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Pharmacological approaches to preventing vascular access failure

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Author: Kevan Polkinghorne

GUIDELINES

Arteriovenous fistula (AVF)

a. Treatment with anti-platelet agents (aspirin, clopidogrel or ticlopidine may reduce the incidence of AVF primary failure at 1 month post-AVF creation. (Level I and Level II evidence)

Arteriovenous graft (AVG)

a. Therapy with aspirin/clopidogrel combination does not reduce AVG thrombosis and increases the risk of adverse effects. (Level II evidence)

b. Therapy with low dose warfarin (INR 1.4 to 1.9) does not reduce AVG thrombosis and increases the risk of adverse effects. (Level II evidence)

c. Whether therapy with aspirin alone, dipyridamole alone, or aspirin plus dipyridamole reduces AVG thrombosis is not clear. (1 trial, mixed results, Level II evidence)

d. Fish oil (80% omega-3 fatty acid ethyl esters) therapy may reduce AVG thrombosis. (Small pilot study, Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Nil.

BACKGROUND

The establishment and maintenance of vascular access in haemodialysis patients represent a major cause of morbidity in nephrology units. The native arteriovenous fistula (AVF) is the vascular access of first choice for haemodialysis with superior long-term patency, lower costs and infection rates compared to arteriovenous grafts and central venous catheters. However, primary failure (failure of the created AVF to be suitable for dialysis) in AVF is a major problem. While rates of primary failure are lower for AVG, this access has unacceptably high overall thrombosis rates compared to AVF. The objective of this guideline is to review the evidence for pharmacological interventions aimed at reducing thrombosis of vascular access for haemodialysis.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for haemodialysis were combined with MeSH terms and text words for anti-platelets agents, Clopidogrel, Dipyridamole, Ticlopidine, Sulphinpyrazone, anti-coagulants, fish oil and ACE inhibitors. The search was carried out in Medline (1966 – July Week 3, 2006). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline. **Date of search:** 22 July 2006.

WHAT IS THE EVIDENCE?

Pharmacological approaches to preventing vascular access failure

Preventing vascular access thrombosis with anti-platelet agents was first proposed as a therapeutic option in 1967.[1] Since then, there have been a number of randomised controlled trials (RCTs) using a variety of different agents, with the primary aim of reducing vascular access thrombosis. The drug therapy used has broadly been either using anti-platelet agents or anti-coagulants.

Nine RCTs with a total of 929 subjects have been performed (Tables 1 and 2). The majority of the studies have assessed anti-platelet agents.[2–8] One trial assessed low dose warfarin[9] and one fish oil.[10] In addition, a Cochrane systematic review was published in 2003[10,11] although this did not include all studies published to that date. One additional trial by Michie *et al.*,[12] despite being randomised, did not present any statistical analysis of the data (likely due to the small numbers) and therefore has not been included in the

summary table. In this study, 16 patients with either an AVF or AVG were randomised to either Sulfinpyrazone or placebo and followed for 3 months. There were three thrombotic episodes in the placebo group and one in the treatment group.

AVF primary failure: randomised controlled trials

All four published studies with AVF have assessed the effect of aspirin or ticlopidine on early (primary) AVF failure (at 1 month).[2–5] Ticlopidine was used in three of the trials.[3–5] and aspirin in one.[2] Study end-points were AVF patency assessed by physical examination/auscultation and not whether the AVF was successfully used for dialysis.

