Chapter

Pathogenesis and Prevention of Vascular Access Failure

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Abstract

Dialysis vascular access failure is common, is rated as a critical priority by both patients and health professionals, and is associated with excess morbidity, mortality and healthcare costs. This chapter will discuss the mechanisms underpinning vascular access failure as well as strategies for preventing this adverse outcome, including systemic medical therapies (such as antiplatelet agents, fish oils, statins, inhibitors of the renin-angiotensin-aldosterone system, and calcium channel blockers), and local therapeutic interventions including innovative surgical techniques, minimally invasive AVF creation, far infra-red therapy, perivascular application of recombinant elastase, endothelial loaded gel foam wrap (Vascugel), and antiproliferative agents such as sirolimus (Coll-R) and paclitaxel-coated balloon angioplasty.

Keywords: arteriovenous fistula, arteriovenous graft, arteriovenous shunt, aspirin, cardiovascular agents/therapeutic use, clinical research, endovascular procedures, end-stage kidney disease, fish oils, graft occlusion, hemodialysis, maturation, risk factors, statins, thrombosis, treatment outcome, vascular access, vascular patency

1. Introduction

The prevalence of end-stage kidney disease (ESKD) is increasing in the presence of a growing diabetic and aging population [1, 2]. Hemodialysis remains the most common form of kidney replacement therapy [3–5], with over 2 million people on hemodialysis worldwide [6]. To maintain successful hemodialysis, functional vascular access is required [7]. Hemodialysis vascular access consists of three forms: the arteriovenous fistula (AVF), the arteriovenous graft (AVG), and the central venous catheter (CVC). The AVF is a connection between a native artery and vein that is created via an end-to-side vein-to-artery anastomosis [8]. AVGs are created by interposing a prosthetic graft (classically with polytetrafluorethylene [PTFE]) between an artery and a vein [8]. The key requirements of such access are sufficient blood flow rate, low flow resistance, a low rate of complications and, for AVF and AVG, ease of cannulation.

A mature native AVF is considered superior to a synthetic AVG or CVC due to better long-term outcomes, including reduced rates of thrombosis, infection and interventions to maintain patency [9–11]. Balanced against these benefits, as a result of early thrombosis, neointimal hyperplasia formation and inadequate vasodilation (outward remodeling), between 20 and 60% of AVFs fail to mature to an adequate caliber to allow repeat cannulation and provide sufficient blood flow for

hemodialysis and thereby prevent timely usability of the AVF for hemodialysis [9]. AVGs can be used within days of access creation but long-term, they are at higher risk of developing venous stenosis, thrombosis and infection compared to a functioning AVF [12]. More than 50% of AVGs thrombose within 12 months of creation and they require significantly more interventions to maintain patency compared to a functioning AVF [12–14]. CVCs can be used immediately after insertion, but their long-term use is discouraged in light of the significantly higher risks of thrombosis, catheter-associated bacteremia and inadequate solute clearance [15–17].

Vascular access dysfunction is a major cause of morbidity, mortality and excess healthcare costs [9, 18–20]. Indeed, healthcare professionals, patients and caregivers consider vascular access function a top priority of research in hemodialysis and clinical practice [21]. There have been recent advances in the understanding of the biology of vascular access and its dysfunction, with neointimal hyperplasia leading to venous stenosis and inadequate outward remodeling being identified as the two major causes of dialysis vascular access dysfunction [7, 22]. This knowledge has led to the identification of potential therapeutic targets and the development of novel interventions to improve and maintain vascular patency [17].

This chapter will discuss the risk factors for, and pathogenesis of arteriovenous access failure. The advances in the understanding of arteriovenous access failure have led to the development of therapeutic targets and novel therapeutic interventions including systemic medical therapies with pleiotropic effects (such as antiplatelet agents, fish oils, statins, inhibitors of the renin-angiotensin-aldosterone system [RAAS], and calcium channel blockers), and local therapeutic interventions including innovative surgical techniques, minimally invasive AVF creation, far infra-red therapy, perivascular application of recombinant elastase, endothelial loaded gel foam wrap (Vascugel), and antiproliferative agents such as sirolimus (Coll-R) and paclitaxel-coated balloon angioplasty.

2. Clinical predictors of arteriovenous access failure

Key contributors to successful AVF maturation and long-term function include adequate inflow properties determined by the size and quality of the feeding artery, cardiac output and blood pressure; anastomotic properties concerning the patent anastomosis between the artery and vein/interposition graft; and adequate outflow properties, which in turn are determined by the size and quality of the vein and presence or absence of collateral or accessory veins. The significance of these three factors in determining vascular access success highlight the importance of vascular mapping and planning prior to fistula creation.

Inflow properties are influenced by the location of the AVF, with patency increasing as the size of the feeding artery is increased (distal to proximal) [23]. Despite this, the distal radio cephalic AVF on the non-dominant side of the patient is the preferred initial site of AVF for vascular access [23], partly due to patient comfort along with the preservation of additional vascular access sites for future use. Female gender has been identified as a risk factor for failure of fistula maturation and survival, with investigations discovering significantly poorer outcomes of AVFs in females in comparison to males, though the reasons underpinning this are unclear [24–27]. It has been proposed that females have smaller vessels with associated decreased luminal diameters in comparison to males; however, this has not been consistently found to be a factor in unsuccessful AVFs [28, 29].

Key determinants of both inflow properties and anastomosis patency are the comorbidities of the patient undergoing AVF creation, influencing outcome via unfavorable effects on hemodynamics, with the most adverse effects seen from

peripheral arterial disease, cardiovascular disease and diabetes mellitus. Peripheral arterial disease interferes with the remodeling process required to achieve a functioning fistula, involving the development of neointimal hyperplasia and calcification, causing increased arterial stiffness and decreased elasticity [30]. Woods et al. [31] conducted a study involving 784 incident hemodialysis patients and found a 24% increased risk of AVF failure in those with peripheral arterial disease. This failure is attributable to the fact that for vascular access to be a success, it is essential that the artery used in the creation of the fistula is able to adequately increase diameter allowing for the increased blood flow required to supply the fistula and distal tissues [32, 33].

In relation to cardiac disease, its adverse impact on fistula maturation is due to poor cardiac output and associated poor blood flow to the fistula, resulting in worse outcomes [34].

Diabetes mellitus is associated with increased risks of intimal hyperplasia [35], and peripheral arterial disease [36], with these risks exaggerated further in the chronic kidney disease population leading to an appreciable rate of AVF failure in this group [27, 37, 38].

Advancing age has been cited as a risk factor for failure of AVF maturation and survival, although this proves difficult to quantify with age also being a surrogate marker for increasing burden of comorbidities. Studies have indicated an increased failure rate of AVFs in 'older patients' with the definition of those greater than or equal to 65 years of age [39–41], contrasting with other literature which were unable to identify significant differences in functional access outcomes for older patients [26, 42].

Race and ethnicity have also been identified as risk factors for failure of AVF maturation, though again this has not been consistently replicated in the literature [43]. Studies however have identified AVF failure rate being more common in those of African racial background in comparison to Caucasians; along with Hispanics when compared with non-Hispanics [40, 41, 44].

A pertinent factor affecting the anastomosis and therefore the outcomes of AVFs includes both the experience of the surgeon in creating the fistula, as well as the technical issues associated with utilizing and managing the fistula. The formation of AVFs is difficult, with numerous studies indicating that there is a higher incidence of successful AVFs if the surgery is performed by an experienced vascular surgeon [45–49], with the emphasis being placed on the number of AVFs created over the total years of training [48, 50].

Outflow dynamics are influenced by several factors, one of which is obesity. Obesity is described as a risk factor for failure of vascular access separate to the increased incidence of diabetes in this group. It was observed that obese patients experienced poor secondary patency in a study by Kats et al. [51], with the underlying theory that this was due to the increased soft tissue mass leading to venous compression and outflow tract obstruction [52]. Diabetes has also been shown to be a negative predictor of venous remodeling [53], directly impacting the outflow from an AVF.

Following arteriovenous access creation, ongoing access surveillance, care and cannulation by well trained staff/patient are paramount for preventing access failure [54–59].

3. Pathophysiology of arteriovenous access dysfunction

The pathogenesis of vascular access failure is complex with the common final pathway being the combination of insufficient vessel vasodilation, negative

(inward) vascular remodeling and neointimal hyperplasia resulting in luminal narrowing and often associated thrombosis formation. The Achilles heel of this process is the graft-vein anastomosis in AVG and the perianastomotic region in AVF, respectively [1, 13]. The pathophysiologic cascade of events that lead to AVF and AVG failure [16, 17] have been categorized into upstream events, characterized by factors that lead to injury of endothelial—and smooth muscle cells and downstream events describing the cellular and cytokine responses that leads to neointimal hyperplasia and inward remodeling [16] (**Figure 1**).

There are multiple factors that contribute to the upstream events of vascular access dysfunction: (1) the proinflammatory uremic milieu that promotes endothelial dysfunction [16, 60], (2) hemodynamic stressors at the anastomosis site due to a combination of small and non-compliant vessels, low shear stress and turbulence [16, 61, 62], (3) vascular injury at the time of fistula or graft formation due to vessel manipulation through surgical technique or angioplasty [16, 61, 62], (4) a localized inflammatory response involving cytokine release and macrophage migration caused by the synthetic graft material used in the formation of the AVG [16], (5) possible genetic predisposition to neointimal hyperplasia and vasoconstriction [11, 16] (6) and repeat cannulation injury [16, 54].

