

The pathogenesis of hemodialysis vascular access failure and systemic therapies for its prevention: Optimism unfulfilled

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Abstract

In patients receiving hemodialysis, the provision of safe and effective vascular access using an arteriovenous fistula or graft is regarded as a critical priority by patients and healthcare professionals. Vascular access failure is associated with morbidity and mortality, such that strategies to prevent this outcome are essential. Inadequate vascular remodeling and neointimal hyperplasia resulting in stenosis and frequently thrombosis are critical to the pathogenesis of access failure. Systemic medical therapies with pleiotropic effects including antiplatelet agents, omega-3 polyunsaturated fatty acids (fish oils), statins, and inhibitors of the renin-angiotensin-aldosterone system (RAAS) may reduce vascular access failure by promoting vascular access maturation and reducing stenosis and thrombosis through anti-proliferative, anti-aggregatory, anti-inflammatory and vasodilatory effects. Despite such promise, the results of retrospective analyses and randomized controlled trials of these agents on arteriovenous fistula and graft outcomes have been mixed. This review describes the current understanding of the pathogenesis of arteriovenous fistula and graft failure, the biological effects of antiplatelet agents, fish oil supplementation, RAAS blockers and statins that may be beneficial in improving vascular access survival, results from clinical trials that have investigated the effect of these agents on arteriovenous fistula and graft outcomes, and it explores future therapeutic approaches combining these agents with novel treatment strategies.

Introduction

A functioning vascular access is an important determinant of the well-being and survival of hemodialysis patients and has been referred to as both the ‘lifeline’ and ‘Achilles Heel’ of hemodialysis¹. Vascular access dysfunction is a major cause of morbidity and mortality in hemodialysis patients and accounts for 20-30% of annual hospital admissions²⁻⁴. In several research priority setting workshops held in Australia and North America, improving vascular access outcomes was considered a critical priority by patients, caregivers and health care professionals^{5,6}. Therefore, strategies that prevent hemodialysis access failure are necessary in order to improve patient and healthcare outcomes.

Vascular access can be obtained by use of a native (autologous) arteriovenous fistula (AVF), a prosthetic interposition graft between artery and vein (AVG) or a central venous catheter. For most patients, an AVF is considered the hemodialysis access of choice due to its longevity and lower rates of thrombosis, infection, interventions to maintain patency and overall mortality when compared with central venous catheters and AVGs^{3,4,7-10}. However, native AVFs take longer to establish and approximately 20-50% fail to develop adequately to support dialysis¹¹⁻¹⁴. Compared with a functioning AVF, AVGs have a lower primary failure rate but have a higher risk of thrombosis and require more interventions to maintain patency¹⁵. More than half of all AVGs will thrombose within the first year after creation and >75% will require a salvage procedure resulting in significant health costs¹⁶. Patients with AVF and AVG complications will often require temporary placement of a central venous catheter, which is the least desirable type of vascular access due to significantly higher rates of catheter-associated bacteremia, fatal infections and cardiovascular events, inadequate solute clearance, and all-cause mortality^{3,4,17}.

Over the past four decades, significant progress has been made in the understanding of vascular access biology and techniques for creating and maintaining vascular access, but effective treatments to prevent vascular access failure are currently still lacking. This review describes a) the current understanding of the pathogenesis of AVF and AVG failure, b) the different biological effects of systemic therapies including antiplatelet agents, omega-3 polyunsaturated fatty acids (ω 3FA), statins and renin-angiotensin-aldosterone system (RAAS) blockers

(angiotensin converting enzyme inhibitors [ACEI] and angiotensin II type I receptor blockers [ARB]) that may be beneficial in improving vascular access outcomes, c) results from clinical trials that have investigated the effect of these treatments on AVF and AVG outcomes, and d) possible future therapeutic approaches combining these agents with novel treatment strategies.

Pathogenesis of vascular access failure

In order to provide adequate dialysis, formation of a vascular conduit with the properties of easy cannulation, sufficient blood flow rate and low flow resistance is required. Failure of the vascular access to achieve these properties is usually the result of a vascular stenosis with or without resulting thrombosis due to neointimal hyperplasia, inadequate vascular remodeling or a combination of the two¹⁸.

AVF failure

AVF maturation is a complex process involving the progressive increase in arterial and venous vessel diameter and blood flow following creation of an arteriovenous anastomosis¹⁹. Formation of an arteriovenous anastomosis leads to a sudden increase in blood flow, pressure and shear stress, which prompts compensatory vascular remodeling and vasodilation aimed at preserving the original level of shear stress¹⁹. Compensatory mechanisms include secretion of the endothelial-cell derived smooth muscle relaxants nitric oxide (NO) and prostacyclin, which promote vasodilation and inhibit thrombus formation as well as smooth muscle migration and proliferation. Nitric oxide further combines with free radical oxygen to form peroxynitrite, which stimulates matrix metalloproteinases (MMP-2 and MMP-9) and promotes further vasodilation. In addition, structural outward remodeling occurs via the breakdown of elastin fibers and vascular smooth muscle cell hypertrophy to increase the cross-sectional vessel wall diameter without compromising the vessel lumen. Resultant re-alignment of endothelial cells to the new vascular flow direction also takes place^{13,19-24}.

Maturation failure most commonly occurs because of luminal narrowing due to the combined impacts of neointimal hyperplasia and unfavorable remodeling (i.e. inward instead of outward remodeling with vasoconstriction instead of vasodilation)¹⁸. The characteristic pathology identified in primary nonfunctioning AVFs is a stenotic lesion due to neointimal hyperplasia

commonly located at the juxta-anastomotic site²⁵⁻²⁷. Neointimal hyperplasia describes fibromuscular thickening of the vascular wall due to myofibroblasts and differentiated contractile smooth muscle cells that have migrated from the media into the intima where they proliferate to form a subintimal layer associated with increased extracellular matrix. Additional cell-types can include fibroblasts that migrate from the adventitia into the intima and transform into myofibroblasts, and bone marrow-derived smooth muscle cells. The presence of adventitial and neointimal microvessel formation is also characteristic^{18,25}.

