis patients	
Can identify clinically occult veins	
<b>Disadvantages</b>	
Relatively Expensive	
Less readily available than DUS	
<b>MRI</b>	
<b>Advantages</b>	
Can identify arterial and venous disease	
Lends itself to computational modelling	
<b>Disadvantages</b>	
Less readily available	
Expensive	
NSF associated with contrast media	
Overestimates venous diameters	
<b>Arterial stiffness</b>	
<b>Advantages</b>	
Associated with adverse cardiovascular outcomes in large prospective studies of patients with ESRD	
<b>Disadvantages</b>	
No evidence of utility in vascular access	
<b>Endothelial dysfunction</b>	
<b>Advantages</b>	
Reduced endothelial function in uraemia	
Reduced nitric oxide production	
<b>Disadvantages</b>	
No evidence of utility in vascular access	
<b>Biomarkers and AGEs</b>	
<b>Advantages</b>	
Readily available	
Value in predicting outcome patients in end stage renal disease	
<b>Disadvantages</b>	
No evidence of utility in vascular access	

**Fig. 1.** Summary of advantages and disadvantages associated with preoperative assessment tools. DSA, digital subtraction angiography; MRV, magnetic resonance venography; DUS, Doppler ultrasound scan; MRI, magnetic resonance imaging; NSF, nephrogenic systemic fibrosis; ESRD, end-stage renal disease; AGE, advanced glycation end-products.

In a systematic review performed by Al-Jaishi *et al.*, it was shown that the primary AVF failure rates were higher in more distal compared with proximal upper limb sites [primary failure rates of 28% for lower arm AVF and 20% for upper arm AVF ( $P=0.001$ )]. Similarly, the primary AVF

patency rates at 1 year were significantly worse in lower arm versus upper arm sites (55 versus 65% for lower and upper arm AVFs, respectively) [18].

Older age, female gender, presence of diabetes and distal AVFs have all been identified as risk factors for

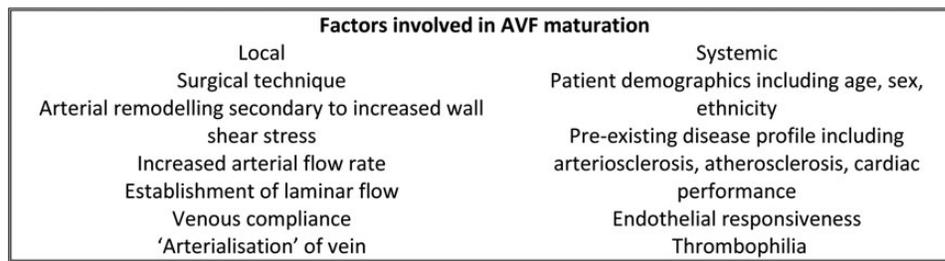


Fig. 2. Summary of factors involved in AVF maturation.

Table 2. Summary of clinical assessment prior to arteriovenous fistula formation

Clinical assessment for vascular access	
History	Previous central venous catheterization Presence of diabetes and hypertension Use of anticoagulant or antiplatelet agents
Peripheral arterial assessment	Palpation of axillary, brachial, radial and ulnar pulses bilaterally noting presence, absence or diminished character Bilateral blood pressure assessing for discrepancies Allen's test
Peripheral venous assessment (performed with proximal tourniquet)	Assess cephalic and basilic systems Assess for patency, presence of a linear segment, collateral engorgement of chest wall veins

primary AVF failure and should be taken into consideration when planning an AVF procedure.

### Doppler ultrasound

Doppler ultrasound (DUS) is one of the key techniques currently employed for enhancing clinical examination of the patient prior to AVF construction. This is used not only as a preoperative tool in assessing arterial and venous anatomy but also in post-operative monitoring of AVF maturation and ongoing AVF surveillance. DUS assessment does require more clinical skill, equipment and time to perform (compared with clinical examination alone), but it remains non-invasive, safe, has reproducible results and helps to identify clinically occult veins [19]. DUS allows for observation of arterial diameter, vessel wall thickness, wall alterations, blood vessel course, localization of any obstructive or stenotic lesions present and can also perform a functional assessment. The 2007 European Renal Best Practice guidelines suggest the use of DUS assessment in all patients being considered for vascular access formation [20].