After formation of an AVF, rapid increase in blood flow through the feeding artery and draining vein causes vascular distension [63] leading to nitric oxide (NO) synthesis by endothelial cells which results in vascular smooth muscle relaxation and vasodilatation [64]. This response leads to structured vascular remodeling with the driving forces of wall shear stress and tension [63] leading to an increase in arterial and venous lumen size [65] and moderate thickening of the venous wall assisting in maturation [66] and positive (outward) remodeling, which overall results in a larger lumen and greater vascular success (**Figure 2**). In comparison, the smooth muscle and endothelial injury sustained from the upstream events described previously, trigger a cascade of downstream responses mediated through proinflammatory leukotrienes, chemokines, cytokines, vasoactive molecules, metalloproteinase and adhesion molecules that promote neointimal hyperplasia

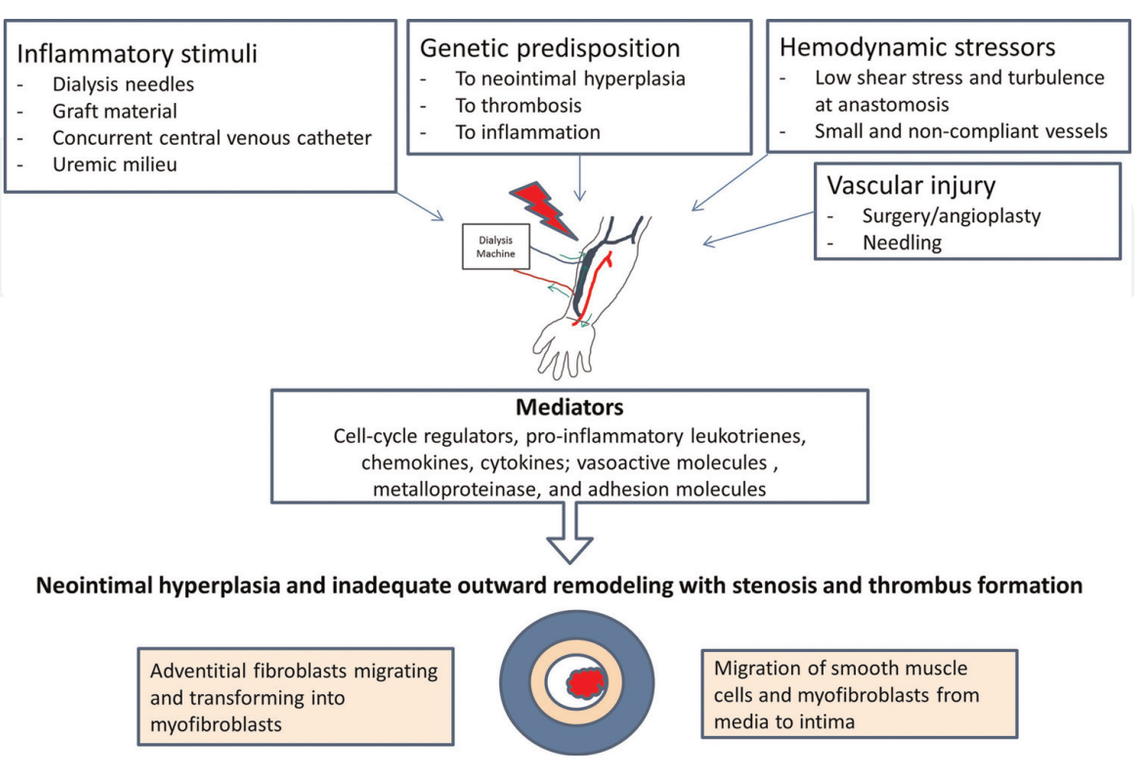

Figure 1.
Pathogenesis of vascular access failure. This figure illustrates the different pathogenic mechanisms that result in vascular access failure. Image re-used from Viecelli et al. [13] with permission from Wiley.

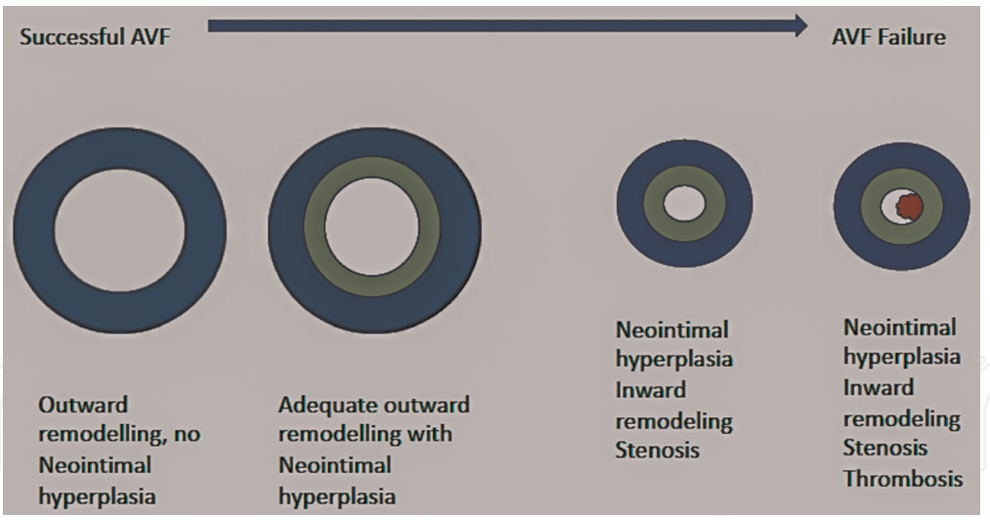

Figure 2.
Vascular remodeling response post fistula creation: comparison of the effects of neointimal hyperplasia with outward and inward vascular remodeling.

formation and negative (inward) remodeling. In comparison to outward remodeling, inward remodeling results in small lumen diameter and an increased risk of access failure [17]. As such, neointimal hyperplasia if combined with compensatory outward remodeling may not result in flow limiting stenosis due to preservation of the luminal caliber, whereas neointimal hyperplasia combined with impaired outward remodeling can result in hemodynamically significant vascular stenosis and resultant thrombosis [17, 63].

4. Therapeutic interventions to prevent VA dysfunction

The following section will discuss systemic medical and local interventions developed to minimize luminal narrowing caused by neointimal hyperplasia and negative (inward) vascular remodeling.

4.1 Systemic medical therapies

4.1.1 Antiplatelet agents

Antiplatelet agents including aspirin, dipyridamole, clopidogrel and ticlopidine are thought to prevent arteriovenous access failure primarily through their antithrombotic effect. Clinical trial results will be discussed separately for each agent given the differences in action of individual agents upon platelet aggregation, function and vascular biology including anti-inflammatory and antiproliferative properties.

4.1.1.1 Aspirin

Aspirin irreversibly inhibits platelet cyclooxygenase-1 and -2 enzymes via acetylation, resulting in decreased formation of prostaglandin precursors and prostaglandin derivative thromboxane A2 [13]. Randomized controlled trials (RCT) on the efficacy of aspirin in preventing arteriovenous access failure have shown inconsistent results, with two small studies favoring aspirin [67, 68] and two studies showing no significant treatment benefit for the prevention of arteriovenous access thrombosis and failure (**Table 1**) [5, 69]. In a small RCT of 44 patients, AVG thrombosis was significantly reduced with 160 mg of aspirin daily compared to

Aspirin									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment duration (months)**	**Primary outcome (aspirin vs placebo)**	**Secondary outcome (aspirin vs placebo)**
Irish et al. [5].	RCT	388	HTN (94%), smoking history (54%), DM (49%), CAD (11%), PVD (4%), CHD (4%), CVD (3%)	AVF	Aspirin 100 mg daily	Placebo	3	Proportion of subjects with AVF failure (thrombosis, abandonment or cannulation failure) at 12 months *45% vs 47%, RR 1.05, 95% CI 0.84–1.31, p = 0.68*	AVF thrombosis at 12 months *20% vs 18%, RR 1.09, 95% CI 0.72–1.64, p = 0.70* AVF abandonment at 12 months *24% vs 18%, RR 1.31, 95% CI 0.89–1.95. p = 0.17* Cannulation failure at 12 months *40% vs 39%, RR 0.99, 95% CI 0.76–1.27, p = 0.92*
Harter et al. [67]	RCT	44	NR	AVG	Aspirin 160 mg daily	Placebo	4	Thrombosis at study end (mean 5 months) *32% vs 72%, OR o.18, 95% CI 0.05–0.66, p < 0.01*	Number of thrombotic events per patient month *0.16 vs 0.46, p < 0.05*
Andrassy et al. [68]	RCT	92	NR	AVF	Aspirin 1000 mg alternate days	Placebo	1	Thrombosis at 28 days *4% vs 23%, p < 0.05*	NR
Dipyridamole and/or aspirin									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment duration (months)**	**Primary outcome (antiplatelet agent(s) vs placebo)**	**Secondary outcome (antiplatelet agent(s) vs placebo)**
Sreedhara et al. [69]	RCT	107 (84 type I [new AVG] and 23	NR	AVG	Aspirin 325 mg daily, or Dipyridamole 225 mg + Aspirin	Placebo	18	Thrombosis at 18 months **Aspirin**—type I 50% vs	RR of thrombosis with new AVG Aspirin 1.99, 95% CI