Even in the absence of a stenotic lesion, AVF may fail to mature due to insufficient arterial or venous dilatation and inadequate outward vascular remodeling. This failure to mature may occur due to accessory veins that direct blood flow away from the venous segment of the fistula, thereby reducing flow and shear stress-mediated dilation and maturation²⁶. Selection of poorly compliant or “stiff” arterial vessels due to vascular calcification and arteriosclerosis associated with diabetes, hypertension and chronic kidney disease mineral and bone disorder may further compromise remodeling and maturation^{25,28}.

AVG failure

The most common cause of AVG failure is a venous outflow stenosis near the graft-vein anastomosis site caused by neointimal hyperplasia²⁹. Progression of neointimal hyperplasia to a flow-limiting stenosis eventually leads to thrombosis and AVG failure. The pathogenesis is similar to neointimal hyperplasia formation in AVFs but, histologically, the prominence of macrophages indicates an additional inflammatory response likely due to the foreign graft material^{25,30}. Further distinct histological features of stenotic graft lesions include an abundance of extracellular matrix within the neointima, neovascularization and macrophage infiltration in the adventitia and periadventitial region, which may further compromise vascular function³⁰.

Neointimal hyperplasia and remodeling

The mechanistic pathways that lead to neointimal hyperplasia and maladaptive vascular remodeling in hemodialysis access are best characterized as a cascade of ‘upstream’ and ‘downstream’ events, as first described by Roy-Chaudhury et al.²⁵. ‘Upstream’ events describe factors responsible for endothelial and smooth muscle cell injury, such as hemodynamic shear

stress, surgical manipulation, repeat cannulation, angioplasties and the use of bioincompatible graft material. These events initiate a complex cascade of ‘downstream’ events characterized by the interplay of pro-inflammatory mediators such as cytokines, chemokines, metalloproteinases and adhesion molecules. These in turn result in cell activation, proliferation and migration with neointimal hyperplasia formation and unfavorable vascular remodeling (Figure 1). Other factors that may modulate these changes include the uremic milieu characterized by inflammation, oxidative stress and endothelial dysfunction³¹⁻³³, and genetic pre-dispositions to neointimal hyperplasia formation, vasoconstriction, inflammation and thrombosis^{18,34-37}.

Considering the pathogenesis of access failure, the most effective therapeutic interventions to improve vascular access outcomes would ideally target the prevention of neointimal hyperplasia and thrombosis and the promotion of maturation by optimizing hemodynamic factors and compensatory mechanisms, such as vasodilation and remodeling³⁸.

The following sections provide a summary of the biological effects (Figure 2) and clinical trials which have studied the effect of systemic medical therapies on arteriovenous access outcomes.

Biological rationale for using antiplatelet agents to improve vascular access outcomes

Platelets are key components of coagulation initiation and propagation and provide targets for inhibition exemplified in their benefits in the management of arterial atherothrombosis. Hence the effect of antiplatelet agents (i.e. aspirin, dipyridamole, ticlopidine, and clopidogrel) on platelet aggregation and function, which varies by agent, was considered to be a potentially effective means of reducing the occurrence of access thrombosis and patency loss.

Clopidogrel and *ticlopidine* are thienopyridines and inhibit platelet adenosine diphosphate (ADP)-induced platelet activation. Once bioactivated to their active metabolites, they irreversibly inhibit ADP P2Y₁₂ receptors on platelets and thereby reduces platelet aggregation³⁹.

Dipyridamole impairs platelet aggregation by increasing cyclic adenosine monophosphate (cAMP) levels in platelets via inhibition of cAMP phosphodiesterase, by blocking cellular re-uptake of adenosine and by enhancing the biosynthesis and anti-aggregatory effect of prostacyclin⁴⁰. It may also decrease adhesion of platelets to the injured vessel wall by increasing endothelial production of 13-hydroxyoctadecadienoic acid⁴¹. In addition to antiplatelet effects, dipyridamole may reduce neointimal hyperplasia formation by inhibiting platelet derived growth

factor (PDGF) and basic fibroblast growth factor (bFGF)-induced vascular smooth muscle cell proliferation⁴² and promote vasodilation by inhibiting cyclic guanosine monophosphate (cGMP) phosphodiesterase in vascular smooth muscle cells⁴³. Dipyridamole exerts additional anti-oxidative and anti-inflammatory effects mediated through attenuation of NF-kB and reactive oxygen species⁴³.

Aspirin is a well-established antiplatelet agent whose action is mediated through irreversible inhibition of platelet cyclooxygenase 1, resulting in decreased synthesis of thromboxane A2. Aspirin reduces endothelial cell damage via the NO-cGMP pathway and anti-inflammatory effects, as shown in experimental and clinical models^{44,45}.

Clinical trials of antiplatelet agents and vascular access outcomes in hemodialysis patients

Table 1 summarizes randomized controlled trials (RCT) that have investigated the effect of antiplatelet agents on hemodialysis access failure. A meta-analysis of 21 RCT using any type of antiplatelet agents to prevent vascular access complications reported a 51% reduction in thrombosis or patency loss in AVF (6 trials, 1,222 participants; relative risk [RR], 0.49; 95% confidence interval [CI], 0.30-0.81) but uncertain effects on AVG patency (3 trials, 374 events, 956 participants; RR, 0.94, 95% CI, 0.80-1.10)⁴⁶.

Aspirin: Conflicting results were found in RCT investigating the effect of aspirin therapy on access outcomes with two trials showing a marked reduction in thrombosis^{47,48} and one trial reporting an increase in thrombosis compared to placebo⁴⁹. Based on a meta-analysis of these trials, the summary effect of aspirin on access thrombosis remained uncertain (OR 0.40, 95% CI 0.07-2.25, $p=0.3$)⁵⁰. The most recent and largest RCT included 488 patients receiving a new AVF showed no significant reduction in access thrombosis, AVF abandonment or cannulation failure with low dose aspirin (100 mg daily) therapy compared to placebo (RR 1.09, 95% CI 0.72-1.64)¹⁴.

