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Pharmacotherapy to improve outcomes in vascular access surgery: a review of current treatment strategies

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Abstract

Background. Renal failure is a major cause of morbidity in western Europe, with rising prevalence. Vascular access complications are the leading cause of morbidity among patients on haemodialysis. Considering the health care burden of vascular access failure, there is limited research dedicated to the topic.

Methods. Randomised control trials of medications aimed at improving vascular access patency were identified using a medline search between January 1950 and January 2011.

Results. Thirteen randomised trials were identified, investigating antiplatelets, anticoagulants and fish oil in preserving vascular access patency. Outcomes are presented and reviewed in conjunction with the underlying pathophysiological mechanisms of failure of vascular access.

Discussion. Vascular access failure is a complex process. Most clinical trials so far have involved medications primarily aimed at preventing thrombosis. Other contributing pathways such as neointimal hyperplasia have not been investigated clinically. Improved outcomes may be seen by linking future therapies to these pathways.

Introduction

Renal failure is a major cause of morbidity in western Europe, with 117.1 per million population requiring haemodialysis and the prevalence predicted to rise in the next decade [1]. Complications of vascular access are the leading cause of morbidity among patients on haemodialysis, accounting for 30% of all hospital admissions per annum [2]. The annual cost to the UK's National Health Service in percutaneous interventions alone to maintain patency of vascular access is £84.1 million [3].

Creation of an autologous arteriovenous fistula (AVF) is the intervention of choice to create a vascular access point for haemodialysis [4]. Vascular access can be obtained by creation of an autologous AVF, insertion of a prosthetic interposition graft between artery and vein (AVG) or insertion of a prosthetic central dialysis line (Permacath). Prosthetic AVGs for peripheral dialysis access have the advantage of being useable almost immediately for dialysis, but they are limited by infective complications and poor patency rates when compared with autologous AVF. The primary patency of AVGs is estimated at 50% at 1 year, with a 6-fold intervention rate required to achieve similar patency to autologous grafts [5]. Permacath use is limited by frequent infective complications, central venous stenosis and is mainly used as a temporary measure, while other routes of vascular access are established. Autologous AVF have an annual primary patency of 85% if they mature adequately for use [6]; however, successful maturation has been reported to be as low as 50% [7]. The autologous AVF is therefore the access method of choice, with a national target that 67% of patients requiring haemodialysis have a working AVF [8]. For the rest of this article, autologous AVF will be referred to as AVF and prosthetic AVGs as AVG.

This article will review the pathophysiological mechanisms responsible for failure of AVF and AVG, followed by the outcomes of trials aimed at improving vascular access patency using both established and novel agents and how these relate to the underlying pathophysiology of vascular access failure.

Failure of vascular access

For vascular access to be successful, a conduit is required that has the properties of easy cannulation, flow rates of ~400 mL/min and low resistance. Autologous arteriovenous fistula failure and prosthetic AVG failure occurs due to different pathophysiological processes and should therefore be considered separately. Furthermore, autologous AVF failure can be sub-categorized into lack of maturation, which is rapidly evident following AVF creation or failure of a mature AVF. Lack of maturation occurs in up to 50% of AVF and failure of a mature AVF occurs in

~15% by 1 year. Prosthetic AVG failure occurs primarily due to stenosis at the graft-venous anastamosis segment, afflicting 50% of AVGs by 1 year.

Autologous AVF failure

Failure of maturation

The mechanisms behind failure of AVF to mature are complex. Successful maturation depends upon increased shear stress in the venous segment and subsequent compensation. Shear stress is a function of blood flow, blood viscosity and vessel radius. To maintain constant shear stress levels, the vein must dilate to increase the radius, as the other parameters are relatively fixed. High shear stress prompts vascular remodelling with endothelial cell alignment in the direction of flow, nitric oxide (NO) secretion and vasodilation [9]. Vasodilation alone, however, is not enough to normalize shear stress [10], and fragmentation of the elastic lamina is required to permit further dilatation. This has been shown to be influenced by matrix metalloproteinase release [11]. In addition, vascular smooth muscle cell (VSMC) hypertrophy occurs, with an increase in the vein wall cross-sectional area [12]. If compensatory mechanisms do not occur and shear stress is not high enough, a low flow state occurs with local release of prothrombotic and vasoconstrictive mediators [13]. Ultimately, this leads to failure of AVF maturation.

Multiple factors can therefore influence failure of AVF maturation by potentially limiting flow rates such as vein diameter [14], presence of a central stenosis and distal location. The role of surgical expertise is not well studied, though one study has shown that AVF created in low throughput units have poorer outcomes when compared with those with high volume [15]. In addition, identifying a pharmacological target to enhance AVF maturation is also difficult. Prevention of thrombosis within the graft may enhance the patency over a short period of time but may not lead to more useable AVF. Enhancing endothelial function and NO production may be a useful therapeutic target, though in the case of lack of maturation, technical factors such as vein calibre may be overwhelming.