		type II [thrombosed AVG requiring new AVG])			325 mg daily or Dipyridamole 225 mg daily			32%, type II 50% vs 80% **Aspirin + Dipyridamole**—type I 23% vs 32%, type II 100% vs 80% **Dipyridamole**—type I 17% vs 32%, type II 83% vs 80%	0.88–4.48, p = 0.18 Dipyridamole 0.35, 95% CI 0.15–0.80, p = 0.02
Clopidogrel									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment duration (months)**	**Primary outcome (clopidogrel vs placebo)**	**Secondary outcome (clopidogrel vs placebo)**
Ghorbani et al. [73]	RCT	93	DM (26.9%)	AVF	Clopidogrel 75 mg daily	Placebo	1.5	Primary AVF failure at 8 weeks *5.2% vs 21.6%; HR 0.72, 95% CI 0.41–1.01, p = 0.03*	Successful HD within 6 months of AVF creation *92% vs 71%, p = 0.008*
Dember et al. [15]	RCT	877	Smoking history (62%), DM (48%), CAD (28%), CVD (6%), PVD (3%)	AVF	Clopidogrel 300 mg loading dose followed by 75 mg daily	Placebo	1.5	Thrombosis at 6 weeks post fistula creation *12% vs 20%, RR 0.63, 95% CI 0.46–0.97, p = 0.018*	Failure to attain suitability for dialysis *62% vs 60%, RR 1.05, 95% CI 0.94–1.17, p = 0.40*
Clopidogrel and aspirin									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment duration (months)**	**Primary outcome (antiplatelet agents vs placebo)**	**Secondary outcome (antiplatelet agents vs placebo)**
Kaufman et al. [74]	RCT	200	DM (47%)	AVG	Aspirin 325 mg daily + Clopidogrel 75 mg daily	Placebo	NR	Cumulative incidence of thrombosis *HR 0.81, 95% CI 0.47–1.40, p = 0.45*	Cumulative incidence of first graft thrombosis for patients with grafts without previous thrombosis (n = 111) *HR 0.52, 95% CI 0.22–1.26, p = 0.14*

Ticlopidine

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment duration (months)	Primary outcome (ticlopidine vs placebo)	Secondary outcome (ticlopidine vs placebo)
Grontoft et al. [77]	RCT	250	DM (27%)	AVF	Ticlopidine 250 mg twice daily	Placebo	1	Thrombosis at 4 weeks *12% vs 19%, OR 0.6, 95% CI 0.30–1.18, p = 0.1*	NR
Grontoft et al. [75]	RCT	36	DM (61%)	AVF	Ticlopidine 250 mg twice daily	Placebo	1	Thrombosis at 4 weeks *11% vs 47%, p < 0.05*	NR
Fickerstrand et al. [76]	RCT	18	NR	AVF	Ticlopidine 250 mg twice daily	Placebo	1	Thrombosis at 4 weeks *25% vs 50%*	NR

Omega-3 fatty acid supplementation (fish oil)

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment duration (months)	Primary outcome (fish oil vs placebo)	Secondary outcome (fish oil vs placebo)
Irish et al. [5]	RCT	536	HTN (94%), smoking history (54%), DM (49%), CAD (11%), PVD (4%), CHD (4%), CVD (3%)	AVF	4 g of fish oil daily	Placebo	3	AVF failure (thrombosis, abandonment or cannulation failure) at 12 months *47% both groups, RR 1.03, 95% CI 0.86–1.23, p = 0.78*	AVF thrombosis at 12 months *22% vs 23%, RR 0.98, 95% CI 0.72–1.34, p = 0.9* AVF abandonment at 12 months *19% vs 22%, RR 0.87, 95% CI 0.62–1.2, p = 0.43* Cannulation failure at 12 months *40% vs 39%, RR 1.03, 95% CI 0.83–1.26, p = 0.81*
Lok et al. [89]	RCT	196	HTN (86%), smoking history (55%), DM	AVG	4 g of fish oil daily	Placebo	12	Proportion of participants	Rate of loss of graft patency

			(53%), CAD (33%), CHD (20%), PVD (15%), CVD (14%)					experiencing graft patency loss (thrombosis or radiological or surgical interventions) at 12 months *48% vs 62%, RR 0.78, 95% CI 0.60–1.03, p = 0.06*	*IRR 0.58, 95% CI 0.44–0.75* Radiological or surgical intervention to maintain patency *IRR 0.59, 95% CI 0.44–0.78* Thrombotic events *IRR 0.5, 95% CI 0.35–0.72*
Bowden et al. [90]	RCT	29	DM (69%), smoking history (3%)	AVG	6 g of fish oil daily	Placebo	8	Primary patency loss (thrombosis or venous outflow stenosis >50% requiring angioplasty) *254 ± 52 days, SEM 51.8 vs 254 ± 35 days, SEM 34.6, NS*	NR
Schmitz et al. [88]	RCT	24	DM (58%)	AVG	4 g of fish oil daily	Placebo	12	Primary patency (thrombosis free) at 12 months *75.6% vs 14.9%, p = 0.03*	NR
Statin therapy									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment follow-up (years)**	**Primary outcome (statin vs placebo)**	**Secondary outcome (statin vs placebo)**
Herrington et al. [94]	Post hoc analysis of RCT	2353	DM (22%), smoking history (15%)	AVF (94%), AVG (6%)	Simvastatin (20 mg) plus Ezetimibe (10 mg) daily	Placebo	5	Vascular access occlusive event (access requiring any revision procedure, access thrombosis, removal of an old dialysis access, or formation of new permanent dialysis access)	Access revision 18.6% vs 21.4% RR 0.85, CI 0.67–1.08 Access thrombosis 9.3% vs 10.3% RR 0.90, CI 0.64–1.27 Removal of old or formation of new vascular access

								29.7 vs 33.5% RR 0.87, 95% CI 0.75–1.00, p = 0.05	15% vs 16.2% RR 0.93, CI 0.75–1.00
Herrington et al. [94]	Post-hoc analysis of RCT	2439	DM (27%), smoking history (14%)	AVF (89%), AVG (11%)	Rosuvastatin 10 mg daily	Placebo	4.5	Vascular access occlusive event 28.9% vs 27.6% RR 1.06, 95% CI 0.91–1.23, p = 0.44	NR
Birch et al. [91]	Retrospective analysis	265	HTN (93%), DM (53%)	AVF	Statin therapy of variable doses (Simvastatin, Atorvastatin, Pravastatin, Lovastatin)	No statin therapy	1.8	Interval of time to angioplasty to maintain AVF function *Mean time 8.9 vs 7.3 months, p = 0.25* Number of stenotic lesions *98 vs 99 stenoses, p = 0.28*	Primary AVF patency (time from creation to first intervention) *HR 1.17, 95% CI 0.747–1.834, p = 0.49*
Pisoni et al. [97]	Retrospective observational cohort analysis	601	HTN (92%), DM (52%), CAD (29%), PVD (18%), CVD (10%)	AVF (53%), AVG (47%)	Statin therapy not specified	No statin therapy	6	Primary access failure (access never useable for dialysis) **AVF** *37% vs 38%, OR 0.97, 95% CI 0.59–1.58, p = 0.9* **AVG** *20% vs 14%, OR 1.52, 95% CI 0.76–3.09, p = 0.23* Cumulative access survival **AVF** *HR 1.26, 95% CI 0.76–2.16, p = 0.35* **AVG** *HR 0.88, 95% CI 0.59–1.32, p = 0.54*	NR
Righetti et al. [34]	Case-control study	60	HTN, dyslipidemia	AVF	Atorvastatin 10–20 mg or Simvastatin 10–20 mg daily and/or folic acid 5 mg daily	No statin or folic acid therapy	3	Primary access patency *71.5% vs 39.1% after 2 years, p < 0.05*	NR