Dipyridamole: In a single parallel group RCT including 84 patients with a new AVG, dipyridamole therapy led to a significant 65% risk reduction of graft thrombosis at 18 months compared to placebo (21% versus 42%) whereas the combination of aspirin and dipyridamole had no additional benefits (25%)⁴⁹.

Ticlopidine: The effect of ticlopidine was studied in three RCT⁵¹⁻⁵³ and meta-analysis of these trial results suggested a reduction in access thrombosis (OR 0.45, 95% CI 0.25- 0.82)⁵⁰.

Clopidogrel: In the largest randomized vascular access trial of 877 patients undergoing AVF creation, the short-term use of clopidogrel reduced early access thrombosis compared with placebo (12.2% versus 19.5%, $p=0.018$) but did not increase the proportion of AVFs suitable for hemodialysis assessed over a 1-month period (61.8% versus 59.5%, $p=0.40$)⁵⁴. A smaller RCT including 93 patients confirmed the reduced risk in early thrombosis (22% versus 5%, $p=0.03$) and reported a significant improvement in the first successful dialysis⁵⁵ with clopidogrel compared to placebo.

In summary, results suggest that inhibition of platelet function can reduce AVF thrombosis, but is probably insufficient to increase the sustained usability of the access for hemodialysis suggesting that a therapeutic approach targeting neointimal hyperplasia formation and vascular remodeling may be more effective.

Biological rationale for using fish oil to improve vascular access outcomes

Omega-3 fatty acids are commonly found in fish and fish oils. These polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to decrease blood viscosity and improve red blood cell deformability^{56,57}, promote vasodilation⁵⁸⁻⁶⁰, inhibit smooth muscle proliferation⁶¹ and platelet aggregation⁶²⁻⁶⁵, and reduce inflammation⁶⁶⁻⁷⁰, all of which have the potential to improve vascular access maturation and reduce access stenosis and thrombosis (Figure 2). Omega-3 fatty acid supplementation promotes a shift in eicosanoid production towards an anti-aggregatory, anti-inflammatory, anti-proliferative and vasodilatory direction by reducing the availability of omega-6 fatty acid-derived arachidonic acid and competing with arachidonic acid for the enzymes, cyclooxygenase and lipoxygenase⁷¹. The anti-thrombotic and antiplatelet effects are likely mediated through reduced production of thromboxane A₂, a potent vasoconstrictor and aggregator, and increased production of prostaglandin-I₃, which inhibits platelet aggregation and promotes vasodilation equipotent to prostaglandin-I₂ (prostacyclin)⁶²⁻⁶⁵.

The anti-inflammatory and immunomodulatory effects of ω 3FA are mediated through a number of mechanisms, including reduction in pro-inflammatory cytokines, such as tumor necrosis factor α , interleukins-1 and -6, formation of leukotriene B₄ and attenuation of leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions^{66,68-70}. In addition,

DHA- and EPA-derived resolvins and DHA-derived protectins and maresins promote resolution of inflammation^{58,69}. The inhibition of neointimal smooth muscle cell proliferation may be explained by alterations in cell membrane phospholipid composition, and decreased production of endothelial-derived paracrine growth factors⁶¹.

Omega-3 fatty acids improve blood flow dynamics by reducing blood viscosity, increasing erythrocyte deformability and promoting vasodilation^{57,58}. Data from experimental animal models and human studies have shown that ω 3FA supplementation improves flow-mediated vasodilation via endothelium-dependent and independent vasodilation⁵⁸⁻⁶⁰ but this effect may be dose-dependent requiring ω 3FA doses of ≥ 1.83 gram/day for effectiveness⁷². In addition, ω 3FA may improve cardiovascular health in patients with chronic kidney disease through modification of lipids, especially lowering of triglycerides, and reductions in blood pressure and heart rate^{71,73,74}.

Clinical trials of omega-3 polyunsaturated fatty acid supplementation and vascular access outcomes in hemodialysis patients

Omega-3 fatty acid supplementation and AVG outcomes

Table 2 summarises RCT that have investigated the effect of ω 3FA supplementation on hemodialysis access failure. Three RCT have assessed their effect on AVG patency⁷⁵⁻⁷⁷. The largest study showed a notable but non-significant reduction in the proportion of participants experiencing either AVG thrombosis or radiological or surgical intervention during 12 months of follow-up (48% in participants randomized to daily ω 3FA compared to 62% in participants randomized to placebo, $p=0.06$). However, participants treated with ω 3FA had significantly *lower event rates* with respect to the secondary outcomes 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 (IRR 0.5, 95% CI 0.35-0.72). In addition, significant cardiovascular benefits were observed in ω 3FA-treated participants, including an increase in cardiovascular event-free survival, blood pressure lowering and a reduction in antihypertensive medications⁷⁵. A small RCT of 24 participants receiving ω 3FA or placebo reported a dramatic improvement in graft thrombosis at 12 months (14.9% versus 75.6%, respectively, $p<0.03$)⁷⁷. However, these findings were not replicated in a subsequent trial of 29 patients undergoing new

forearm loop graft formation in which patients randomized to receive over-the-counter ω 3FA had almost identical primary graft patency duration (254 ± 52 days) compared to the placebo group (254 ± 35 days) during an 8 months follow-up period⁷⁶.

The variability of these results may have been due to differences in sample size, outcome definitions, and dose and duration of therapy; For example, small sample size and low doses of EPA and DHA may have contributed to the negative findings reported in the latter study⁷⁵ and measuring event *rates* as opposed to *proportion* of participants with an event may be a more sensitive metric for detecting statistically significant differences in outcomes⁷⁴ (Table 2).