Failure of mature AVF

The commonest cause of failure of a mature AVF is stenosis of the venous segment, with 20–40% occurring within the first few centimetres of vein distal to the anastamosis [16]. The underlying cause of stenosis is neointimal hyperplasia formation [5]. Neointimal hyperplasia is an inflammatory process in response to injury, with intimal layer thickening, VSMC proliferation and matrix deposition [17]. As neointimal hyperplasia formation progresses, the AVF becomes stenosed causing haemodynamic disturbance and limitation of flow, with eventual thrombosis and AVF failure.

The process of neointimal hyperplasia is initiated by endothelial damage, with subsequent endothelial cell dysfunction causing an inflammatory response, which drives the recruitment of leucocytes, proliferation, migration and differentiation of VSMCs and extracellular matrix deposition from fibroblasts and myofibroblasts (commonly differentiated VSMC). Endothelial damage can be induced by inevitable endothelial disruption by surgical trauma and haemodyamic changes to flow within the vein as it becomes arterialized. This hypothesis of AVF failure is largely extrapolated from studies of peripheral bypass grafts. Small animal studies have confirmed that haemodynamic changes associated with AVF formation promote similar pathobiological changes, in particular VSMC proliferation, migration and differentiation [18, 19].

Figure 1 illustrates the underlying pathways of neointimal hyperplasia in AVF.

Prosthetic AVG failure

Stenosis in prosthetic AVGs occurs most commonly at the graft-venous anastamosis segment. Histological analysis of stenoses demonstrates a pathophysiological process similar to neointimal hyperplasia formation in AVF [20]. However, in the prosthetic graft segment, the most abundant cellular element is macrophages [20], a pathophysiologically distinct process characterized by the additional feature of an inflammatory foreign body reaction which, by virtue of the inflammatory mediators produced is likely to accelerate the process. Evolution of neointimal hyperplasia creates a flow limiting stenosis with eventual thrombosis and AVG failure.

A therapeutic approach to improving patency of established AVF and AVG would be either to prevent thrombus

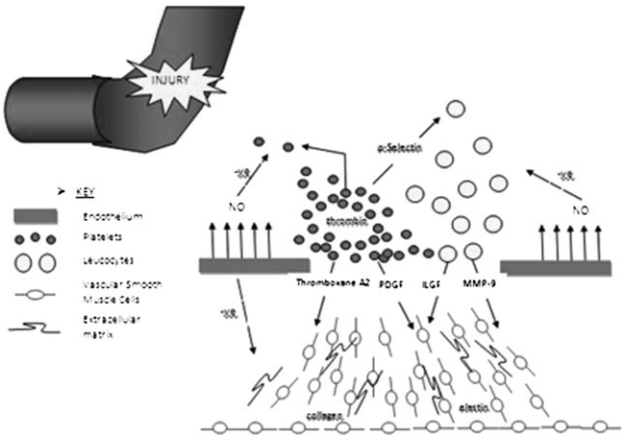

Fig. 1. Pathophysiological pathways underlying stenosis and neointimal hyperplasia formation in matured AVF. Endothelial dysfunction occurs and the normal, protective effect of NO is lost. Exposure of the subendothelial matrix stimulates platelet activation and thrombus for formation at the site. Activated platelets release thrombin, Thromboxane A2, platelet derived growth factor (PDGF) and P-selectin. Thromboxane A2 and PDGF stimulate VSMC proliferation and migration from the tunica media to neointimal. P-selectin is a chemoattractant for leucocytes, which also migrate to the lesion. Once activated at the site, they secrete insulin-like growth factor (ILGF) and matrix metalloproteinases (MMP). Again, these stimulate proliferation and migration of VSMCs. Under the influence of these growth factors, VSMCs change from a quiescent to proliferative phenotype to form the abundant cellular element of the lesion. When proliferative, they also produce significant extracellular matrix: collagen and elastin. As the lesion of neointimal hyperplasia advances, it intrudes the lumen, limiting flow and causes AVF failure.

formation, prevent evolution of the underlying stenosis or a combination of these treatments. Obvious targets to prevent stenosis evolution are the inhibition of VSMC proliferation and maintenance of endothelial integrity. Most established approaches' primary aim is to prevent thrombosis in either the AVF or AVG. Potential 'downstream' effects on stenosis formation do exist with these approaches as will be discussed. More novel therapeutic strategies aimed at preventing stenosis evolution will also be reviewed.