A number of studies have been conducted to assess the utility of arterial diameter in predicting AVF outcomes. Malovrh [21] reported immediate AVF failure rates of 44% and early failure rates of 64% where radial arterial diameters were <1.5 mm on pre-operative DUS. This contrasts with immediate and early AVF failure rates of 8 and 17%, respectively, where radial arterial diameters were >1.5 mm [22]. These findings have been supported by Parmar *et al.* [22] who found arterial diameters of <1.5 mm had an AVF failure rate of 45% compared with 0% when radial arterial diameter was >1.5 mm. Wong *et al.* [23] found a significant difference at an arterial diameter cut-off of 1.6 mm. Silva *et al.* [24] proposed a cut-off of 2

mm for arterial diameter as they found this to be associated with a very low early AVF failure rate of 8% and an excellent 1-year AVF patency rate of 83%. AVF patency beyond 6 weeks is considered an important parameter in the analysis of AVF outcomes.

DUS can be used to assess the functional ability of the artery to dilate by using a reactive hyperaemia test. This is performed by asking the patient to clench their fist while observing the phasic flow via DUS. The patient then releases the fist and the arterial 'reaction' is measured. This simulates the change from high pressure to low pressure which occurs in AVF formation and therefore provides a surrogate measurement of how the artery will respond to the 'stress' of AVF surgery. Malovrh [19] demonstrated that an absence of reactive hyperaemia characterized by a resistance index of <0.7 on opening of the fist is predictive of immediate postoperative AVF failure. These findings have been challenged by Lockhart *et al.* [25] who found no difference in AVF outcomes, except in functional patency of AVFs in women and Wall *et al.* [26] who found no difference in primary functional AVF patency but a significant difference in secondary AVF patency following surgical revision. These studies do not lend themselves to direct comparison but do suggest that the ability of the artery to dilate plays a significant functional role in AVF maturation.

DUS is also used to assess the cephalic and basilic veins in the arm, including the venous wall, route, patency, calibre, distensibility and collateral circuits. The ideal vein for AVF formation has a relatively straight course and should lie <6 mm from the skin surface [27].

Due to the superficial nature of the veins, transducer gel should be applied copiously to prevent excessive pressure on the vein in question and therefore underestimation of vein diameter. Several studies have suggested the ideal diameter of the vein to be used for AVF formation. Small veins of <1.6 mm in diameter are associated with a high risk of early AVF failure within 12 weeks [23]. Silva *et al.* [24] suggested a minimum diameter of 2.5 mm with a tourniquet applied, whereas Mendes *et al.* [28] suggest a minimum diameter of >2 mm.

Venous distensibility is assessed by measuring the diameter of the vein before and after at least 2 min of tourniquet placement. This can be achieved by inflating a sphygmomanometer to 60 mmHg. The percentage increase in the size of the vein is then evaluated by ultrasound. Malovrh [29] found that venous distensibility was predictive of outcomes since subsequently successful AVFs showed a mean percentage dilatation of 44% compared with only 11% in the unsuccessful AVF group. Lockhart *et al.* [30] similarly found DUS useful in the identification of suitable veins by concluding that veins with a luminal diameter of >2.5 mm and those smaller veins that dilated up to 2.5 mm with placement of a tourniquet were equally

suitable for AVF formation. The presence of accessory veins has also been suggested to be a factor in non-maturation of AVF. An accessory vein <5 cm from the anastomosis can alter the functionality of the AVF [23], while the size of the collaterals rather than their position may impact on the rate of AVF non-maturation [31].

A recent systematic review [32] has concluded that the use of pre-operative DUS is associated with a higher rate of commencing dialysis, but this association did not reach statistical significance and therefore additional novel predictors of AVF outcomes may help improve clinical management of ESRD patients. This systematic review conclusion is supported by Smith *et al.* [33] who randomized patients into either routine or selective preoperative ultrasound imaging. They reported that routine pre-operative does not reduce early failure rates, influence site of AVF formation or reduce complications concluding that routine preoperative imaging may not be necessary where clinical evaluation detects suitable anatomy for AVF formation.