Saran et al. [96]	Retrospective observational cohort analysis	2462	HTN (87.8%), DM (49.7%), Obesity (35.9%)	AVF 900 (8.3% on statin), AVG 1944 (9.6% on statin)	Statin therapy of varying doses (Simvastatin, Atorvastatin, Pravastatin, Lovastatin) Fluvastatin)	NR	4	Primary access patency (unassisted access patency) ***AVG*** *RR 0.97, p = 0.805* ***AVF*** *RR 0.93, p = 0.762* Secondary access patency (assisted access survival) ***AVG*** *RR 1.01, p = 0.920* ***AVF*** *RR 1.03, p = 0.903*	NR
Renin-angiotensin-aldosterone system blockers (angiotensin-converting enzyme inhibitors and angiotensin II type I receptor blockers) therapy									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment follow-up (years)**	**Primary outcome (ACEI/ARB vs placebo)**	**Secondary outcome**
Chen et al. [108]	Retrospective analysis	42,244	HTN (81%), DM (51%), CAD (24%), Dyslipidemia (17%), CVD (6%), PVD (3%)	AVF 89.4% (32.3% on an ACEI, 15% on an ARB) AVG 10.6% (6.2% on an ACEI, 7.1% on an ARB)	ACEI/ARB therapy of varying doses **ACEI** (Benazepril, Enalapril, Lisinopril, Quinapril, Captopril, Fosinopril, Ramipril, Cilazapril) **ARB** (Candesartan, Losartan, Irbesartan, Valsartan, Olmesartan)	Non-use	8	Primary patency loss **AVF** *ACEI-HR 0.59, 95% CI 0.56–0.62, p < 0.05* *ARB-HR 0.53, 95% CI 0.51–0.56, p < 0.05* **AVG** *ACEI-HR 0.56, 95% CI 0.48–0.64, p < 0.05* *ARB-HR 0.54, 95% CI 0.47–0.61, p < 0.05*	NR
Jackson et al. [99]	Retrospective cohort analysis	332	DM (75%), HTN (62%), smoking history (36%)	AVF (64%) AVG (36%)	ARB therapy of varying doses (Irbesartan, Losartan, Valsartan)	Non-use	4	Primary patency loss **AVF** *HR 0.35, 95% CI 0.16–0.76, p = 0.008* **AVG** *HR 0.41, 95% CI 0.18–0.95, p = 0.04*	NR

Saran et al. [96]	Retrospective analysis	2462	HTN (87.8%), DM (49.7%), Obesity (35.9%)	AVF 900 (18.7% on ACEI, 4.1% on ARB), AVG 1944 (17% on ACEI, 3.8% on ARB)	ACEI/ARB therapy of varying doses **ACEI** (Benazepril, Enalapril, Lisinopril, Quinapril, Captopril, Fosinopril, Moexipril, Ramipril) **ARB** (Candesartan, Losartan, Irbesartan, Valsartan)	Non-use	4	**AVF** Unassisted primary access patency *ACEI-RR 0.77, p = 0.09* *ARB-RR 1.45, p = 0.06* Secondary access patency *ACEI-RR 0.56, p = 0.01* *ARB-RR 1.33, p = 0.31* **AVG** Primary access patency *ACEI-RR 1.02, p = 0.85* *ARB-RR 1.09, p = 0.63* Secondary access patency *ACEI-RR 1.16, p = 0.13* *ARB-RR 1.3, p = 0.17*	NR
Sajgure et al. [98]	Multicentre observational study	266	HTN (95%), DM (57%)	AVF (33%) AVG (67%)	ACEI of varying doses	Placebo	2	Primary patency duration (mean ± SEM) in days **AVG** *672 ± 68 vs 460 ± 48, HR 0.48, 95% CI 0.31–0.73, p = 0.01* **AVF** *530 ± 80 vs 501 ± 76, p = 0.45*	NR

Calcium channel blocker therapy

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment follow-up (months)	Primary outcome	Secondary outcome
Saran et al. [96]	Retrospective observational	2462	HTN (87.8%), DM (49.7%), Obesity (35.9%)	AVF 900 (44.1% on CCB), AVG	CCB therapy of varying doses (Amlodipine,	Non-use	4	Unassisted primary access patency ***AVG*** *RR 0.86, p = 0.034*	NR

	cohort analysis			1944 (40.8% on CCB)	Felodipine, Mibefradil, Nifedipine, Verapamil, Diltiazem, Isradipine, Nicardipine, Nisoldipine)			***AVF*** *RR 1.14, p = 0.3* Secondary access patency ***AVG*** *RR 0.88, p = 0.153* ***AVF*** *RR 1.16, p = 0.374*	
Chen et al. [108]	Retrospective analysis	42,244	HTN (81%), DM (51%), CAD (24%), Dyslipidemia (17%), CVD (6%), PVD (3%)	AVF 89.4% (32.3% on CCB), AVG 10.6% (20.6% on CCB)	CCB therapy of varying doses (Amlodipine, Felodipine, Nifedipine, Verapamil, Diltiazem, Isradipine, Nicardipine)	Non-use	8	Primary patency loss ***AVF*** *HR 0.485, CI 0.470–0.501* ***AVG*** *HR 0.482, CI 0.442–0.526*	NR

New surgical techniques to optimize flow dynamics

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment follow-up (months)	Primary outcome	Secondary outcome
Chemla et al. [127]	Prospective study	41	NR	AVF	Optiflow device	NR	3	Unassisted maturation (outflow vein >/= 5 mm in diameter and flow >/= 500 ml/min not requiring intervention to maintain or promote maturation) *72% at 42 days & 68% at 90 days* Unassisted patency *88% at 42 days & 78% at 90 days*	NR
Bharat et al. [126]	Comparative study	125	HTN (43%), DM (41%)	AVF	pSLOT vs SLOT vs ETS	NR	19	Formation of juxta-anastomotic stenosis *pSLOT (3.7%, p = 0.04)* *vs SLOT (8.3%, p = NS)* *vs ETS (14%, p = NS)* Fistula failure	NR

								(pSLOT 16.7%, p = 0.01), SLOT (33.3%, p = NS), ETS (40.3%, p = NS)	
Endovascular AVF creation									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment follow-up (months)**	**Primary outcome**	**Secondary outcome**
Lok et al. [114]	Prospective study	80	HTN (92%), DM (65%), CAD (22%), CVD (15%), CHD (12%), PVD (5%)	AVF	Endovascular AVF creation	NR	12	Percentage of endovascular AVF suitable for HD at 3 months *91%, 95% CI 81–97%*	Primary patency at 12 months *69%, 95% CI 54–79%* Cumulative patency at 12 months *84%, 95% CI 71–91%*
Far infrared therapy									
Trial	**Study**	**Number of participants**	**Co-morbidities**	**Access type**	**Intervention**	**Control**	**Treatment duration (months)**	**Primary outcome (FIT vs placebo)**	**Secondary outcome (FIT vs placebo)**
Lin et al. [115]	RCT	122	HTN (65%), DM (40%)	AVF	40 min FIT, 3 times weekly	Placebo	12	Rate of AVF malfunction within 12 months (thrombosis, intervention required) *12% vs 29%, p = 0.02*	Cumulative primary unassisted AVF patency *87% vs 70%, p = 0.01* Physiologic AVF maturation *82% vs 60% p = 0.008*
Lin et al. [116]	RCT	145	HTN (54%), DM (33%)	AVF	40 min FIT, 3 times weekly	Placebo	12	Effect of FIT on access flow at 12 months *13.2 ± 114.7 vs 33.4 ± 132.3 ml/min, p < 0.021* AVF malfunction *12.9% vs 30.1%, p < 0.01* AVF unassisted patency *85.9% vs 67.6%, p < 0.01*	NR

Perivascular application of recombinant elastase

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment follow-up (months)	Primary outcome (PRT-201 vs placebo)	Secondary outcomes (PRT-201 vs placebo)
Dwivedi et al. [118]	RCT	89	DM (44%), HTN (40%)	AVG	Single dose escalation of low (0.01, 0.03 mg), medium (0.1, 0.3, 1.0 mg) and high (3.0, 6.0, 9.0 mg) PRT-201 immediately at AVG placement	Placebo	12	Safety (adverse events) 13% vs 14%, NS >/−25% increase in outflow vein diameter intraoperatively *33% vs 15%, high, p = 0.052*	Percentage change in intraoperative outflow vein diameter *Low 13%, p = 0.01; medium 15% p = 0.070; high 12%, p < 0.001; vs 5% placebo* Percentage change in intraoperative blood flow volume *Low 19%, p = 0.34; medium 36%, p = 0.09, high 46%, p = 0.02; vs 15% placebo*
Hye et al. [117]	RCT	151	CAD (55%), DM (45%), HTN (28%), PVD (24%), CVD (20%)	AVF	PRT-201 at 0.01 mg or 0.03 mg applied once to newly formed AVF	Placebo	12	Unassisted primary patency at 12 months *10 mcg vs placebo; HR 0.69, 95% CI 0.39–1.22, p = 0.19* *30 mcg vs placebo; HR 0.67, 95% CI 0.38–1.19, p = 0.17*	Secondary patency at 12 months *10 mcg vs placebo; HR 0.79, 95% CI 0.33–1.92, p = 0.61 30 mcg vs placebo; HR 0.76, 95% CI 0.31–1.89, p = 0.55* Unassisted maturation at 3 months *10 mcg 67%, 30 mcg 70% vs placebo 54%, NS* Luminal stenosis (hemodynamically significant) at 3 months *10 mcg 41%, 30 mcg 35% vs placebo 40%, NS*

Vascugel

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment follow-up (months)	Primary outcome (Vascugel vs placebo)	Secondary outcomes (Vascugel vs placebo)
Conte et al. [121]	Phase I/II clinical study	57	CAD (100%), DM (68%), Dyslipidemia (51%)	AVF (47%) AVG (53%)	Vascugel placement at newly formed access	Placebo	6	Safety at 30 days (incidence of infection, intervention and thrombosis) *10.9% vs 21.1%, NS*	Primary patency **AVG** *38% vs 23%, NS* **AVF** *60% vs 62%, NS* Assisted primary patency **AVG** *72% vs 58%, NS* **AVF** *96% vs 88%, NS*