Only thirteen randomized control trials were identified investigating outcomes in AVF and AVG. Table 1 summarizes the primary outcomes, secondary outcomes and adverse events of these trials by drug class. Table 2 lists confounding variables by baseline patient characteristics of each study. Table 3 by reported blood parameters and Table 4 by published relevant technical data. The trials will be summarized by drug class and results linked to underlying pathophysiological mechanisms.

Anti-platelet agents

Anti-platelets are well established in the treatment of patients with end-stage renal failure where use significantly reduces the risk of cardiovascular events [34]. Aspirin, dipyridamole and thienopyridines have all been investigated. The majority of randomized control trials have investigated anti-platelet use with thrombosis as an end point of graft survival. Aspirin inhibits platelets through irreversible inhibition of the prostaglandin H-synthase C (COX) enzyme [35], part of the arachidonic acid pathway that forms thromboxane A_2. Dipyridamole inhibits cyclic adenosine monophosphate (cAMP) phosphodiasterase, affecting the NO/cyclic guanosine monophosphate signalling pathway [36], part of the platelet activation pathway. Ticlopidine and clopidogrel both irreversibly inhibit adenosine diphosphate (ADP)-dependent pathways of platelet aggregation mainly via $P2_{Y12}$ G-protein-coupled receptor, which initiates platelet aggregation and amplifies the response to thromboxane A_2 and thrombin [37].

Aside from direct anti-platelets effects, administration of aspirin and dipyridamole at physiologically relevant doses has been shown to reduce neointimal hyperplasia in a primate bypass graft model [38]. Dipyridamole alone has been shown to inhibit VSMC proliferation induced by platelet-derived growth factor (PDGF) and fibroblast growth factor [39, 40]. Subsequent research, however, has demonstrated no effect of aspirin on VSMC proliferation and an inhibition using dipyridamole at concentrations in excess of physiological relevance if taken systemically [41], so the 'pleiotropic' effects of anti-platelets agents have yet to be fully established. There is little evidence that Ticlopidine or clopidogrel have direct effects upon VSMC. While direct effects of anti-platelet agents on cellular pathways of neointimal hyperplasia are contentious, inhibition of platelet activation may have down-stream effects on such pathways. Platelet activation results in release of over a dozen chemokines, growth factors and small molecules [42]. PDGF is mitogenic to VSMCs [43], as is Thromboxane A2 [44]. P-selectin binds to P-selectin glycoprotein ligand 1 on leucocytes [45]. This further contributes to pathways of intimal hyperplasia with activated leucocytes releasing matrix metalloproteinase 9 and insulin-like growth factor 1 [46]. Figure 2 summarizes potential downstream effects of platelet activation that may inhibit pathways of AVF and AVG stenosis.

With regard to facilitating maturation of AVF, anti-platelet agents may prevent thrombus formation in a low-flow graft, potentially 'buying time' for maturation to occur. In addition, aspirin has been shown to induce NO release from the endothelium experimentally, an effect that may encourage AVF maturation [47].

Outcome of clinical trials

Three trials were identified examining the use of aspirin. There was a consistent trend for aspirin to reduce graft thrombosis with reductions measured in AVF and AVG $>$1–6 months when compared to placebo. Thrombosis rates of 4 versus 23% (Andrassy [21]) and 32 versus 72% (Harter [22]) were reported with minimal side effects of use. These trials, however, are old and have small numbers, with little reporting of patient and graft confounding variables.

Dipyridamole has potential pleiotropic effects on pathways of neointimal hyperplasia formation such as VSMC proliferation. The most recent trial [24] demonstrated primary AVF patency of 23 versus 25% at 1 year in 649 patients taking dipyridamole and aspirin. AVF survival time was shown to be prolonged by 6 weeks with dipyridamole treatment compared to control. Confounding variables were well reported with minimal side effects. Unfortunately, primary patency rates in this trial were lower than expected, potentially leading to an effect of treatment being lost.

Thienopyridines have been investigated in seven trials as summarized in Table 1. Ticlopidine has been investigated in four trials [28–31], with an overall consistent trend to improve thrombosis over a short period in both AVF and AVG. These trials were limited by small numbers, short follow-up periods and lack of reporting of confounding variables.

Clopidogrel has been the focus of three trials. The most recent trial [25] investigated 877 patients undergoing AVF creation and demonstrated a reduction in AVF occlusion at 6 weeks (relative risk reduction 0.63). The secondary outcome was the number of AVF useable for dialysis. There was no significant difference in either group at 6 weeks.

The Kaufman [27] trial raised an issue over the safety of clopidogrel in patients undergoing haemodialysis in a trial of 200 patients that was halted early due to a significant increase in bleeding risk.