A novel computational model has been suggested by Caroli *et al.* [34] which is completely automated, fast, involves operator-independent calculations and enables the observer to quantitatively estimate patient-specific postoperative blood flow volume change over different AVF configurations. This model uses preoperative vessel dimension and arterial blood flow volume measurements taken during ultrasound assessment as input parameters to predict postoperative diameters and blood flow volumes at different time points after surgery. The computational model was found to be accurate in predicting blood flow volumes in individual patients 40 days postoperatively with highly significant correlation for different AVFs. As Roy-Chaudhury *et al.* [35] comment, this is a step towards individualization of AVF creation and a good example of the multidisciplinary research collaboration necessary to achieve a significant impact on vascular access outcomes.

### Venography

Digital subtraction venography is considered to be the gold standard for assessment of the venous system and has been investigated as a potential adjunct to pre-operative assessment of patients with ESRD referred for AVF formation. Traditional iodinated contrast can be used in patients who are being dialysed; however, in patients who are pre-dialysis, magnetic resonance venography had been shown to have acceptable sensitivity and specificity when compared with venography with good inter-observer correlation regarding imaging quality and strategy planning [36]. Gadolinium-based magnetic resonance contrast media are no longer considered safe for persons with chronic kidney disease because of the risk of nephrogenic systemic fibrosis [37]. Carbon dioxide-based venography is a promising alternative contrast choice for use in patients with advanced chronic kidney disease and ESRD [38].

Hyland *et al.* [39] have shown that venography is able to identify clinically occult veins which may be usable for AVF formation, a conclusion which is supported by Patel *et al.* [40] who found that while this imaging modality can identify a greater number of suitable veins, paradoxically, the combined use of DUS and venography was associated with a decreased AVF maturation rate. The 2007 European Best Practice Guidelines advocate central venous imaging for all patients with a history of CVC placement to identify central venous stenosis or occlusion prior to AVF formation [21].

### Magnetic resonance imaging

Magnetic resonance angiography (MRA) has been shown to enable accurate detection of upper limb arterial and venous stenosis and occlusions prior to AVF creation [41]. These stenoses are undetectable by conventional DUS and therefore identification could potentially reduce the early AVF failure and non-maturation rate. The recognition of nephrogenic systemic fibrosis and its association with gadolinium-based contrast media has prompted comparison of contrast-enhanced versus non-contrast-enhanced MRA [42] (NCE-MRA) and shown that while image quality and vessel-to-background ratios were lower, NCE-MRA is a feasible alternative in patients with ESRD.

Merkx *et al.* [43] assessed the merits of NCE-MRA for predicting vascular access outcomes based around a computer model. Postoperative arm inflows were predicted by computer modelling following pre-operative NCE-MRA and compared with blood flow measurements assessed by DUS postoperatively. They concluded that NCE-MRA is able to provide geometrical details of arterial stenoses which could assist the vascular surgeon in AVF planning. This expensive and less readily available investigation is unlikely to replace clinic-based DUS in the assessment of patients for AVF formation but may have applications in patients with peripheral arterial disease, thrombosis or reduced arm inflows due to local stenoses or global narrowing within the arterial lumen. Another limitation of this method is the necessity for DUS assessment of venous diameters since NCE-MRA grossly overestimates venous diameters [44].

### Novel techniques for prediction of AVF outcomes

#### Assessment of arterial stiffness

Arterial stiffness, which is common in patients with chronic kidney disease, refers to the distensibility, compliance and elastic modulus of the arterial vascular system and can be measured locally, regionally and systemically. Aortic pulse wave velocity is considered the gold standard [45] for assessing arterial stiffness as it gives the clearest pathophysiological significance since the majority of the buffering of pulse waves occurs within the aorta. The pulse wave Vicorder™ (Smart Medical, Moreton-in-Marsh, UK) is a non-invasive, easy to learn and reproducible method of assessing stiffness along an arterial section. Although other systems exist to measure aortic pulse wave velocity such as the SphygmoCor™ system (AtCor Medical, West Ryde, NSW, Australia) and Complior™ apparatus (Artech Medical, Pantin, France), these require greater operator instruction and are more intrusive to patients as they require palpation and assessment at the femoral artery. Increased aortic pulse wave velocity has been independently associated with adverse cardiovascular outcomes in large prospective studies, including specifically patients with ESRD [46]. Assessment of arterial stiffness has yet to be extensively investigated in relation to AVF outcomes and is an area of interest for future research projects.