Andrassy *et al.*[2] assessed high-dose aspirin (1 gram), given pre-operatively and continued for 1 month in 92 subjects with new radiocephalic AVF. Thrombosis rates at 1 month were significantly lower in the treatment group compared to the placebo group (2 of 45 compared to 11 of 47, $P < 0.05$). Both Fiskerstrand *et al.*[3] and Grontoft *et al.*[5] assessed ticlopidine in small studies demonstrating a significant reduction in AVF failure at 1 month post-AVF creation. Two[2,5] of the three smaller studies demonstrated significant reduction in the thrombosis rate in the treatment group. However, a subsequent larger study in 26[illegible] patients failed to confirm the significant reduction shown in the earlier studies although even this study was under-powered due to both a slow recruitment and lower than expected event rate.[4]

AVG thrombosis: randomised controlled trials

Four studies assessed thrombosis in AVG at a variety of different follow-up times.[6,8–] Two used anti-platelet agents[6,8] either alone or in combination, while one assessed low dose warfarin[9] and another fish oil.[10] Kobayashi *et al.*[7] presented a trial of 107 patients with Scribner shunts, AVG and AVF, using ticlodopine. Two-thirds of the patients had Scribner shunts with the majority of the remaining patients with AVG although the results were presented by vascular access type. Overall, there was a reduction in thrombosis after 3 months of therapy.

Sreedhara *et al.*[8] assessed the effect of anti-platelet agents on AVG thrombosis in a study of 84 subjects with three active treatment arms (aspirin alone, dipyridamole alone, and aspirin plus dipyridamole) in addition to the placebo group. In the aspirin versus placebo group, 18-month cumulative thrombosis rates were 80% versus 42%, respectively, producing a non-significant trend to an increased thrombosis rate in the aspirin-treated group (RR 1.99, 95% CI 0.88, 4.48, $P = 0.18$). In contrast, thrombosis in the dipyridamole group was significantly lower compared to the placebo group (21% versus 42%, RR 0.35, 95% CI 0.15, 0.80, $P = 0.02$). The combination aspirin and dipyridamole group had a cumulative thrombosis rate of 25%, however, no calculation of the RR was performed in the study. In view of the conflicting results between the effect of aspirin and dipyridamole, further work by the same group was done which has demonstrated that dipyridamole inhibits and aspirin promotes PDGF-stimulated intimal hyperplasia. This could possibly explain the difference in thrombosis rates.[13,14]

The combination of aspirin and clopidogrel was assessed by Kaufman *et al.*[6] The study was powered for a sample size of 320 patients but the trial was stopped early due to adverse events with 200 patients recruited. There was a two-fold increase in the cumulative incidence of bleeding events in those treated with aspirin and clopidogrel (HR 1.98, 95% CI 1.19, 3.28, $P = 0.007$). This increased risk was attributed to an increase in the incidence of both minor and intermediate bleeding events. Major bleeding (defined as confirmed retroperitoneal, intra-articular, intraocular, or cerebral haemorrhage or any bleeding episode that resulted in a 2 g/L decrease in haemoglobin concentration and necessitated hospitalisation or transfusion) was not significantly different between the two groups, although the incidence was higher in the treatment group (12% vs 5% of all bleeding episodes, $P = 0.2$). In terms of the primary endpoint, there was no difference between the two groups in terms of thrombosis rates (HR 0.81, 95% CI 0.47, 1.40, $P = 0.45$). Thus, at present, the evidence that anti-platelet agents prevent thrombosis in AVG is weak and certainly the combination of agents may cause harm with an increased bleeding risk.

Warfarin is commonly used (particularly in the USA)[9] as prophylaxis against thrombosis despite a lack of RCT evidence to support its use. Stemming from this practice, Crowther *et al.*[9] performed an RCT of low-dose warfarin (INR 1.4 to 1.9) for the prevention of AVG thrombosis. This study was well designed, with blinding of both patients and physicians by using central warfarin monitoring and sham INR values. One hundred and seven patients were enrolled with a follow-up over 2 years. Treatment with warfarin did not reduce the thrombosis rate in the treatment group and in fact there was a non-significant trend to an increased thrombosis rate in the warfarin group (HR 1.76, 95% CI 0.72, 4.34, $P = 0.21$). In addition, six major bleeding events occurred in the warfarin group compared to none in the placebo group ($P = 0.03$).