Omega-3 fatty acid supplementation and AVF outcomes

The omega-3 fatty acids (Fish oils) and Aspirin in Vascular access OUcomes in REnal Disease (FAVOURED) study is the only RCT to have examined the effect of ω 3FA on AVF outcomes¹⁴. Among 536 participants randomized to receive 4 gram daily of oral ω 3FA or placebo for 3 months, AVF failure (a composite of thrombosis and/or abandonment and/or cannulation failure) at 12 months after AVF creation occurred in 47% of participants assigned to ω 3FA compared to 47% of participants assigned to placebo (RR adjusted for aspirin use 1.03, 95% CI 0.86-1.23, p=0.78). Regarding each component of AVF failure, ω 3FA did not reduce the risk of AVF thrombosis (22% versus 23%, RR 0.98, 95% CI 0.72-1.34, p=0.90), AVF abandonment (19% versus 22%, RR 0.87, 95% CI 0.62-1.22, p=0.43) or cannulation failure (40% versus 39%, RR 1.03, 95% CI 0.83-1.26, p=0.81). Measured red blood cell fraction of EPA and DHA increased significantly in the treatment arm. There was no increase in adverse events, such as bleeding and gastrointestinal side effects, reported with ω 3FA compared to placebo.

Despite their pleiotropic actions, ω 3FA supplementation did not improve AVF outcomes. Reasons for this might include an inadequate duration or dose of treatment. The treatment duration of three months is consistent with the expected maturation time and early failure of AVFs^{19,78}, although it cannot be entirely excluded that ω 3FA supplementation beyond 3 months may have resulted in delayed benefits upon vascular remodeling, patency and usability of AVFs. The significant increase in red blood cell ω 3FA levels in FAVOURED trial participants receiving ω 3FA supports compliance with the study treatment and suggests that the dose was

sufficient to modify the lipid composition of cells. Reductions in blood viscosity, platelet aggregation, inflammation and blood pressure, have been demonstrated in patients with chronic kidney disease receiving a comparable dose of ω 3FA^{56,73,79,80}. The uremic milieu of patients with advanced renal failure characterized by endothelial dysfunction, enhanced oxidative stress and inflammation^{33,81}, and other non-modifiable risk factors such as older age, diabetes mellitus, smoking, and peripheral vascular disease²⁸, may also have limited the effectiveness of ω 3FA supplementation in improving AVF outcomes.

The results of RCT performed with ω 3FA supplementation do not support their use for the purpose of preventing AVF failure and uncertainty exists regarding their efficacy in preventing AVG failure.

Biological rationale for using statins to improve vascular access outcomes

Statins have pleiotropic actions beyond lipid lowering that could reduce vascular access stenosis and thrombosis (Figure 2). In a murine hemodialysis vascular access model, statins reduce neointimal hyperplasia and promote outward remodelling by decreasing vascular endothelial growth factor-A (VEGF-A) and MMP-9 and 2 expression⁸². Statins may also promote vasodilation by increasing endothelial-derived NO and reducing endothelin-1 release⁸³. Multiple anti-inflammatory effects including reduction of C-reactive protein levels, proinflammatory cytokines (IL-6 and 8) and adhesion molecules, and antithrombotic effects could reduce stenosis and thrombosis⁸³.

Clinical trials of statin therapy and vascular access outcomes in hemodialysis patients

The evidence for benefits of statin use on vascular access complications in hemodialysis patients is based on observational trial data and post-hoc analysis of RCT. Exploratory analyses of 2352 participants with a pre-existing vascular access from the Study of Heart and Renal Protection (SHARP) trial showed a 13% reduction in vascular access occlusive events in participants treated with simvastatin (20 mg) plus ezetimibe (10 mg) compared to placebo (RR 0.87, 95% CI 0.75-1.00; p=0.05). This finding was not replicated in a post-hoc analysis of a RCT of 2439 dialysis patients where 29% receiving rosuvastatin had an occlusive vascular access event versus 28% in the placebo group (RR 1.06, 95% CI 0.91-1.23)⁸⁴. A case-control study of 60 incident

dialysis patients suggested a treatment benefit of folic acid and/or statin on primary patency loss of AVF compared to non-use⁸⁵. Several retrospective analyses suggested no significant benefits of statin use on primary or secondary patency of AVF or AVG⁸⁶, access maturation⁸⁷, stenosis formation⁸⁸, time to recurrent angioplasties⁸⁸ or cumulative access survival (after excluding primary failure)^{86,87}. In summary, there is insufficient trial evidence to suggest a benefit of statin therapy on hemodialysis vascular access outcomes and RCT investigating statin effects on newly created arteriovenous access are needed.

Biological rationale for using ACEI/ARB to improve vascular access outcomes

The RAAS plays an important role in vascular proliferation via induction of extracellular matrix and smooth muscle cell proliferation⁸⁹. Based on predominantly pre-clinical studies, RAAS blockade by ACEI or ARB has been shown to reduce intimal hyperplasia formation, promote vasodilation and prevent platelet activation and adhesion⁹⁰ (Figure 2).

Clinical trials of ACEI/ARB therapy and vascular access outcomes in hemodialysis patients

Clinical evidence for beneficial treatment effects of ACEI and/or ARB on arteriovenous access outcomes is based on retrospective analyses⁹⁰⁻⁹⁴ including data of large registries from Taiwan (37771 AVF, 4473 AVG)⁹⁵ and the United States (900 AVF, 1944 AVG)⁸⁶. Treatment benefits with use of ACEI and/or ARB have been reported for primary and secondary fistula and graft patency with conflicting results across trials depending on medication (ACEI/ARB) and access type (AVF/AVG) as summarized in Table 3. These findings require confirmation in RCT due to the limitations inherent to retrospective analyses such as unadjusted confounding.