Antiproliferative agents—COLL-R (drug-eluted combination product of collagen membrane and sirolimus)

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment follow-up (months)	Primary outcome	Secondary outcomes
Paulson et al. [122]	Phase II clinical study	12	HTN (83%), DM (8%)	AVG	Surgical placement of PTFE grafts and COLL-R	NR	24	Safety (freedom from device related adverse events) *Endpoint met, nil adverse events*	Pharmacokinetics of sirolimus release *Whole blood sirolimus levels reached a mean peak of 4.8 ng/mL at 6 h and were less than 1 ng/mL at 1 week* Success of COLL-R implantation *100% success* Primary unassisted graft patency *75% at 12 months and 38% at 24 months*

Paclitaxel-coated balloon angioplasty

Trial	Study	Number of participants	Co-morbidities	Access type	Intervention	Control	Treatment follow-up (months)	Primary outcomes (PCB vs HPB)	Secondary outcomes (PCB vs HPB)
Kitrou et al. [123]	RCT	40	NR	AVF	PCB treatment of failing AVF	HPB	12	Device success *35% vs 100%, $p < 0.001$* Anatomic success *100% both groups* Clinical success *100% both groups* Target lesion revascularization-free survival *PCB 308 days; HPB 161 days; HR 0.478; 95% CI 0.236–0.966, $p = 0.03$*	Dialysis circuit primary patency *PCB 270 days; HPB 161 days; HR 0.479; 95% CI 0.237–0.968; $p = 0.04$* Procedure related complications *Nil*
Katsanos et al. [124]	RCT	40	DM (20%), HTN (13%)	AVF (35%), AVG (65%)	PCB treatment of failing access	HPB	6	Primary patency of treated lesion *70% vs 25% $p < 0.001$, HR 0.30, 95% CI 0.12–0.71, $p = 0.006$* Device success *45% vs 100%, $p < 0.001$* Procedural success *100% both groups*	Dialysis circuit survival *95% vs 90%, $p = 0.274$; HR 0.33, 95% CI 0.03 to 3.36, $p = 0.349$*

RCT, randomized controlled trial; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; PVD, peripheral vascular disease; CHD, congestive heart disease; CVD, cerebrovascular disease; AVF, arteriovenous fistula; AVG arteriovenous graft; mg, milligrams; RR, relative risk; CI, confidence interval; NR, not reported; OR, odds ratio; HR, hazard ratio; IRR, incident rate ratio; SEM, standard error of the mean; NS, not significant; HD, hemodialysis; ACEI, angiotensin-converting enzyme inhibition; ARB, angiotensin II typ. 1 receptor blockers; pSLOT, piggybacking straight-line onlay technique; SLOT, side-to-side straight-line onlay technique; ETS, end-to-side; FIT, far infrared therapy; PRT-201, perivascular application of recombinant elastase; PTFE, polytetrafluoroethylene; PCB, paclitaxel-coated balloon angioplasty; HPB, high pressure balloon angioplasty.

Table 1.
Summary of trial results of systemic medical therapies and local interventions on vascular access outcomes in hemodialysis patients.

placebo (32% vs 72%, odds ratio [OR] 0.18, 95% confidence interval [CI] 0.05–0.66, $p < 0.01$) after a mean follow-up of 5 months [67]. In contrary, a randomized, double-blind, placebo-controlled parallel group study [69] assessing the effect of dipyridamole and/or aspirin on AVG thrombosis showed a non-significant increase in thrombosis in 10 of 20 patients (50%) treated with 325 mg of aspirin daily compared to 6 of 19 (32%) patients on placebo (relative risk [RR] 1.99, 95% CI 0.88–4.48, $p = 0.18$) over a 18-month follow-up period. Inconsistent outcomes have also been described for aspirin used for prevention of AVF failure. In a study of 92 participants [68] randomized to 1000 mg of aspirin on alternate days over a 28 day period or placebo, the frequency of AVF thrombosis was reduced more than 4-fold by aspirin compared to placebo (2 of 45 [4.4%] vs 11 of 47 [23.4%], $p < 0.05$). However, the most recent and largest RCT showed no significant reduction in AVF failure at 12 months in 488 patients randomized to receive 100 mg of aspirin or placebo for 3 months following AVF creation. AVF failure was defined as a composite of AVF thrombosis, AVF abandonment and cannulation failure [5]. Neither the composite binary outcome (45% participants treated with aspirin vs 43% treated with placebo, RR 1.05, 95% CI 0.84–1.31, $p = 0.68$) nor the individual outcome components were reduced by low-dose aspirin: AVF thrombosis (20% vs 18%, RR 1.09, 95% CI 0.72–1.64, $p = 0.70$), AVF abandonment (24% vs 18%, RR 1.31, 95% CI 0.89–1.95, $p = 0.17$) and cannulation failure (40% vs 39%, RR 0.99, 95% CI 0.76–1.27, $p = 0.92$) [5]. Differences in treatment dose, duration, sample size and outcome definition makes comparison of treatment efficacy across trials difficult. Considering the cumulative evidence to date, there remains considerable uncertainty as to whether aspirin reduces arteriovenous access failure.

4.1.1.2 Dipyridamole

Dipyridamole impairs platelet aggregation by inhibition of adenosine deaminase and phosphodiesterase, causing an increase of adenosine, adenine nucleotides and cyclic adenosine monophosphate (cAMP) levels [70]. As a phosphodiesterase inhibitor, it reduces vascular smooth muscle proliferation, and may prevent neointimal hyperplasia, stenosis and thrombosis of arteriovenous access [70, 71]. A randomized, double-blind, placebo-controlled parallel group study [69] of 107 patients with ESKD assessed the effect of dipyridamole (225 mg daily) and/or aspirin (325 mg daily) on the rate of AVG thrombosis over a treatment duration of 18 months (**Table 1**). The treatment groups were divided into two cohorts, type I which included patients with new AVGs (84 patients) vs type II which included patients with previously placed AVGs who had suffered graft thrombosis requiring thrombectomy or revision (23 patients). Dipyridamole reduced AVG thrombosis rates compared to placebo (RR 0.35, 95% CI 0.15–0.80, $p = 0.02$), used alone (17% vs 32%) or in combination with aspirin (23% vs 32%). A multicenter RCT involving 649 patients with new AVGs randomized individuals to dipyridamole (200 mg extended release twice daily) plus aspirin (25 mg twice daily) or placebo over 4.5 years with an additional 6-month follow-up [72]. At 12 months, the primary outcome of primary unassisted patency loss (patency without thrombosis or requirement of an intervention) occurred in 28% of patients treated with dipyridamole and aspirin compared to 23% receiving placebo (hazard ratio [HR] 0.82; 95% CI 0.68–0.98, $p = 0.03$) [72]. Pertaining to the evidence presented, dipyridamole alone or in combination with aspirin may be beneficial in preventing primary AVG failure.

4.1.1.3 Clopidogrel

Clopidogrel and ticlopidine are classed as thienopyridines. The active metabolite they produce irreversibly blocks the protein P2y12 component of the adenosine

diphosphate (ADP) receptors on the platelet surface, preventing activation of the GPIIb/IIa receptor complex and reducing platelet aggregation [13]. The effects of clopidogrel (300 mg load followed by 75 mg daily) on access failure were evaluated in an RCT involving 877 patients undergoing AVF formation (**Table 1**). The rate of early fistula thrombosis (within 6 weeks) was lower with treatment (53 of 436 patients, 12.2%) compared to placebo (84 of the 430, 19.5%; RR 0.63, 95% CI 0.46–0.97, p = 0.18) [15], however, this benefit did not translate into an increase in the proportion of AVFs that became suitable for hemodialysis (61.8% vs 59.5%; RR 1.05, 95% CI 0.94–1.17, p = 0.4) [15]. A smaller RCT of 93 patients found that, compared with placebo, clopidogrel resulted in a lower risk of early fistula thrombosis (5.2% vs 21.6%; HR 0.72, 95% CI 0.41–1.01, p = 0.03) and a higher rate of first successful dialysis using the newly created AVF (92.3% vs 70.5%) [73]. In contrast, no benefit was identified from clopidogrel 75 mg and aspirin 325 mg vs placebo on graft thrombosis in an RCT involving 200 participants undergoing hemodialysis with newly formed AVGs (HR 0.81, 95% CI 0.47–1.40, p = 0.45) [74]. Considering the evidence to date, there remains uncertainty as to whether clopidogrel results in a clinically meaningful benefit beyond prevention of early thrombosis.

4.1.1.4 Ticlopidine

Three RCTs investigated the effects of ticlopidine on AVF thrombosis at 4 weeks (**Table 1**). Two small RCTs [75, 76] demonstrated that AVF thrombosis occurred in fewer patients receiving ticlopidine as compared with placebo. Grontoft et al. [75] studied 36 participants and showed that AVF thrombosis at 4 weeks was reduced in participants treated with 250 mg ticlopidine twice daily (11%) compared to placebo (47%, $p < 0.05$). In a pilot study of 18 participants [76], 250 mg ticlopidine given twice daily over 1 month resulted in half the thrombosis rates compared to placebo (25% vs 50% respectively). A multicenter RCT involving 250 participants [77] showed that ticlopidine did not significantly reduce AVF thrombosis compared to placebo at 4 weeks (12% vs 19%, OR 0.6, 95% CI 0.30–1.18, p = 0.1). A subsequent systematic review and meta-analysis of these trials [78] favored the use of ticlopidine in access thrombosis as a beneficial treatment (OR 0.45, 95% CI 0.25–0.82, p = 0.009).