Finally, Schmitz *et al.*[10] performed a small RCT assessing fish oil (80% omega-3 fatty acid ethyl esters) versus a control oil (corn oil). Dietary administration of fish oils have been demonstrated to inhibit cyclooxygenase and to prolong bleeding times and evidence suggests that fish oil may inhibit intimal hyperplasia in autogenous vein grafts.[15] In this study, the administration of fish oil produced a significant reduction in the thrombosis rate, 24.4% versus 85.1% in the control group at 1 year ($P < 0.05$). Given the small sample size, a confirmatory trial with a larger sample size is needed to confirm not just efficacy but also safety, before treatment with fish oil can be recommended.

Systematic review

Da Silva and colleagues performed a systematic review that was published in 2003.[11] Three summary meta-analyses were presented for aspirin, ticlopidine and dipyridamole. For aspirin, three studies were assessed, each with a different

vascular access, making it difficult to interpret the results. One study assessed the AV (Scribner) shunt,[16] one the AVF[2] and one the AVG.[8] The overall treatment effect of aspirin was for a reduced risk of thrombosis (OR 0.42, 95% CI 0.20, 0.86, P = 0.02). A fixed effects model was presented although the test for heterogeneity was significant, which was likely due to the different vascular access populations and the trend to a negative effect of aspirin in the AVG trial. Overall, ticlopidine was associated with a significant reduction in AVF thrombosis when all three trials detailed above were combined (OR 0.47, 95% CI 0.26, 0.85, P = 0.01). As there was only one trial assessing dipyridamole, the results are as presented above for the study by Sreedhara *et al.*[8]

SUMMARY OF THE EVIDENCE

AVF primary failure

Three small RCTs have suggested a positive effect of anti-platelet agents on AVF primary failure.[2,3,5] However, a larger study did not confirm this effect although it was under-powered due to poor recruitment.[4] The systematic review suggests a possible positive effect for ticlopidine although the safety of this drug over other agents is an important issue, given the increased risk of severe neutropenia. Clopidogrel is currently under assessment in a large RCT with preliminary results recently presented (see 'Impending and ongoing randomised trials' section below).

AVG thrombosis

The effect of anti-platelet agents on AVG thrombosis is unclear, with both trials to date being largely negative.[6,8] Aspirin alone was associated with an increased rate of thrombosis in the only trial to date.[8] The use of aspirin and clopidogrel or warfarin are associated with increased adverse events without any benefit.[9] A small pilot study of fish oil demonstrated a significant benefit on AVG thromboses, which needs confirmation in a larger clinical trial.[10]

Impending and ongoing randomised trials

1. Fish oil and Aspirin in Vascular access Outcomes in Renal Disease: The FAVOURED Trial.[17]
This study aims to determine whether the use of the anti-platelet agents aspirin and fish oil, either alone or in combination (in a factorial design), will effectively reduce the risk of early thrombosis in de novo arteriovenous fistulae. The study population is patients with stage IV or V chronic kidney disease who require or will require haemodialysis, are scheduled to undergo creation of an AVF and are not currently taking anti-platelet agents (n = 1200). The primary outcome is patency of the AVF at 3 months after randomisation. Other outcomes include functional patency at 6 months, primary patency time, secondary (assisted) patency time, and adverse events, particularly bleeding. Trial recruitment is to commence in early 2008.

2. Dialysis Access Clinical Trials Consortium
Two randomised placebo-controlled clinical trials have been designed and run by the Dialysis Access Clinical Trials Consortium. The first trial is assessing the effects of dipyridamole on the prevention of stenosis in new arteriovenous grafts.[18] This study is still recruiting patients.