Novel and future treatment strategies

Previous clinical research has largely focused on using *systemic* pharmacological treatment approaches to reduce access failure. Considering the complex interplay of ‘upstream’ and ‘downstream’ events that occur predominantly *at the site of vascular access creation*, perhaps systemic therapies alone are insufficient to provide effective drug concentrations at the anastomotic or stenotic sites. Applying *local* interventions which reduce vascular injury, improve shear stress-induced vasodilation, promote outward remodeling and inhibit neointimal hyperplasia formation maybe more innovative and effective. Such interventions include the use

of new surgical techniques to alter wall shear stress⁹⁶, endovascular access creation⁹⁷, far-infrared therapy^{98,99}, paclitaxel-coated balloon angioplasty^{100,101}, and perivascular application of recombinant elastase^{102,103}, endothelial loaded gel foam wrap (Vascugel)¹⁰⁴⁻¹⁰⁶ or antiproliferative agents such as sirolimus (Coll-R)¹⁰⁷. Table 4 provides an overview of mode of action and expected outcomes of these local and novel interventions that predominantly prevent vascular injury, modulate the response to vascular injury and/or promote outward remodeling rather than targeting thrombosis prevention.

An important question at this juncture is whether combining different interventions that target sequential events in the pathogenesis of arteriovenous access failure may be more effective than a single targeted intervention. In particular, the combination of interventions that target both the upstream “injury pathway” (devices that optimize hemodynamics) and the downstream “response to injury” (anti-inflammatory or anti-proliferative therapies) might be most effective at reducing AVF maturation failure. In this context, it is possible that combining systemic approaches such as statins or ω 3FA supplementation (used as a downstream anti-inflammatory therapy) with targeted local therapies that modulate upstream injury may be more effective than either strategy alone. This approach may have the advantage of providing the additional cardiovascular benefits of these systemic agents and reduce the burden of cardiovascular morbidity and mortality.

Conclusion

Vascular access failure remains one of the greatest challenges in caring for hemodialysis patients. The pathogenesis of access failure, whilst complex and incompletely understood, is characterized by neointimal hyperplasia, insufficient vasodilation, and adverse vascular remodeling resulting in access stenosis and thrombus formation. Systemic medical therapies, including antiplatelet agents, ω 3FA supplementation, RAAS inhibition, and statins, have theoretical appeal in promoting vascular access maturation and reducing access stenosis and thrombosis through anti-proliferative, anti-aggregatory, anti-inflammatory and vasodilatory effects. However, in the clinical trial setting, the use of these therapies has not been shown to reliably improve vascular access outcomes and there is insufficient high-quality trial evidence to recommend their routine use.

Future studies might consider the use of combined systemic and local treatment approaches targeting both upstream injury pathways (e.g. novel surgical or endovascular techniques) and downstream responses to injury pathways (e.g. ω 3FA supplementation or statins). Such therapeutic approaches would need to be evaluated in large RCT.

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Figure Legends

Figure 1: Pathogenesis of vascular access failure

Figure 1: This figure illustrates the different pathogenic mechanism that result in vascular access failure. Hemodynamic and surgical stressors, inflammatory stimuli such as bioincompatible graft material, uremia and recurrent needling as well as genetic predisposition trigger off a cascade of pro-inflammatory mediators that promote inadequate outward remodeling, migration and transformation of smooth muscle cells and fibroblasts with resulting neointimal hyperplasia, luminal narrowing and thrombus formation.

Figure 2: Biological effects of antiplatelet agents, omega-3 polyunsaturated fatty acids, statins, and renin-angiotensin-aldosterone system blockers with the potential to improve hemodialysis vascular access failure

Figure 2 presents the pleotropic biological effects of antiplatelet agents (red), omega-3 polyunsaturated fatty acids (blue), statins (yellow), and renin-angiotensin-aldosterone-system blockers (purple) that may be beneficial in preventing vascular access failure.

Table 1: Randomized placebo-controlled trials on antiplatelet agents and vascular access outcomes in hemodialysis patients

Trial	Intervention	Control	Access type	n^a	Treatment duration (months)	Primary outcome (antiplatelet agent(s) versus placebo)	Major secondary outcome (antiplatelet agent(s) versus placebo)	Adverse events (antiplatelet agent(s) versus placebo)
Andrassy et al. 1974	Aspirin 1000 mg alternate days	Placebo	AVF	92	1	Thrombosis at 28 days 4% versus 23%, p<0.05	NR	Gastric pain: 11% versus 4% Epistaxis: 11% versus 4% Melena: 4% versus 4% Wound hematoma: 4% (greater severity) versus 4%
Harter et al. 1979	Aspirin 160 mg daily	Placebo	AV shunt	44	4	Thrombosis at study end (mean 5 months) 32% versus 72%, p<0.01	Rate of thrombosis ^b 0.16 versus 0.46, p<0.005	Transfusion: 26% versus 52%
Kaufman et al. 2003	Aspirin 325 mg + Clopidogrel 75 mg daily	Placebo	AVG	200	NR	Cumulative incidence of thrombosis: HR 0.81, 95% CI 0.49-1.40, 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	Bleeding: 42% versus 24%, p=0.006 HR 1.98, 95% CI 1.19-3.28, p=0.007

Sreedhar a et al. 1994^c	Aspirin 325 mg daily	Place bo	AVG	117 (84 Type I ^d and 23 Type II ^e)	18	Thrombosis at 18 months 50% versus 32% ^d 50% versus 80% ^e 23% versus 32% ^d 100% versus 80% ^e	RR of thrombosis ^d Aspirin 1.99, 95% CI 0.88- 4.48, p=0.18 Dipyridamole 0.35, 95% CI 0.15-0.80, p=0.02	Gastrointestinal events (including bleeding) ^{d,e} , NS Aspirin 15% versus 11% Aspirin and dipyridamole 23% versus 11% Dipyridamole 22% versus 11% Cardiac events ^{d,e} , NS Aspirin 10% versus 11% Aspirin and dipyridamole 14% versus 11% Dipyridamole 9% versus 11%
Irish et al. 2017^f	Aspirin 100 mg daily	Place bo	AVF	388	3	Proportion of subjects with AVF failure (composite of AVF thrombosis, abandonment or cannulation failure) at	AVF thrombosis at 12 months 20% versus 18%, RR1.09, 95% CI 0.72-1.64, p=0.70 AVF abandonment at 12	Bleeding events 6% versus 6%, p>0.99 Gastrointestinal side effects 6% versus 5%, p=0.52