A meta-analysis of 21 RCTs using any type of antiplatelet drug to prevent arteriovenous access failure demonstrated a 51% reduction in patency loss of AVFs with antiplatelet therapy compared to placebo (6 trials, 1222 participants, RR 0.49, 95% CI 0.30–0.81), while clinical benefits in preventing AVG thrombosis remained uncertain (3 trials, 956 participants, RR 0.94, 95% CI 0.80–1.10) [79].

Based on the available evidence, there may be a short-term benefit of antiplatelet agents in reducing arteriovenous access thrombosis [15, 78–80], though clinically meaningful benefits, including improved long-term patency or access usability for dialysis, have not been found [15, 79]. Therapeutic approaches targeting vascular remodeling and neointimal hyperplasia may be more beneficial in the longer term [13].

4.1.2 Omega-3 fatty acid supplementation (fish oil)

Omega-3 fatty acids (the active component of fish oil) are thought to reduce arteriovenous access thrombosis and improve maturation [81] through their antiproliferative [82], antiaggregatory [83], anti-inflammatory [84], antioxidant and vasodilatory effects [85–87].

Two RCTs have assessed the effect of fish oil on AVG patency (**Table 1**) [88, 89]. The largest study involved 196 patients with newly created AVGs treated with 4 g of fish oil or placebo for 12 months [89]. There was no statistically

significant difference in the *proportion* of participants experiencing graft patency loss (thrombosis or radiological or surgical interventions) at 12 months between fish oil (48%) and placebo (62%, RR 0.78, 95% CI 0.60–1.03, p = 0.06). However, participants treated with fish oil experienced lower *rates* of loss of graft patency (incident rate ratio [IRR] 0.58, 95% CI 0.44–0.75), radiological or surgical interventions (IRR 0.59, 95% CI 0.44–0.78) and thrombotic events (IRR0.5, 95% CI 0.35–0.72). Another RCT including 24 patients randomized to treatment with fish oil or placebo for 12 months found that fish oil treatment led to greater primary patency (thrombosis free) after 12 months of follow-up (75.6% vs 14.9% respectively, p = 0.03) [88]. An RCT by Bowden et al. [90] was unable to replicate these findings in 29 participants, with no difference in the mean time to primary patency loss (thrombosis or venous outflow stenosis >50% requiring angioplasty) in the treatment group (254 ± 52 days, standard error of the mean [SEM] 51.8) compared to the placebo group (254 ± 35 days, SEM 34.6) over the 8-month follow-up period. The heterogeneity in outcome definitions (primary patency loss vs thrombosis) makes comparison across trials difficult. Although a risk reduction in graft thrombosis was described in a meta-analysis of data from four trials, this analysis incorporated events other than graft thrombosis including infection [86] and interventions [90]. When only including the trials that assessed the frequency of graft thrombosis [78], fish oil was no longer associated with a significant treatment benefit compared to placebo (OR 0.24; 95% CI, 0.03–1.95).

A large multicenter trial (Omega-3 fatty acids (fish oils) and aspirin in vascular access outcomes in renal disease [FAVORED]) [5] is the only RCT to date to examine the effect of fish oil on AVF failure. This trial included 567 patients with newly created AVF randomized to 4 g of fish oil daily or matching placebo for 3 months post AVF creation. At 12-month follow-up, no significant differences between the fish oil and placebo groups were identified for the primary composite outcome of AVF failure (47% identified in both groups, RR 1.03, 95% CI 0.86–1.23, p = 0.78) or for the individual components of the composite including AVF thrombosis (22% vs 23%, RR 0.98, 95% CI 0.72–1.34, p = 0.9), fistula abandonment (19% vs 22%, RR 0.87, 95% CI 0.62–1.2, p = 0.43) or cannulation failure (40% vs 39%, RR 1.03, 95% CI 0.83–1.26, p = 0.81) [5].

A recent meta-analysis of all RCTs (5 trials, 833 participants) evaluated the effect of fish oil supplementation in preventing arteriovenous access failure using standardized outcome definitions [81]. Key findings included that fish oil supplementation prevented primary patency loss with moderate certainty (RR 0.81, 95% CI 0.68–0.98), and that low quality evidence suggested that fish oil may have little effect on dialysis suitability failure (RR 0.95, 95% CI 0.73–1.23), access abandonment (RR 0.78, 95% CI 0.59–1.03), need for interventions (RR 0.82, 95% CI 0.64–1.04) or all-cause mortality (RR 0.99, 95% CI 0.51–1.92).

4.1.3 Statin therapy

Statins have been shown to reduce inflammation in the ESKD population, while also improving endothelial function beyond the effect of cholesterol lowering [91]. There is experimental evidence that statins reduce neointimal hyperplasia and vascular remodeling, which appears to be mediated by the reduction of vascular endothelial growth factor-A and matrix metalloproteinase (MMP) [92], and promotion of vasodilatation (via endothelial derived NO) [93].

An ancillary analysis of the Study of Heart and Renal Protection (SHARP) RCT comparing the effects of simvastatin/ezetimibe 20 mg/10 mg vs placebo on vascular access occlusive events (defined as any access revision procedure, access thrombosis, removal of an old dialysis access, or formation of new permanent dialysis

access) in 2353 participants (94% AVF, 6% AVG) (**Table 1**) [94]. Simvastatin plus ezetimibe resulted in a 13% reduction in vascular occlusive events compared with placebo (RR 0.87, 95% CI 0.75–1.00, p = 0.05). Results were broadly similar for the individual components of the composite outcomes. However, the same group was unable to replicate this result in a post hoc analysis of the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial cohort [94]. Specifically, occlusive vascular events were comparable between the rosuvastatin and placebo groups (28.9% vs 27.6%, respectively, RR 1.06, 95% CI 0.91–1.23, p = 0.44). When the SHARP and AURORA results were pooled, low density lipoprotein cholesterol (LDL-C) lowering therapy did not significantly reduce vascular occlusive events. These results were limited by the post hoc analysis of exploratory trial outcomes and the failure to include other large studies of cholesterol-lowering therapy (such as the Der Deutsche Diabetes Dialyze [4D] study [95]), such that results should be considered hypothesis-generating only.

Retrospective observational cohort analyses by Saran et al. [96] and Pisoni et al. [97] found statins were not beneficial in improving cumulative fistula survival. Specifically, statin therapy did not improve access maturation [97] or primary access patency [96]. Similarly, a retrospective review of 265 patients, of which 90% were on either simvastatin or atorvastatin, found that statin therapy did not affect the number of stenotic lesions in AVFs or time to primary angioplasty [91]. Whereas a case-control study of 60 dialysis patients receiving either folic acid and/or statin discovered improved primary patency in 35 patients with AVFs [34].

In summary, the evidence for benefits of statin use in the prevention of vascular access complications in hemodialysis patients is based on observational trial data and post hoc analysis of RCTs. To date, no RCT has been developed to determine the effect of statin therapy on primary patency rates in newly formed vascular access. There is currently insufficient evidence to support the routine use of statin therapy for preserving vascular access.

4.1.4 Renin-angiotensin-aldosterone system blockers (angiotensin-converting enzyme inhibitors and angiotensin II type I receptor blockers)

The renin-angiotensin-aldosterone system (RAAS) is an important modulator of the vascular smooth muscle cell proliferation that occurs in the intimal layer of the vein in response to injury [98]. Additionally, angiotensin II produced locally at the site of injury can induce growth factors that further promote vascular smooth muscle proliferation and a prothrombotic environment [98]. Blocking these pathways in animal models with the use of angiotensin-converting enzyme inhibition (ACEI) has been shown to prevent smooth muscle cell proliferation and migration [99, 100], inhibit intimal hyperplasia and extracellular matrix deposition [100–102], promote venous dilation [103] and prevent platelet activation [104, 105].