Taking the trials using anti-platelet treatment together, it appears that treatment does appear to reduce thrombosis within both AVF and AVG. What is unclear is if this translates into any clinical benefit. The largest long-term trial using dipyridamole demonstrated a prolongation of AVG survival by 6 weeks. This may be of critical benefit to haemodialysis patients, allowing time for 'rescue' endovascular procedures for example. However, it indicates that treatment goes little beyond preventing graft thrombosis

Table 1. Main outcomes of identified trials[a]

Trial	Intervention	Control	Graft type	*n*	Duration	Outcome 1	Outcome 2	Reported patency rates	Adverse events
Aspirin									
Andrassy *et al.* [21]	Aspirin 1 g (alternate days)	Placebo	AVF	92	28 days	Thrombosis: 4% aspirin versus 23% control, OR 0.15			Nil
Harter *et al.* [22]	Aspirin 160 mg od	Placebo	AVG	49	5 months	Thrombosis: 72% placebo versus 32% aspirin			Nil: patients with history of GI bleed excluded from study
Diypridiamole									
Sreedhara [23] 1994	Dipyridamole 75 mg tds or aspirin 325 mg od or dipyridamole and aspirin.	Placebo	AVG	107 (84 Type I, 23 Type II)	18 months	Graft thrombosis: 21% dipyridamole alone, 80% aspirin alone, 25% dipyridamole + aspirin, 40% placebo.	Relative risk of thrombosis, 0.35 dipyridamole and 1.99 aspirin.	As outcome 1	Nil
DAC Study Group *et al.* [24]	Diypridamole 200 mg bd and aspirin 25 mg.	Placebo	AVG	649	1 year	Loss of primary graft patency: 17% RRR in favour treatment.	Median graft survival: 22.1 months, prolonged 6 weeks by treatment.	23% versus 25% at 1 year.	15% died/lost to follow-up primary outcome, 30% for secondary outcome, 40% did not get monthly flow monitoring
Thienopyridines									
DAC Study Group [25]	Clopidogrel (300 mg loading→75 mg maint)	Placebo	AVF	877	6 weeks	Fistula thrombosis 6 weeks: RRR 0.63 in favour treatment (12.2 versus 19.5%).	Fistula useable for dialysis: 61.8 versus 59.5%, not significant.	In 6 weeks, 61.8 versus 59.5% matured suitably to be considered for dialysis.	No increase bleeding risk
Trimarchi 2006 [26]	Clopidogrel 75 mg	Placebo	AVG	24	3 years	Time to thrombosis: 380 versus 90 days in favour treatment, OR 0.01.	Mortality: 100% in control versus 16.7% treatment		100% mortality control versus 16.7% treatment. No increase bleeding risk.
Kaufman *et al.* [27]	Clopidogrel 75 mg and aspirin 325 mg	Placebo	AVG	200	Stopped 7 months	Time to first episode thrombosis: non-significant benefit treatment (hazard ratio 0.81)	Significant increase major bleeding events: every case of graft failure prevented, 1.21 major bleeding episodes occurred.	Incomplete	44 significant bleeding events treatment versus 23 control

Continued

Table 1. *Continued*

Trial	Intervention	Control	Graft type	*n*	Duration	Outcome 1	Outcome 2	Reported patency rates	Adverse events
Grontoft *et al.* [28]	Ticolpidine 250 mg bd initiated 7/7 pre-operatively	Placebo	AVF and AVG	258	4 weeks	Thrombosis at 4 weeks assessed by USA: 12 versus 19% in favour of control, not significant.	NR	84% at 4 weeks.	5.8% patients died before completing study.
Grontoft *et al.* [29]	Ticlopidine 250 mg bd	Placebo	AVF	42	4 weeks	Fistula function at 4 weeks: 47% not functioning in placebo versus 10.5% treatment arm.		Overall, 72% patency at 4 weeks.	15% patients did not complete study. No increased bleeding risk.
Fiskerstrand *et al.* [30]	Ticlopidine 250 mg bd	Placebo	AVF	18	4 weeks	Fistula failure: 33.3% ticlopidine versus 55.5% placebo			11% patients did not complete study.
Kobayashi *et al.* [31]	Ticlopidine 200 mg bd	Placebo	Established AVF and AVG	107	3 months	Patients requiring thrombectomy: reduction 1.18×/ patient/4 weeks in favour treatment.	NR	n/a: established grafts	29% enrolled patients did not complete 12 weeks follow-up
Warfarin									
Crowther *et al.* [32]	Warfarin: target INR 1.4–1.9	Placebo	AVG	107	24 months	Graft loss: 73% warfarin versus 61% control	Average time to graft failure: 199 days warfarin versus 83 days control (ns)	27 versus 39% at 24 months. 9.3% of grafts did not function suitably for access (n.s. difference between groups).	Major haemorrhage: significant increase warfarin, 6 versus 0 major bleeding episodes.
Fish oil									
Schmitz *et al.* [33]	Fish oil 4000 mg	Placebo	AVG	12	12 months	Primary patency: 75.6% fish oil versus 1.49% control	Graft thrombosis: 75% control versus 16.6% fish oil	75.6% fish oil versus 14.9% control	Nil

[a]od, once daily; bd, twice dailty; tds, three times daily.