12 months after AVF creation: 45% versus 47%, RR 1.05, 95% CI 0.84-1.31, p=0.68

months 24% versus 18%, RR 1.31, 95% CI 0.89-1.95, p=0.17

Cannulation failure during CAP 40% versus 39%, RR 0.99, 95% CI 0.76-1.27, p=0.92

Trial	Intervention	Control	Access type	n^a	Treatment duration (months)	Primary outcome (antiplatelet agent(s) versus placebo)	Major secondary outcome	Adverse events (antiplatelet agent(s) versus placebo)
Fiskerstrand et al. 1984	Ticlopidine 250 mg twice daily	Placebo	AVF	18	1	Thrombosis at 4 weeks 25% versus 50%	ADP-induced platelet aggregation Clotted versus non-clotted AVF, NS	Rash: 13% versus 0%
Grontoft et al. 1985	Ticlopidine 250mg twice daily	Placebo	AVF	36	1	Thrombosis at 4 weeks 11% versus 47%, p<0.05	NR	Bleeding: 11% versus 12% Dyspepsia: 0% versus 6%

Grontoft et al. 1998	Ticlopidin e 250 mg twice daily	Place bo	AVF AVG	242	1	Thrombosis at 4 weeks 12% versus 19%, p=0.10	Predictors of access occlusion including biochemical markers (urea, hemoglobin and cholesterol levels), vessel condition, age and gender.	Gastrointestinal: 11% versus 13% Hemostatic: 4% versus 7%
Dember et al. 2008	Clopidogr el 300 mg loading dose followed by 75 mg daily	Place bo	AVF	877	1.5	Thrombosis 6 weeks after fistula creation 12% versus 20%, RR 0.63, 95% CI 0.46- 0.97, p=0.018	Failure to attain suitability for dialysis 62% versus 60%, RR 1.05, 95% CI 0.94-1.17, p=0.40	Bleeding: 3% versus 3%, p>0.9 Hospitalizations: 15% versus 18%, p=0.16
Ghorbani et al. 2009	Clopidogr el 75 mg daily	Place bo	AVF	75	1.5	Primary AVF failure at 8 weeks 5% versus 22%, p=0.03, HR 0.72, 95% CI 0.41-1.01	Successful HD within 6 months of AVF creation ^g : 92% versus 71%, p=0.008	Non-gastrointestinal bleeding: 5% versus 4%, p=0.6 Gastrointestinal bleeding: 3% versus 4%, p=0.6

^anumber of participants analyzed for primary outcome; ^bnumber of thrombotic events per patient month, ^cparallel group study; ^dpatients with new AVG; ^epatients with thrombosed AVG requiring new AVG; ^fsubgroup of participants randomized to aspirin or placebo; ^gParticipants requiring hemodialysis within 6 months. Abbreviations: ADP – adenosine diphosphate; AV –arteriovenous; AVF – arteriovenous fistula; AVG – arteriovenous graft; CI –

confidence interval; HD – hemodialysis; HR – hazard ratio; NR – not reported; NS – not significant; RR – relative risk.

Table 2: Randomized controlled trials on ω 3FA supplementation and vascular access outcomes in hemodialysis patients

Trial	Intervention	Control	Access type	n^a	Treatment duration (months)	Primary outcome (ω3FA versus placebo)	Major secondary outcome (ω3FA versus placebo)	Adverse events (ω3FA versus placebo)
Schmitz et al. 2001	4x1g ω 3FA (44% EPA, 24% DHA)	Placebo (corn oil)	AVG	24	12	'Primary patency' (thrombosis-free) proportion at 12 months 75.6% versus 14.9%, p<0.05	Mean venous pressure at 12 months 88 \pm 7 mmHg versus 112 \pm 10 mmHg Reduction in BP compared to placebo: systolic BP 30mmHg; diastolic BP 15mmHg, p<0.05	Bleeding events 0% in both groups Gastrointestinal side effects 25% versus 0%
Bowden et al. 2007	6x1g ω 3FA (16% EPA, 10% DHA)	Placebo (canola oil)	AVG	29	8	Primary patency loss (thrombosis or venous outflow stenosis of >50% requiring angioplasty) 254.2 days (SEM 51.8) days versus 254.1 days (SEM 34.6), NS	NR	Gastrointestinal side effects 36% versus 13%
Lok et al. 2012	4x1g ω 3FA (48%	Placebo (corn oil)	AVG	196	12	Proportion of subjects with loss of AVG patency (thrombosis or intervention to	Rate of patency loss ^b 3.43 versus 5.95, IRR 0.58, 95% CI 0.44-0.75, p<0.001	Bleeding events 9% versus 8%, p>0.99

	EPA, 25% DHA)					maintain patency) within 12 months 48% versus 62%, RR 0.78 (95% CI 0.60 to 1.03), p=0.06	Rate of thrombosis ^b 1.71 versus 3.41, IRR 0.50, 95% CI 0.35-0.72, p<0.001 Rate of interventions to maintain patency ^b 2.89 versus 4.92, IRR 0.59, 95% CI 0.44-0.78), p<0.001 Cardiovascular event rate [§] 0.39 versus 0.95, IRR 0.41, 95% CI 0.20-0.85, p=0.02 Cardiovascular event free survival 0.88 versus 0.75, HR 0.43, 95% CI 0.19-0.96, p=0.04 Mean change in systolic BP -3.61 versus 4.49 mmHg, difference -8.1 mmHg, 95% CI -15.4-0.85, p=0.01	
Irish et al 2017	4x1g ω3FA (46% EPA, 38%	Placebo (olive oil)	AVF	536	3	Proportion of subjects with AVF failure (composite of AVF thrombosis, abandonment or cannulation	AVF thrombosis at 12 months 22% versus 23%, RR 0.98, 95% CI 0.72, 1.34), p=0.90	Bleeding events 6% versus 4%, p=0.23