In the clinical setting, the effects of ACEI and/or angiotensin II type 1 receptor blockers (ARB) on primary and secondary arteriovenous access outcomes has been confined to retrospective observational cohort studies with conflicting findings (**Table 1**) [98, 99, 106–108]. A multi-center observational study by Sajgure et al. [98] compared the use of ACEI vs placebo on primary patency duration in AVGs (179 participants) and AVFs (87 participants) over a 24 month period. A longer primary patency duration was observed in the treatment AVG group compared with placebo (HR 0.48, 95% CI 0.31–0.73, p = 0.01), though no benefit was observed with the use of ACEI in AVFs (p = 0.45). Chen et al. [108] performed a retrospective analysis of the efficacy of ACEI and/or ARB therapy on primary patency loss of AVGs and AVFs in 42,244 patients over a 96-month period

(37,771 with AVFs [32.3% on an ACEI, 15% on an ARB], 4473 with AVGs [6.2% on an ACEI, 7.1% on an ARB]). ACEI use was associated with prolonged primary patency in both AVFs (HR 0.59, 95% CI 0.56–0.62, $p < 0.05$) and AVGs (HR 0.56, 95% CI 0.48–0.64, $p < 0.05$). Similarly, ARB use was shown to be beneficial in AVFs (HR 0.53, 95% CI 0.51–0.56, $p < 0.05$), and AVGs (HR0.54, 95% CI 0.47–0.61, $p < 0.05$) [108]. Furthermore, Jackson et al. [99] reported that ARB use prolonged 1- and 2-year primary patency in both, AVFs (55.2% at 1 year, 49.1% at 2 years; HR 0.35, 95% CI 0.16–0.76, $p = 0.008$) and AVGs (50.2% at 1 year, 29.7% at 2 years; HR0.41, 95% CI 0.18–0.95, $p = 0.039$). An international, prospective, observational study by Saran et al. [96] elucidated a clinically significant relationship between ACEI use and reduction in secondary AVF failure (RR 0.56, $p = 0.01$) and a trend toward improving primary AVF patency failure, while there was no significant treatment benefit in AVGs (primary RR 1.02, $p = 0.846$, secondary RR 1.16, $p = 0.133$). The same study found no significant benefit associated with the use of ARB in preventing primary or secondary patency failure in AVFs or AVGs. Available evidence is limited by substantial heterogeneity of treatment agents, dose, outcome definitions and study populations and unadjusted confounding associated with the observational study design. Randomized-controlled trials to confirm potential benefits of RAAS inhibitors are required.

4.1.5 Calcium channel blockers

Based on animal and human studies, calcium channel blockers (CCB) may inhibit neointimal hyperplasia [109, 110] and thereby reduce maturation failure [111] and restenosis post angioplasty [112]. In a prospective, observational study of 2313 participants (of which 970 were on CCB) [96], CCB use was associated with prolonged primary patency of AVGs (RR 0.86, $p = 0.034$), while no association with CCB was found for secondary AVG patency (RR 0.88, $p = 0.153$) as well as primary (RR 1.14, $p = 0.3$) and secondary AVF patency (RR 1.16, $p = 0.374$) (**Table 1**). A retrospective study by Chen et al. [108] including 42,244 patients (37,771 with AVFs [32.3% on a CCB], 4473 with AVGs [20.6% on a CCB]), described a significant relationship between CCB use and prolonged primary patency in both AVF (HR 0.485, CI 0.470–0.501) and AVG (HR 0.482, CI 0.442–0.526) groups. While there has currently been minimal investigation into the use of CCB in prevention of vascular access failure, further research may be warranted given the wide use of this antihypertensive agent in the hemodialysis population.

4.2 Local interventions

Targeted interventions to reduce upstream injury include new surgical techniques [113] and endovascular access creation [114], interventions to mitigate downstream responses include far infra-red therapy [115, 116], perivascular application of recombinant elastase [117, 118] and endothelial loaded gel foam wrap (Vascugel) [119–121], whereas antiproliferative agents including sirolimus [122] and paclitaxel [123, 124] have been developed to prevent neointimal hyperplasia and promote outward remodeling and vasodilatation [1, 13].

4.2.1 New surgical techniques to alter wall shear stress

Turbulent low-flow with low shear stress at the anastomosis leads to endothelial dysfunction, increased oxidative stress and an inflammatory and prothrombotic state, promoting AVF/AVG inward remodeling and neointimal hyperplasia [16, 125]. Optimization of flow dynamics through novel surgical techniques aimed

at changing the anatomical configuration is a potential strategy to minimize this injury [17]. Baharat et al. [126] compared the use of the piggybacking Straight-Line Onlay Technique (pSLOT) to the traditional end-to-side (ETS) and side-to-side Straight-Line Onlay Techniques (SLOT), in a study of 125 patients (**Table 1**). They found a significant reduction in juxta-anastomotic stenosis using the novel pSLOT (3.7%) compared to traditional methods of ETS (14%) and SLOT (8.3%) ($p = 0.04$). This was accompanied by a significant reduction in overall fistula failure (pSLOT 16.7%, ETS 40.3%, SLOT 33.3%, $p = 0.01$) over the median 19-month follow-up.

The Optiflow Vascular Anastomotic device is a sutureless device that is able to provide reproducible anastomosis at a controlled geometry of 60° between the artery and vein, resulting in reduced surgical time, and optimized flow patterns and shear stress [13, 113], with a likely capability of shielding the perianastomotic region and preventing stenosis with its prosthetic material [13, 113]. This device is thought to clinically improve both vascular access maturation and patency [13]. Manson et al. [113] demonstrated safety and technical practicality in a human pilot study involving 10 patients. Subsequently, a prospective study of 41 patients performed at two centers by Chemla et al. [127] evaluated the maturation, patency, and safety of AVF using the Optiflow device. Unassisted maturation (defined as an outflow vein >/= 5 mm in diameter and flow >/= 500 ml/min not requiring intervention to maintain or promote maturation) was achieved in 72% of AVFs at 42 days and 68% at 90 days, unassisted patency in 88% of AVFs at 42 days and 78% at 90 days, and no serious device-related adverse events were reported [127]. In summary, the Optiflow device has shown promise in very small sample sizes and requires further evaluation in an RCT that is powered to confirm these clinical benefits.

4.2.2 Endovascular AVF creation

The creation of an AVF with an endovascular approach using a radiofrequency magnetic catheter-based system is suggested to cause less vessel trauma, resulting in a reduced stimulus for the formation of neointimal hyperplasia [13, 128]. Clinically this has the potential to translate into improved vascular access maturation and patency [13]. A prospective, single-arm, multicenter study (Novel Endovascular Access Trial [NEAT]) enrolled 80 patients (57% pre-dialysis and 43% on dialysis) who underwent endovascular arteriovenous anastomosis creation (**Table 1**) [114]. The AVF was successfully created in 98% of participants (95% CI 91–100%). Physiologically suitable AVF dialysis, defined as a brachial artery flow ≥500 mL/min and vein diameter ≥ 4 mm within 3 months, was achieved in 87% of participants (95% CI 75–94%) and 64% (95% CI 48–78%) were able to receive prescribed hemodialysis through the AVF using two-needle cannulation. Primary patency at 12 months was 69% (95% CI 54–79%) and cumulative patency 84% (95% CI 71–91%), and 24 secondary AVF interventions were required in 19 participants (0.46/patient-year). Serious procedure-related adverse events (access-site management, hemostasis and pseudoaneurysm) occurred in 8% of participants. These results suggest that endovascular AVF creation may be a viable, minimally invasive alternative for creating vascular access. However, long-term outcomes are currently lacking and comparison to open surgical techniques in a randomized controlled fashion may be difficult due to the unique location and type of vessels used for AVF.

4.2.3 Far infrared therapy

Infrared radiation is an invisible electromagnetic wave, with wavelengths ranging from 5.6 to 1000 μm [17]. This energy is perceived as heat by the thermoreceptors in the surrounding skin [116]. Far infrared therapy (FIT) has been shown to

inhibit vascular smooth muscle cell proliferation and platelet aggregation [116], promote vasodilation [129], improve endothelial function [130] and reduce oxidative stress [13]. These pleiotropic effects upon vascular biology may be beneficial in improving maturation and vascular patency [13, 116]. An RCT by Lin et al. [116] involving 145 hemodialysis patients evaluated the effect of FIT on access blood flow and unassisted patency in native AVFs over a 12-month period (**Table 1**). Compared to placebo, FIT resulted in increased blood flow (13.2 ± 114.7 vs 33.4 ± 132.3 ml/min, $p < 0.021$) and unassisted patency (85.9% vs 67.6% respectively, $p < 0.01$) [116]. Additionally, Lin et al. [115] conducted an RCT involving 122 patients with advanced CKD pre-dialysis who underwent AVF creation. FIT applied for 40 min three times a week for 12 months, resulted in lower rates of AVF malfunction (thrombosis or requirement of intervention) compared with placebo (12% vs 29% respectively $p = 0.02$), higher maturation rates (82% vs 60% $p = 0.008$), and higher rates of cumulative unassisted AVF patency (87% vs 70% $p = 0.01$) at 12 months [115]. A subsequent meta-analysis of RCTs and quasi-RCTs by Wan et al. [131] included 21 studies and 1899 patients of whom 960 were treated with FIT. The result of this meta-analysis demonstrated that FIT improved primary AVF patency (pooled risk ratio [PRR] 1.24; 95% CI 1.12–1.37, $p < 0.001$), improved vascular access blood flow (mean difference [MD], 81.69 ml/min; 95% CI 46.17–117.21, $p < 0.001$), superior vascular access diameter level compared to control (MD 0.36 mm; 95% CI, 0.22–0.51, $p < 0.001$) and reduced AVF occlusion rates (PRR 0.2; 95% CI 0.08–0.46, $p < 0.001$) [131]. The quality of evidence provided in this meta-analysis is limited by small-scale studies of short duration (maximum 12 months). Given the convenience of FIT application during dialysis sessions and its non-invasive nature, this treatment strategy warrants further study to confirm the proposed benefits in improving vascular access maturation and patency.