Table 2. Patient characteristics

Trial	Age	Male	Race	BMI	Diabetes	Smoking	BP/HTN	Other	Compliance	Follow-up
Aspirin										
Andrassy *et al.* [21]	NR	NR	NR	NR	NR	NR	Six HTN placebo versus one aspirin	Reduction arterial flow six placebo versus one aspirin	NR	Complete
Harter *et al.* [22]	49	45%	NR	NR	NR	NR	NR	All variables stated to be 'well matched'	Four non-compliance	29.5% did not complete study
Dipyridamole										
Sreedhara 1994 [23]	54	42%	30% black	24	NR	NR	NR	NR	NR	88%
DAC Study Group *et al.* [24]	60	39%	71% black	30	19.4%	5%	144/74	NR	83%	15% lost primary, 30% secondary
Thienopyridine										
DAC Study Group [25]	53	62%	48% black	30	48%	19%	140/78		87%	8% did not complete
Trimarchi 2006 [26]	71	NR	NR	NR	25%	NR	NR		NR	NR
Kaufman *et al.* [27]	62	99%	70% black	NR	47%	NR	NR	Hx PUD 17%	33% had study medication discontinued prior to termination	Terminated early
Grontoft *et al.* [28]	58	63%	NR	24	NR	NR	NR	NR	Not reported	15% did not complete study
Grontoft *et al.* [29]	44	66%	NR	NR	52%	NR	NR		NR	85% completed study
Fiskerstrand *et al.* [30]	NR	NR	NR	NR	NR	NR	NR	NR		16.6% did not complete study
Kobayashi *et al.* [31]	NR	37%	NR	NR	NR	NR	NR	NR	71% completed study	29% did not complete study
Warfarin										
Crowther *et al.* [32]	65	77%	NR	80 versus 74 kg	43%	31%	NR	NR	INR above 1.45 9.1%, within 47% and below 43.1%	100%
Fish oil										
Schmitz *et al.* [33]	53	45%	79% black	N/a: 79 kg (weight)	58%		160 mmHg: reduction by 30 versus 15 mmHg in treatment arm.	No concurrent anti-platelet use	100%	96%

Table 3. Blood parameters[a]

Trial	Urea (mmol/L)	Cholesterol (g/dL)	Hb (g/dL)	Haematocrit (l/L)	Albumin (g/dL)	Platelets ($\times 10^9$/L)	Other
Aspirin							
Andrassy *et al.* [21]	NR	NR	NR	NR	NR	NR	
Harter *et al.* [22]	NR	NR	NR	NR	NR	NR	
Dipyridamole							
Sreedhara 1994 [23]							
DAC Study Group *et al.* [24]	NR	NR	11.8	NR	37	NR	
Thienopyridine							
DAC Study Group *et al.* [25]	NR	NR	11.6	NR	37	NR	
Trimarchi 2006 [26]	NR	NR	NR	33	NR	NR	
Kaufman *et al.* [27]	Urea reduction ratio: 69	164 mg/dL	11.3	NR	36	NR	
Grontoft *et al.* [28]	29.5	6.05	9.13	NR	NR	NR	
Grontoft *et al.* [29]	NR	NR	NR	NR	NR	NR	
Fiskerstrand *et al.* [30]	NR	NR	NR	NR	NR	250	
Kobayashi *et al.* [31]	NR	NR	NR	NR	NR	NR	
Warfarin							
Crowther *et al.* [32]	NR	NR	10.5	NR	35	216	Average INR 1.45 Rx group, 43.1% below therapeutic range.
Fish oil							
Schmitz *et al.* [33]	NR	180 mg/dL	NR	32	NR	NR	

[a]Av, average.

and may have little effect on pathways of neointimal hyperplasia formation. Similarly, clopidogrel use also appears to prevent graft thrombosis in the short term, but by 6 weeks, there does not appear to be a difference in the number of AVF that have matured suitably for use. Again, this indicates that there is no positive effect on the underlying mechanisms that result in AVF maturation. Anti-platelet use may have a critical role in maintenance of AVF and AVG, but it is likely that supplemental agents, specifically targeting pathways of neointimal hyperplasia formation and AVF maturation will be required to yield more significant clinical benefits.