DHA) failure) at 12 months after AVF creation 47% versus 47%, RR 1.03, 95% CI 0.86-1.23, p=0.78

AVF abandonment at 12 months 19% versus 22%, RR 0.87, 95% CI 0.62 to 1.2, p=0.43

Gastrointestinal side effects 5% versus 5%, p=0.86

Cannulation failure during CAP 40% versus 39%, RR 1.03, 95% CI 0.83-1.26, p=0.81

^anumber of participants analyzed; ^bper 1000 access days. Abbreviations: AVF – arteriovenous fistula; AVG – arteriovenous graft; BP – blood pressure; CAP – cannulation assessment period; CI – confidence interval; EPA - eicosapentaenoic acid; DHA - docosahexaenoic acid; HR – hazard ratio; IRR – incidence rate ratio; NS – not significant; RR – relative risk; SEM – standard error of the mean; ω3FA - omega-3 polyunsaturated fatty acids

Table 3: Retrospective analyses on ACEI and ACB use and vascular access outcomes in hemodialysis patients

Study	Number s per access type	Intervent ion	AVF outcomes (ARB/ACEI use versus nonuse)		AVG Outcomes (ARB/ACEI use versus nonuse)	
			Primary patency loss	Secondary patency loss	Primary patency loss	Secondary patency loss
Chen et al. 2016	37771 AVF	ACEI	HR 0.59, 95% CI 0.56-0.62, p<0.05	NR	HR 0.56, 95% CI 0.48-0.64, p<0.05	NR

	4473 AVG	ARB	HR 0.53, 95% CI 0.51-0.56, p<0.05		HR 0.54, 95% CI 0.47-0.61, p<0.05	
Jackson et al. 2011	212 AVF 120 AVG	ARB	HR 0.35, 95% CI 0.16 to 0.76 ^a , p=0.008	NR	HR 0.41, 95% CI 0.18-0.95, p=0.04	NR
Saran et al. 2002	900 AVF 1944 AVG	ACEI ARB	RR 0.77, p=0.09 RR 1.45, p=0.06	RR 0.56, p=0.01 RR 1.33, p=0.31	RR 1.02, p=0.85 RR 1.09, p=0.63	RR 1.16, p=0.13 RR 1.30, p=0.17
Sajgure et al. 2007	87 AVF 179 AVG	ACEI	Primary patency duration (mean ± SEM) 530 ± 80 days versus 501 ± 76 days, p=0.45	NR	Primary patency duration (mean ± SEM) 672±68 days versus 460±48 days, p=0.01 HR 0.48, 95% CI 0.31- 0.73	NR
Gradzki et al. 2001	121 AVG	ACEI	NR	NR	RR 0.32, p=0.003	NR
Diskin et al.	1126 AVF and	ACEI	Access survival estimated from Figure: ~295 days	NR	Access survival estimated from Figure: ~255 days versus ~110	NR

1998	AVG	versus ~280 days, NS	days, p<0.05
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^asubgroup analysis revealed a treatment benefit of ARB on AVF patency only in combination with antiplatelet therapy (HR 0.16; 95% CI 0.05 to 0.52); Abbreviations: ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; AVF – arteriovenous fistula; AVG – arteriovenous graft; CI – confidence interval; HR –hazard ratio; NR – not reported; NS – not significant; RR – relative risk ratio; SEM – standard error of the mean.

Table 4: Mode of action and expected effects of local interventions studied to improve hemodialysis vascular access outcomes

Intervention	Mode of action	Expected effect on hemodialysis vascular access
PRT-201 (recombinant human type-1 pancreatic elastase)	Vasodilation by fragmentation of elastin in blood vessel wall	Improvement of access patency
	Inhibition of adventitial myofibroblast migration to the intima	Improvement of access maturation
Far infrared therapy	Inhibition of vascular smooth muscle cell proliferation	Improvement of access patency
	Inhibition of platelet aggregation	Improvement of access maturation
	Vasodilation	Reduction in access thrombosis
	Reduction in oxidative stress	
Vascugel (Perivascular placement of implants containing allogeneic aortic endothelial cells)	Inhibition of thrombus formation	Reduction in access thrombosis
	Reduction in negative remodeling following vascular injury (reduction in matrix metalloproteinase-2 expression, neovascularization and adventitial fibrosis)	Improvement of access patency Improvement of access maturation
Paclitaxel-coated balloon	Inhibition of vascular smooth	Reduction in access re-

angioplasty	muscle cell proliferation	stenosis
		Improvement of access patency
Coll-R	Inhibition of vascular smooth muscle cell proliferation	Improvement of access patency
(Drug-eluted combination product of collagen membrane and sirolimus)		Improvement of access maturation
Optiflow device	Optimizing flow and shear stress by fixation of anastomotic angle of AVF at 60 degrees	Improvement of access patency
	Shielding of peri-anastomotic region	Improvement of access maturation
Endovascular AVF creation	Reduction in vessel trauma and resulting triggers for neointimal hyperplasia formation.	Improvement in access patency
(endovascular creation of an AV anastomosis using a radiofrequency magnetic catheter-based system)		Improvement of access maturation
		Reduction in access interventions