#### Assessment of endothelial function

The responsiveness of the endothelium is an important aspect of the remodelling required to establish a mature AVF. The endothelium acts as an interface between the blood and all other tissues in the body performing important roles in maintaining the vascular environment through

release of agents that regulate vasomotor tone, inflammatory responses and homeostatic functions [46]. Nitric oxide is a potent vasodilator, inhibitor of inflammatory activity, smooth muscle cell proliferation and platelet adhesion and aggregation [47]. The loss of the vasodilatory response and promotion of thrombosis, inflammation and cellular proliferation associated with endothelial dysfunction is a potentially worthwhile research topic, since these mechanisms are closely related to AVF maturation. A number of studies have linked endothelial dysfunction with uraemia and reduced nitric oxide production in chronic renal disease [48]. Owens *et al.* [49] found evidence that impairment of endothelial function is associated with decreased arterial remodelling and final venous diameter attained at 3 months post-fistula formation.

Two methods of measuring endothelial dysfunction are flow-mediated dilatation (FMD) and peripheral arterial tonometry (PAT). FMD is the most well-established method of assessing endothelial function and is based on the reactive hyperaemic response following a period of occlusion with a tourniquet. Increased blood flow following release of the cuff causes increased wall shear stress, leading to release of nitric oxide and therefore vasodilatation [50]. Monitoring the response will give a surrogate marker of endothelial performance post-fistula formation and therefore guide vascular surgeons regarding patient suitability and vascular access site placement. PAT is a more recent development which uses pneumatic finger probes to measure the digital pulse wave amplitude when reactive hyperaemia is induced [51]. A recent study assessing the correlation between these two methods in healthy patients and patients with peripheral arterial disease concluded that there was no correlation between these two methods and that FMD is a more accurate measure of nitric oxide-induced endothelial function [52].

A novel method of assessing the hyperaemic response in patients undergoing AVF formation is the use of near-infrared spectroscopy. This is a non-invasive, continuous, real-time determination of chromophore concentration on the basis of spectrophotometric principles. In mammalian tissue, there are three chromophores which demonstrate absorption spectra in the near-infrared range (800–1200 nm wavelength), namely haemoglobin and deoxyhaemoglobin, myoglobin and cytochrome oxidase. The result is a measurement of mixed arterial and venous oxygen concentrations within the tissue being studied which, if placed distal to the site of AVF planning, may provide new information about the physiological response to AVF formation and assist in AVF planning. Another alternative way to assess endothelial dysfunction is the use of laser Doppler flowmetry and imaging to measure cutaneous perfusion accompanied by iontophoresis of acetylcholine and sodium nitroprusside. Hansell *et al.* [53] found a significant correlation between FMD in the brachial artery and laser Doppler flowmetry in small cutaneous vessels supporting the systemic nature of endothelial dysfunction and that microvascular changes in the skin mimic macrovascular changes in the supplying artery.

### Biomarkers

As yet, there have been no biomarkers identified as a useful adjunct to AVF planning. Biomarkers have been extensively investigated in ESRD patients focusing on their usefulness in prognosis, diagnostics, response to therapy and prevention of disease. Elevated fibroblast growth factor 23 and bone alkaline phosphatase have been

identified as having prognostic value in predicting mortality in patient with ESRD-related bone mineral disease while elevated C-reactive protein, interleukin-6 and tumour necrosis factor levels are associated with increased mortality in ESRD patients [54]. Asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide synthase and high circulating levels are associated with endothelial dysfunction and atherosclerosis in patients with pre-dialysis ESRD [55].