4.2.4 Perivascular application of recombinant elastase

Elastin is a protein that provides blood vessels with their elasticity enabling control of vessel diameter [132]. Recombinant human type-1 pancreatic elastase (PRT-201) preferentially cleaves the peptide bonds abundant in elastin [133, 134]. Fragmentation of elastin leads to vasodilation and inhibits migration of adventitial myofibroblasts into the intimal layer [13, 135]. The rationale behind the use of PRT-201 is the theoretical assumption that application after AVF creation should destroy the elastin in the arteries and veins thereby resulting in faster AVF dilatation and maturation [1, 13]. Due to difficulties with inactivation of the enzyme following systemic administration, PRT-201 needs to be applied locally during surgery to provide targeted antiprotease effect [136]. Animal studies reported an increase in vessel diameter, blood flow, and inhibition of intimal hyperplasia with use of PRT-201 [137, 138]. An RCT [118] of 89 patients comparing low (0.01, 0.03 mg), medium (0.1, 0.3, 1.0 mg) and high (3.0, 6.0, 9.0 mg) dose PRT-201 vs placebo applied during AVG creation reported a larger percentage increase in outflow vein diameter intraoperatively with PRT-201 (5% placebo vs 13% [$p = 0.01$], 15% [$p = 0.070$], 12% [$p < 0.001$] in the low, medium and high dose groups, respectively) (**Table 1**). In contrast, only high dose PRT-201 led to a significant increase in blood flow compared to placebo (15% placebo vs 19% [$p = 0.34$], 36% [$p = 0.09$], 46% [$p = 0.02$], low, medium and high doses respectively) [118]. Conversely, a double-blind, randomized, placebo-controlled trial of a single local application of PRT-201 in 151 patients with advanced kidney disease undergoing AVF creation found no significant difference in unassisted primary patency over 1 year with low dose PRT compared to placebo (HR 0.69, 95% CI 0.39–1.22, $p = 0.19$ for 10 μg PRT-201 and HR 0.67, 95% CI 0.38–1.19, $p = 0.17$ for 30 μg PRT-201) [117]. While there

is a potential immediate effect of high dose PRT-201 on intraoperative vein outflow diameter and blood flow, clinically meaningful long-term outcomes have not yet been addressed in adequately powered RCTs.

4.2.5 Endothelial loaded gel foam wrap (Vascugel)

Vascugel is an endothelial-cell-loaded wrap comprising a gel foam with allogeneic aortic endothelial cells [1, 53, 121]. Vascugel mediates its effects through the local delivery of "functional" endothelial cells at the anastomosis to promote outward vascular remodeling and prevent neointimal hyperplasia [1]. Preclinical studies involving porcine models of AVF and AVG have reported that local application of Vascugel resulted in a reduction in thrombus formation and vessel wall inflammation, an increase in luminal diameter and outward remodeling accompanied by reductions in MMP-2 expression, neovascularization and adventitial fibrosis [119, 120]. A phase II trial by Conte et al. [121] suggested that the use of Vascugel was a safe approach for local response to injury control at anastomotic sites, although it did not significantly affect primary and assisted patency rates in treated AVF and AVG compared with placebo (**Table 1**). A retrospective analysis of this trial showed an improved primary patency when Vascugel was used in AVGs of diabetic patients ($p = 0.05$), although the results of such a post hoc analysis should be interpreted with caution [53]. In summary, Vascugel has been identified as a safe intervention, though its clinical benefit on vascular access function has not been consistently demonstrated in human trials. Adequately powered RCTs investigating its clinical application are still needed.

4.2.6 Antiproliferative agents: COLL-R (drug-eluted combination product of collagen membrane and sirolimus)

Sirolimus (rapamycin) is an antiproliferative agent with immunosuppressive, anti-inflammatory and antiproliferative effects [139, 140], that has been shown to reduce vascular smooth muscle cell proliferation [13] and neointimal hyperplasia in vascular access [122]. When delivered locally, sirolimus reduces neointimal hyperplasia in coronary re-stenosis [1, 141–143]. COLL-R is a drug-eluted combination product of sirolimus and a collagen membrane, which can be implanted around the adventitial surface either at the arteriovenous anastomosis of the AVF or at the graft-vein anastomosis of the AVG [1, 13, 122]. Sirolimus is then eluted from the COLL-R, inhibiting neointimal proliferation at the anastomosis [122], translating clinically to a potential improvement in vascular access maturation and patency [13]. A single-arm phase II study by Paulson et al. [122] containing a cohort of 12 hemodialysis patients undergoing AVG formation with intraoperative COLL-R placement demonstrated primary unassisted patency rates of 75% at 12 months and 38% at 24 months and a thrombosis rate of 0.37 episodes per patient year (**Table 1**) [122]. In a sub-group of 5 patients, whole blood sirolimus levels reached a mean peak of 4.8 ng/mL at 6 h and were less than 1 ng/mL at 1 week. Results from a phase III RCT evaluating AVF suitability for dialysis at 6 months with and without a perivascular Sirolimus-Eluting Collagen Implant are currently awaited (NCT02513303).

4.2.7 Paclitaxel-coated balloon angioplasty

Drug-eluting balloons can deliver antiproliferative agents (such as paclitaxel) at angioplasty sites and thereby reduce neointimal hyperplasia and restenosis following endothelial injury caused by the angioplasty [1, 144]. Paclitaxel-coated balloon (PCB) angioplasty has been successfully used to treat coronary stenosis [145] and

peripheral vascular disease [146]. In 40 patients with stenotic AVFs and AVGs, PCB angioplasty resulted in better target lesion and circuit primary patency rates at 6 months compared to high pressure balloon (HPB) angioplasty (70% vs 25% respectively, $p < 0.001$) [124] . Lai et al. [147] also reported improved AVF patency rate at 6 months in 10 patients (70% vs 0%, $p < 0.01$) although this was no longer statistically significant at 12 months (20% vs 0%, $P > 0.05$). A subsequent single center RCT by Kitou et al. [123] randomized 40 patients to receive PCB angioplasty or HPB angioplasty for dysfunctional AVFs, with a 12-month follow-up (**Table 1**). Primary endpoints included device success, anatomic success, clinical success and target lesion revascularization-free survival with secondary endpoints of dialysis circuit primary patency and procedure related complications [123]. Use of PCB angioplasty in dysfunctional AVFs resulted in superior target lesion revascularization-free survival (PCB 308 days; HPB 161 days; HR 0.478; 95% CI 0.236–0.966, $p = 0.03$) and dialysis access circuit primary patency (PCB 270 days; HPB 161 days; HR 0.479; 95% CI 0.237–0.968; $p = 0.04$) in comparison to HPB angioplasty, though, additional HPB post dilatation was required in 65% of cases. Current trial results support the use of PCB angioplasty to prevent re-stenosis in AVF. However, higher costs compared to conventional angioplasty and the lack of larger RCTs currently prevent its routine use in clinical practice.

5. Process of care and individualization

Systemic and local therapies to improve arteriovenous access outcomes have been limited, as outlined above. A multipronged approach including optimization of process of care may be more powerful to increase the use of AVFs or AVGs, as opposed to CVCs, than a single therapeutic intervention. An integrated approach to arteriovenous access care which included nephrologists, vascular surgeons, radiologists, access coordinators, and scheduled access procedures with tracked outcomes was demonstrated by Allon et al. [148] to reduce complications associated with surgical access procedures. These benefits included a 60% decreased rate of AVG thrombosis, improved graft secondary patency procedures, and an increase in the AVF creation rate from 33 to 69%. Arora et al. [149] found that patients who were referred to a nephrologist at least 4 months prior to dialysis initiation were 10 times more likely to have a successful functioning access at the first dialysis session, with 40% in the early referral group initiating dialysis with permanent vascular access (80% AVFs, 20% AVGs) vs 4% in the late referral group. This was supported by Roubicek at el [150] who found that 53% of patients referred early for arteriovenous access creation had functional AVFs vs 12% who were referred late. Having a vascular access coordinator can improve the number of AVFs created and decrease vascular access-related hospitalizations and infections [151]. Other strategies, including vein preservation policies, patient education regarding vein protection and access care, preoperative vein mapping and timely access creation have been found to increase fistula prevalence, decrease primary vascular access failure and increase cumulative patency [152–154]. The literature suggest that superior arteriovenous access success is achieved when the AVF is created by a skilled vascular surgeon, [45–49], with the emphasis being placed on the number of AVFs created over the total years of training [48, 50]. In the post-operative setting, timely assessment of arteriovenous access at 4 weeks is recommended to ensure access function is adequate, and to enable early surgical or endovascular intervention to prevent or treat primary access failure. Finally, arteriovenous access cannulation by appropriately trained staff has been shown to prolong AVF survival, while also minimizing the risk of infection.

6. Conclusion and future direction

The medical community's understanding of the pathology and pathogenesis of vascular access dysfunction has improved dramatically in recent times and enabled the development of novel targeted treatment approaches. The combination of interventions focusing on upstream events (i.e. optimization of hemodynamics and reduction in vascular injury through surgical/endovascular techniques) and downstream pathways (antiproliferative and anti-inflammatory therapies) may be a promising treatment approach to be assessed in future trials. Emphasis of a multipronged approach including optimization of process of care, education, surgical skills and surveillance combined with targeted therapies may yield the best outcomes and should be evaluated with innovative trial designs.

Conflict of interest

The authors have no conflict of interest to declare.

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