Figures

Figure 1: Pathogenesis of vascular access failure

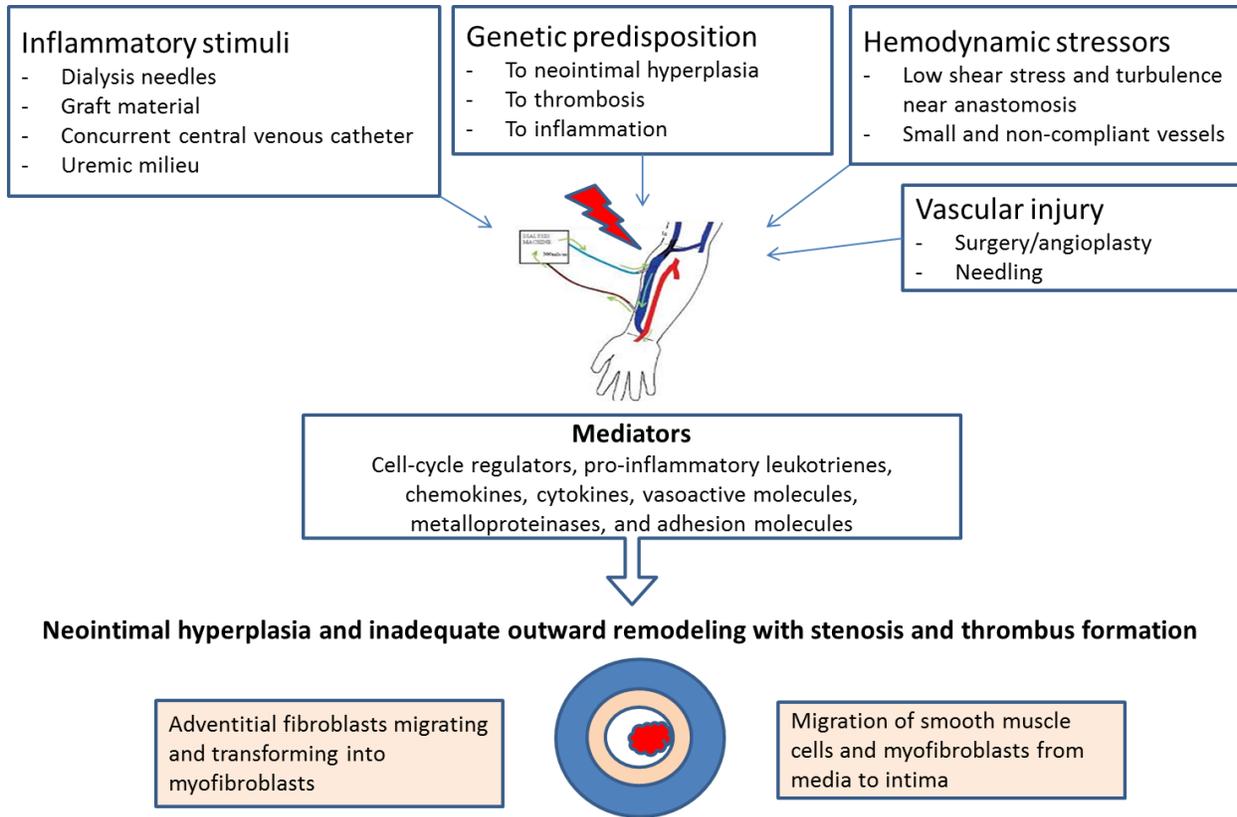


Figure 1: This figure illustrates the different pathogenic mechanism that result in vascular access failure. Hemodynamic and surgical stressors, inflammatory stimuli such as bioincompatible graft material, uremia and recurrent needling as well as genetic predisposition trigger off a cascade of pro-inflammatory mediators that promote inadequate outward remodeling, migration and transformation of smooth muscle cells and fibroblasts with resulting neointimal hyperplasia, luminal narrowing and thrombus formation.

Figure 2: Biological effects of antiplatelet agents, omega-3 polyunsaturated fatty acids, statins, and renin-angiotensin-aldosterone system blockers with the potential to improve hemodialysis vascular access failure

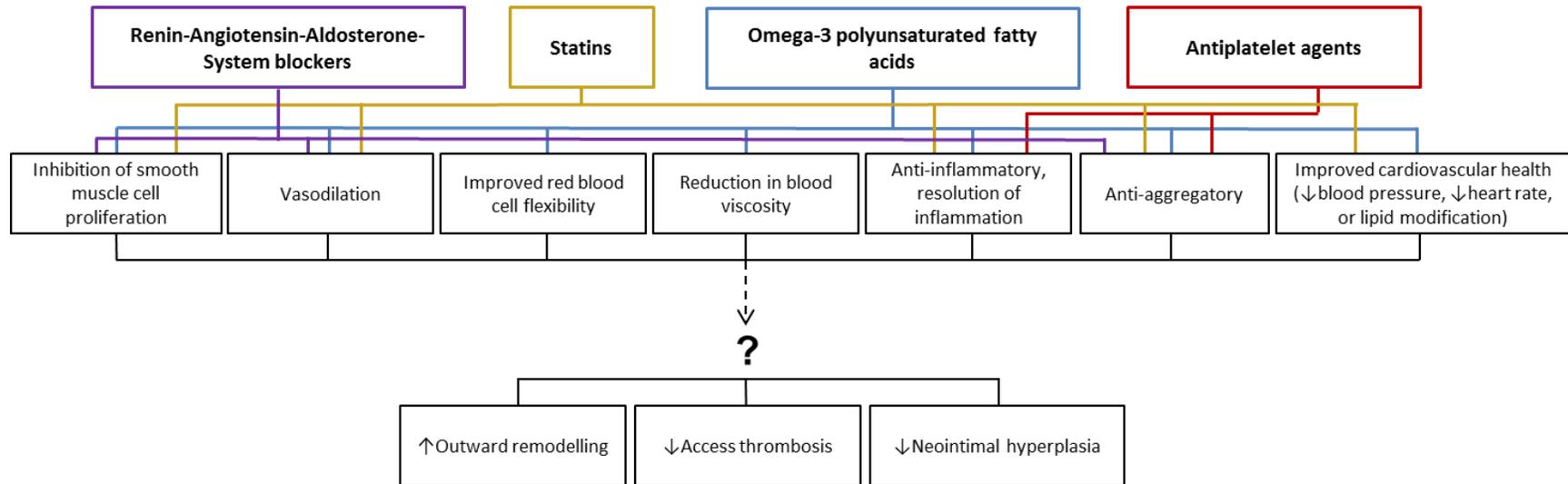


Figure 2 presents the pleotropic biological effects of antiplatelet agents (red), omega-3 polyunsaturated fatty acids (blue), statins (yellow), and renin-angiotensin-aldosterone-system blockers including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (purple) that may be beneficial in preventing vascular access failure.