The second trial, the Clopidogrel Prevention of Early Fistula Thrombosis Trial[19] was designed to assess the effect of clopidogrel on early (6 week) AVF patency. Preliminary results were presented at the American Society of Nephrology Annual Meeting in November 2007. The trial was stopped early because the intervention was efficacious with regard to the primary outcome (patency at 6 weeks). At 6 weeks, 12.2% of the subjects in the clopidogrel group had thrombosis vs. 19% of subjects in the placebo group. However, for the secondary outcome, defined as suitability for dialysis, suitability failed in 63% of the clopidogrel group and in 60% of the placebo group. The full results of the trial are yet to be published.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1. Perform a large adequately powered randomised trial of aspirin on AVF primary failure or AVF thrombosis.
2. Perform a large adequately powered randomised trial of fish oil on AVF primary failure or AVF thrombosis.
3. Perform a large adequately powered randomised trial of clopidogrel on AVF primary failure or AVF thrombosis.
4. Perform a large adequately powered randomised trial of fish oil on AVG thrombosis.

CONFLICT OF INTEREST

Kevan Polkinghorne has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Randomised controlled trials of pharmacotherapy for AVF primary failure

Study ID	Access type	Number	Intervention	Control	Blinding	Intention-to-treat analysis	Outcome & follow up	Result (treatment vs placebo)
Andrassy *et al.* 1974[2]	AVF	92	Aspirin 500 mg	Placebo	Double	No	Thrombosis, 1 month	OR 0.15 (0.03, 0.73)*[a]
Fiskerstrand *et al.* 1985[3]	AVF	18	Ticlopidine 250 mg bd	Placebo	Double	No	Thrombosis, 1 month	OR 0.40 (0.05, 3.42)[a]
Grontoft *et al.* 1985[5]	AVF	36	Ticlopidine 250 mg bd	Placebo	Double	Yes	Thrombosis, 1 month	OR 0.13 (0.02, 0.76)*[a]
Grontoft *et al.* 1998[4]	AVF	261	Ticlopidine 250 mg bd	Placebo	Double	Yes	Thrombosis, 1 month	OR 0.60 (0.30, 1.18)[a]

RCT = randomised controlled trial; AVF = arteriovenous fistula; OR = odds ratio; [a]Results taken from systematic review by Da Silva *et al.* 2003; *P < 0.05.

Table 2 Randomised controlled trials of pharmacotherapy for AVG thrombosis

Study ID	Access type	Number	Intervention	Control	Blinding	Intention-to-treat analysis	Outcome & follow up	Result (treatment vs placebo)
Kobayashi *et al.* 1980[7]	Shunt/AVG/AVF[a]	107	Ticlopidine 200 mg bd	Placebo	Double	NS	Thrombosis, 3 months	↓ Thrombectomy***
Sreedhara *et al.* 1994[8]	AVG[b]	84	Dipyridamole 75 mg tds	Placebo	Double	NS	Thrombosis, 18 months	21% vs 42%***[c,d]
			Aspirin 325 od	Placebo				80% vs 42%[c,e]
			Dipyridamole + Aspirin	Placebo				75% vs 42%[c,f]
Schmitz *et al.* 2002[10]	AVG	24	Fish oil 4000 mg	Placebo	Double	Yes	Thrombosis, 12 months	24.4% vs 85.1%***
Crowther *et al.* 2002[9]	AVG	107	Warfarin (INR 1.4 - 1.9)	Placebo	Double	Yes	Thrombosis, 24 months	HR 1.76 (0.72, 4.34)
Kaufman *et al.* 2003[g6]	AVG	200	Clopidogrel + Aspirin	Placebo	Double	Yes	Thrombosis, 7 months	HR 0.81 (0.47, 1.40)

RCT = randomised controlled trial; AVG = arteriovenous graft; RR = relative risk; HR = hazard ratio; INR = international normalised ratio.
[a]Shunt n = 69 AVG n = 34 AVF n = 4; [b]New AVG only; [c]cumulative thrombosis rates at 18 months; [d]RR 0.35 (0.15, 0.80); [e]RR 1.99 (0.88, 4.48); [f]RR for this comparison not given in the paper; [g]This study was stopped early during recruitment due to adverse effects (see text); *** P < 0.05.