Warfarin

Warfarin prevents coagulation within the AVF or AVG, potentially prolonging the duration of patency. No effects upon pathways of neointimal hyperplasia have been reported. One trial has been performed investigating the use of warfarin in maintaining the patency of prosthetic AVGs [32]. Warfarin therapy (INR target of 1.4–1.9) was compared to placebo in 107 patients followed-up for 2 years. Overall, graft loss was 73% in the warfarin group compared with 61% in the control group. There was a significant increase in major haemorrhage in those treated with warfarin (six cases versus zero). Less than half of the patients enrolled achieved the target INR, which may explain the lack of efficacy seen. Similar to anti-platelet treatment, anticoagulants may delay AVG occlusion but do not attenuate the underlying pathophysiological pathways, therefore adjunctive agents are required.

Fish oil

Fish oils have been demonstrated to have anti-platelet effects, prolong bleeding times and reduce intimal hyperplasia in autogenous grafts [48]. In addition, reductions in neointimal hyperplasia formation following balloon injury in primates [47] and enhanced endothelial function [50] have been reported. Such effects may improve AVF and AVG patency by addressing the problem of both thrombosis and stenosis and enhanced endothelial function may also contribute to improved AVF maturation.

Schmitz *et al.* [33] examined the effect of 4000 mg of fish oil daily versus placebo in a trial of 24 patients undergoing AVG. Patients were followed-up for 1 year with primary patency reported as 75.6% in the fish oil group compared with 14.9% in the control group. The trial was performed at a single centre and confounding variables well reported, with even matching between the two groups. While results were encouraging the failure rate in the placebo arm was high and numbers enrolled were small. This trial has formed the basis of a larger randomized control trial into the effect of fish oil on haemodialysis grafts [51].

Potential future therapies

Clinical research so far has concentrated mainly on the use of anti-platelet or anticoagulant agents to preserve the lifespan of haemodialysis access grafts. Thrombosis is the final result of the underlying pathophysiological mechanism of vascular access failure: either an evolving stenosis caused by neointimal hyperplasia or a low flow state caused by

Table 4. Technical data

Trial	No. Centre	Graft type	Graft location	Anastamosis type	Vessel quality graded?	Graft monitoring	Previous CVC	Previous access
Aspirin								
Andrassy *et al.* [21]	5	AVF	NR	End-to-end: 41 End-to-side: 4 Side-Side: 47	32: 'poor'; 60: 'good'	Clinical	NR	NR
Harter *et al.* [22]	Single surgeon	AVG	All wrist or forearm radio-cephalic.	NR	No	Clinical	NR	NR
Dipyridmaole								
Sreedhara 1994; [23]	1	79% primary grafts, 21% revision or post-thrombectomy		NR	No	Clinical assessment	NR	NR
DAC Study Group *et al.* [24][25]	13	94% PTFE, 5% other prosthetic material, 1% autologous interposition	49% forearm, 44% upper arm, 6% leg, 1% chest	NR	No	US indicator dilution technique + dialysis flow rates.	65%	51%
Thienopyridine								
DAC Study Group *et al.* [25]	9: 71 surgeons at 27 hospitals	99.5% AVF, 0.5% prosthetic excluded from trial.	54% forearm, 46% upper arm of which 69% brachiocephalic and 25% basilic transposition.	NR	No	Clinical assessment	NR	80%
Trimarchi 2006 [26]	1	75% radiocephalic, 25% brachiocephalic		NR	NR	Clinical/venous outlet monitoring	NR	NR
Kaufman *et al.* [27]	multicentre	PTFE	Forearm: 64%	NR	No	Clinical	70%	53%
Grontoft *et al.* [28]	9	AVF: 90%, prosthetic: 6.2%, autologous interposition: 3.4%	75% wrist	75% end-to-side	Good 73%, poor 17%	US	NR	17%
Grontoft *et al.* [29]	1	AVF	'Most' radiocephalic	'Most' end-to-side anastamosis	No	NR	NR	'A few'
Fiskerstrand *et al.* [30]	1	AVF	Brescia-Cimino	NR	No	Clinical	NR	
Kobayashi *et al.* [31]	NR	AV shunt: 64.4%, AV graft: 31.7%, AVF: 3.7%	NR	NR	No	Clinical	NR	NR
Warfarin								
Crowther *et al.* [32]	3	PTFE	Forearm loop: 81%	NR	No	Clinical	NR	6.5%
Fish oil								
Schmitz *et al.* [33]	1	PTFE 7 mm	Upper arm straight: 29%, forearm loop: 42%, forearm straight: 34%	NR	No	Dialysis venous outflow pressure/ clinical	NR	37%

failure of maturation. Thus, agents that treat secondary consequences (anti-platelets and anticoagulants) may 'buy time' for grafts but do not address the primary fundamental underlying stenosis. It is unsurprising that there appears to be a lack of clear clinical efficacy. Key therapeutic targets to improve vascular access outcomes would be to:

(1) Reduce endothelial dysfunction. This may improve AVF maturation and reduce neointimal hyperplasia formation in AVF and AVG.
(2) Inhibit VSMC proliferation and migration, the most abundant cellular element in neointimal hyperplasia.