A number of inflammatory markers, such as interleukin-6, tumour necrosis factor- $\alpha$  and soluble P selectin, have been associated with adverse cardiovascular outcomes [56]; however, high-sensitivity CRP (hs-CRP) has the strongest association with cardiovascular outcomes [57]. It is reported that hs-CRP can destabilize nitric oxide synthase mRNA in endothelial cells [58], suggesting a correlation between high circulating levels of hs-CRP and endothelial dysfunction. Also, 13-hydroxyoctadecadienoic acid (13-HODE) has been found to decrease with age in patients undergoing coronary artery bypass grafting and has been associated with an increase in endothelial cell thrombogenicity [56]. Other surrogate markers of endothelial cell activation and inflammation have been proposed, including lipoprotein-associated phospholipase A<sub>2</sub>, CD40 receptor/CD40 ligand interaction, LOX-1 and direct measurements of circulating endothelial progenitor cells [59]. Further studies are required to establish if assessing biomarkers of baseline endothelial function in patients with ESRD is clinically useful either for prediction of AVF maturation or to target therapies to modify local vascular biology prior to AVF formation.

Creation of an AVF has been shown to have significant effects on atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). An increase in ANP was induced by volume loading and BNP release was stimulated by left ventricular diastolic dysfunction. Additionally, a positive relationship has been shown between MMP-2 gene expression in vein segments evaluated by gelatin zymography and western blotting and AVF maturation [60]. The maximal benefit from biomarkers may lie in the multi-marker approach as evidenced by the Olmsted study which reported that the combination of increased BNP with CRP levels enhanced the ability to predict risk of death compared with standard risk factors for mortality in heart failure [61].

Advanced glycation end-products (AGEs) have been implicated in the pathophysiology of vascular disease where they accumulate in the endothelial cell wall and disrupt cellular structure and function, including decreasing the bioavailability of nitrous oxide and alteration of cell surface structure from an anticoagulant to pro-coagulant state. In theory, reducing the burden of AGEs would offer a potential novel therapeutic option to improve vascular biology and potentially improve maturation of AVFs. There is experimental evidence that agents such as aminoguanidine, ALT-946, ALT-711, statins, pyridoxamine and dietary modifications can help to reduce AGE levels [62]. There is no convincing evidence yet that such therapies improve vascular access outcomes.

### Assisted maturation

Several novel therapies have been proposed to assist AVF maturation, including the use of far-infrared (FIR) therapy [63]. FIR is a non-invasive therapeutic modality which has been reported to improve access flow rates and reduce the incidence of AVF malfunction in

haemodialysis patients. Primary balloon angioplasty has been shown to improve primary AVF patency rates for AVFs with venous diameters of <3 mm [64] and also in AVFs with venous diameters of  $\leq 2$  mm [65]. These conclusions have been supported by more recent data from Turmel-Rodrigues, suggesting that by using an aggressive, multi-disciplinary approach a non-maturing AVF can be identified, evaluated and salvaged [66]. An increased number of interventions required to assist maturation is however associated with reduced primary and secondary patency rates and a higher number of interventions to maintain patency [67].

#### Current studies

The Hemodialysis Fistula Maturation [68] study is currently underway in the USA. This is a multicentre prospective cohort study which is aiming to recruit 600 patients undergoing new AVF creation with a 4-year follow-up period. The primary outcome is unassisted clinical maturation. The results of this study are eagerly anticipated as this is the first, large-scale, adequately powered cohort to address many of the outstanding questions related to predictors of AVF outcomes. Further studies into vascular access outcomes include the 'Antiaggregation in Primary Prevention of Vascular Access for Hemodialysis' (NCT02055131) and 'The Use of Glyceryl Trinitrate Patches in Arteriovenous Fistulas' (NCT01685710) which will provide further information on the use of aspirin in varying doses and the use of glyceryl trinitrate patches applied 5 cm proximal from the site of vascular access surgery in the prevention of early stenoses.

#### Conclusion

The factors leading to failure of AVF maturation are still ill defined and there is a limited ability to predict surgical vascular outcomes. Clinical examination and DUS measurements are the mainstays of current preoperative assessment. Further studies into this under-researched field are currently underway and there are many opportunities to develop better tools to predict AVF outcomes.

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