Potential benefits of existing pharmacological strategies upon these targets will be discussed followed by more novel therapeutic strategies. Table 5 summarizes these more novel therapeutic strategies.

Pharmacological strategies to reduce neointimal hyperplasia

Established agents

Cilostazol. Cilostazol is a phosphodiasterase III inhibitor. It has multiple effects including accumulation of intracellular cAMP, which has anti-platelet and vasodilatory effects [52]. Direct inhibition of VSMC proliferation by cilostazol has been reported, with a putative mechanism being via down-regulation of E2F [53]. Cilostazol inhibits VSMC proliferation in response to PDGF in a concentration-dependent manner [54]. Taken together, cilostazol theoretically could have benefits on AVF and AVG stenosis evolution, AVF maturation and thrombosis. The CREST trial demonstrated significant reductions

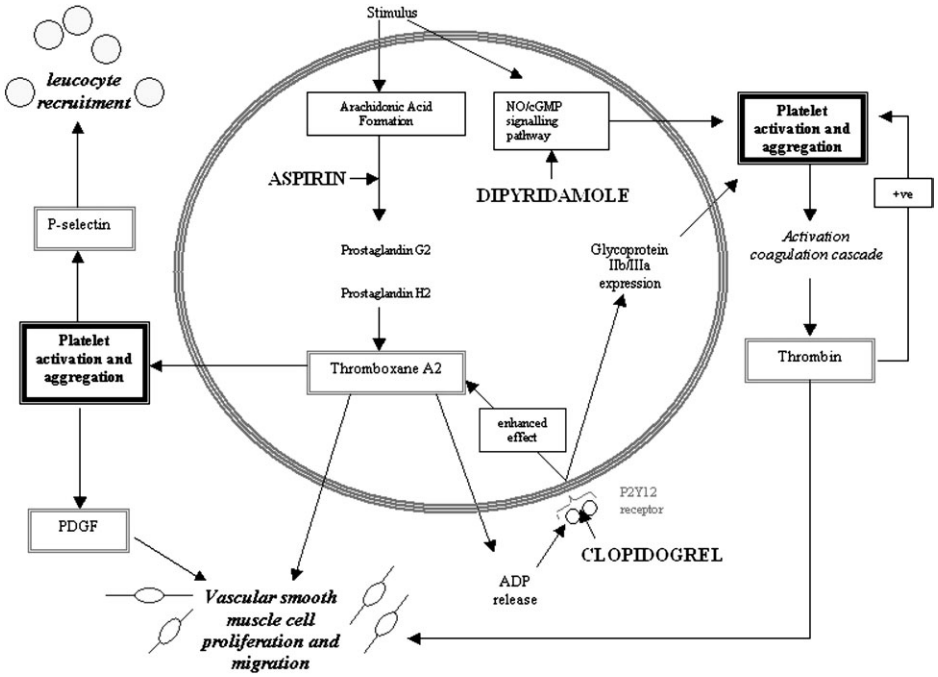

Fig. 2. The potential downstream effects of platelet activation. Activated platelets secrete PDGF, which is directly mitogenic to VSMC, the key cellular element of AVF stenosis. P-selectin attracts circulating leucocytes, which in AVG eventually forms the largest cellular element of the stenosis and contribute to AVF stenosis by secretion of insulin-like growth factor. Thromboxane A2 is also purported to enhance VSMC proliferation, as is the presence of thrombin.

Table 5. Novel therapies to reduce neointimal hyperplasia

Agent	Potential therapeutic benefit(s)	Clinical outcomes reported
Cilostazol	Anti-platelet effect	Improved patency of angioplasty in haemodialysis patients with 100 mg Cilostazol.
	Inhibition of VSMC proliferation Inhibition of neointimal hyperplasia	Reduced restenosis following coronary angioplasty.
Statins	Anti-platelet effect	Improved AVF patency in retrospective analysis (71.5 versus 39.1%).
	Inhibition of VSMC proliferation	Improved infrainguinal bypass graft patency in 2× retrospective analyses.
	Enhanced endothelial function	
Allogenic endothelial cell implants	Enhanced endothelial function	Safety of technique demonstrated. No clinical outcomes as yet.
NO	Enhance endothelial function	Minimal benefit on restenosis following coronary angioplasty, with high incidence side effects.
MAP kinase inhibitors	Inhibit VSMC proliferation	Experimental models only.

in restenosis in patients undergoing coronary angioplasty in those taking cilostazol [55]. In patients on haemodialysis undergoing angioplasty for peripheral vascular disease, 5-year patency of the target vessels in patients receiving 100 mg cilostazol twice daily was 58.4% compared to 34.7% in the control group [56].

It is encouraging that efficacy of cilostazol has been seen in a group of patients with end-stage renal failure on a pathophysiological process similar to neointimal hyperplasia in AVF failure. Experimentally, cilostazol appears to have effects that could impact upon AVF stenosis by reducing pathways of intimal hyperplasia.

Statins. In addition to cardiovascular benefits [57], statins have been demonstrated to have pleiotropic effects [58]. Effects reported include inhibition of VSMC proliferation and migration [59], enhanced endothelial NO release [60] and reduced cytokine secretion [61]. These pleiotropic effects occur as a down-stream effect of mevalonate inhibition on isoprenoid intermediates [62].

One retrospective analysis of 60 patients with autologous AVF demonstrated improved fistula patency (71.5 versus 39.1%) at 2 years in those taking folic acid and statin compared to those on no statin therapy [63]. Two large retrospective studies [64, 65] of patients with infrainguinal bypass grafts demonstrated significant prolongation of graft survival in patients on statin therapy. The positive effect of statins in retrospective analyses, in combination with theoretical benefits upon pathways of neointimal hyperplasia formation suggest that statins could potentially play a role in improving the patency of vascular access grafts, both by inhibiting pathways of neointimal hyperplasia formation and potentially enhancing endothelial function and assist AVF maturation.

Novel therapeutic strategies to reduce neointimal hyperplasia

Allogenic endothelial cell implants. Integrity of the vascular endothelium is critical to vascular tone and health. Endothelial function and adaptation appears critical to AVF maturation, and endothelial injury is central to the theory of neointimal hyperplasia formation and subsequent AVF stenosis. Novel work by Conte *et al.* [16] has investigated perivascular placement of implants containing allogenic aortic endothelial cells to restore vascular endothelial integrity following AVF creation. Reductions in thrombosis, inflammation and stenosis were demonstrated in a porcine model, and Phase I/II trials have been completed demonstrating safety in 57 patients undergoing autologous AVF creation and prosthetic AVG placement. No significant difference in patency was seen; however, the trial was powered to assess safety, not efficacy. A larger randomized trial is expected.

Nitric oxide: exogenous administration and enhancing endogenous production. NO production is important to vascular integrity. It has also been shown to have a key role in vascular remodelling that allows for successful AV fistula maturation and is important in preventing neointimal hyperplasia formation. Enhancement of local NO production either by systemic administration or local application may improve outcomes in vascular access surgery. Systemic therapy with NO donor compounds and NO precursor compounds has successfully reduced neointimal hyperplasia formation in arterial animal models [66, 67]. Results in small trials in humans have been disappointing, however, with conflicting results reported and a high incidence of side effects reported [68, 69]. Local application of NO donor compounds to areas of endothelial injury may circumvent problems with systemic side effects and promising results have been demonstrated in animal studies [70].

Mitogen Activated Protein (MAP) kinase inhibitors. MAP kinases are an intracellular signalling mechanism belonging to the family of serine–threonine protein kinases. Extracellularsignal-regulated kinase 1/2 (ERK 1/2) MAP kinase has been shown to be integral to the signalling pathway for VSMC proliferation, and p38 and ERK1/2 signalling is responsible for VSMC migration in response to PDGF [71, 72].

Systemic administration of both ERK1/2 [72] and p38 [73] inhibitors has been shown to reduce intimal hyperplasia in small animal models. Systemic use in humans is unrealistic as the ubiquity of MAP kinases is such that side effects would be unpredictable. Topical application or pre-incubation of transplanted vein circumvents this and success has been achieved in animal models where anti-proliferative and anti-inflammatory effects have been recorded in the VSMCs of vein grafts [74].

Conclusion

Over 150 years ago, Virchow proposed a triad of factors that cause thrombosis: interruption of blood flow, abnormal vessel wall and blood coagulant constituents. Clinical trials aimed at improving patency of autologous AVF and prosthetic AVGs have mainly focused upon preventing blood coagulation, with minimal benefits demonstrated. There is a paucity of laboratory and clinical research into vascular access failure; however, developments in molecular medicine may demonstrate benefit by addressing the other limbs of the triad. Therapeutic agents aimed at reducing neointimal hyperplasia via VSMC inhibition and restoration of endothelial integrity have potential to improve outcomes in vascular access surgery. Prospective randomized trials of agents in routine clinical use are required, along with greater volume of laboratory-based research to enhance our understanding of the problem.

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