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Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts (Review)

Tanner NC, Da Silva A

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[Intervention Review]

Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts

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ABSTRACT

Background

End-stage renal disease (ESRD) patients often require either the formation of an arteriovenous (AV) fistula or an AV interposition prosthetic shunt for haemodialysis. These access sites should ideally have a long life and a low rate of complications (for example thrombosis, infection, stenosis, aneurysm formation and distal limb ischaemia). Although some of the complications may be unavoidable, any adjuvant technique or medical treatment aimed at decreasing complications would be welcome. This is the second update of the review first published in 2004.

Objectives

To assess the effects of adjuvant drug treatment in ESRD patients on haemodialysis via autologous AV fistulae or prosthetic interposition AV shunts.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched March 2015) and CENTRAL (2015, Issue 2).

Selection criteria

Randomised controlled trials (RCTs) of active drug versus placebo in people with ESRD undergoing haemodialysis via an AV fistula or prosthetic interposition AV graft.

Data collection and analysis

For this update, the two review authors (NCT, ADS) independently assessed trial quality and one review author (NCT) extracted data. Information on adverse events was collected from the trials. The primary outcome was the long-term fistula or graft patency rate. Secondary outcomes included duration of hospital stay, complications and number of related surgical interventions.

Main results

For this update, an additional six studies were deemed suitable for inclusion, making a total of 15 trials with 2230 participants. Overall the quality of the evidence was low due to short follow-up periods, heterogeneity between trials and moderate methodological quality of the studies due to incomplete reporting. Medical adjuvant treatments used in the trials were aspirin, ticlopidine, dipyridamole, dipyridamole plus aspirin, warfarin, fish oil, clopidogrel, sulphinpyrazone, and human type I pancreatic elastase (PRT-201). Where possible, the included studies were pooled into similar medical adjuvant groups for meta-analyses.

All included studies reported on graft patency by measuring graft thrombosis. There was insufficient evidence to determine if there was a difference in graft patency in studies comparing aspirin versus placebo (three RCTs, 175 participants) (odds ratio (OR) 0.40, 95% confidence interval (CI) 0.07 to 2.25; P = 0.30). The meta-analysis for graft patency comparing ticlopidine versus placebo (three RCTs, 339 participants) favoured ticlopidine (OR 0.45, 95% CI 0.25 to 0.82; P = 0.009). There was insufficient evidence to determine if there was a difference in graft patency in studies comparing fish oil versus placebo (two RCTs, 220 participants; OR 0.24, 95% CI 0.03 to 1.95; P = 0.18); and studies comparing clopidogrel and placebo (two RCTs, 959 participants; OR 0.40, 95% CI 0.13 to 1.19; P = 0.10). Similarly, there was insufficient evidence to determine if there was a difference in graft patency in three studies (306 participants) comparing PRT-201 versus placebo (OR 0.75, 95% CI 0.42 to 1.32; P = 0.31); in one trial comparing the effect of dipyridamole versus placebo (42 participants; OR 0.46, 95% CI 0.11 to 1.94, P = 0.29) and dipyridamole plus aspirin versus placebo (41 participants; OR 0.64, CI 0.16 to 2.56, P = 0.52); in one trial comparing low-dose warfarin with placebo (107 participants; OR 1.76, 95% CI 0.78 to 3.99, P = 0.17); and one trial (16 participants) comparing sulphinpyrazone versus placebo (OR 0.43, 95% CI 0.03 to 5.98, P = 0.53). The single trial evaluating warfarin was terminated early because of major bleeding events in the warfarin group. Only two studies published data on the secondary outcome of related interventions (surgical or radiological); there was insufficient evidence to determine if there was a difference in related interventions between placebo and treatment groups. No studies reported on the length of hospital stay and data reporting on complications was limited and varied between studies.

Authors' conclusions

The meta-analyses of three studies for ticlopidine (an anti-platelet treatment), which all used the same dose of treatment but with a short follow-up of only one month, suggest ticlopidine may have a beneficial effect as an adjuvant treatment to increase the patency of AV fistulae and grafts in the short term. There was insufficient evidence to determine if there was a difference in graft patency between placebo and other treatments such as aspirin, fish oil, clopidogrel, PRT-201, dipyridamole, dipyridamole plus aspirin, warfarin, and sulphinpyrazone. However, the quality of the evidence was low due to short follow-up periods, the small number of studies for each comparison, heterogeneity between trials and moderate methodological quality of the studies due to incomplete reporting. It, therefore, appears reasonable to suggest further prospective studies be undertaken to assess the use of these anti-platelet drugs in renal patients with an arteriovenous fistula or graft.

PLAIN LANGUAGE SUMMARY

Medical adjuvant treatment to increase the patency of arteriovenous fistulae and grafts used for renal dialysis

Background

People with advanced kidney disease (end-stage renal disease) need dialysis to perform kidney functions. In haemodialysis, blood is filtered through a machine. To allow a large enough passage for blood to flow between the person and the machine, an artery and a vein can be surgically joined (to form an arteriovenous fistula) or an artificial graft (a substitute for a vein) is used to join the artery to the vein. These access points might last for years but can become blocked or infected. This review investigates if additional medical therapy can keep these dialysis access points functioning.

Key results

The review authors found 15 randomised controlled trials (evidence current to March 2015) with a total of 2230 participants, of anti-platelet drugs (such as ticlopidine, aspirin, dipyridamole and clopidogrel) or anti-thrombotic and other drug treatments used to prevent blockages in the artery and vein access points for dialysis. Where possible, similar studies were pooled. Pooled data from three trials (339 participants) comparing ticlopidine (a platelet aggregation inhibitor) with placebo, showed improved blood flow at one month. There was insufficient evidence of an effect on blood flow from pooled data from three trials comparing aspirin with placebo (175 participants) or from two trials using fish oil for 12 months (220 participants). Three studies assessed the effect of human type I pancreatic elastase (PRT-201) with placebo in 306 participants. Overall the trials showed there was insufficient evidence of an effect on blood flow between active treatment (PRT-201) and placebo. Two trials compared clopidogrel with placebo in 959 participants and again showed there was insufficient evidence of an effect between the treatments. Single trials involving 16 to 36 participants compared dipyridamole, dipyridamole plus aspirin or sulphinpyrazone (a uricosuric drug) with placebo. The estimated effects were compatible with both benefits and harm. One trial comparing warfarin with placebo (107 participants) was terminated early because of major bleeding events in the warfarin group. Only two studies reported on related interventions (surgical or radiological); there was insufficient evidence of an effect on related interventions between placebo and treatment. No studies reported on the length of hospital stay and information on complications of treatment was limited and, if reported, varied from study to study. Most had a short follow-up period so that any benefits in the longer term are not clear.

Quality of the evidence

Overall the quality of the evidence was low due to short follow-up periods, small number of studies for each comparison, and differences between the studies (in follow-up time and dosages used). In addition the methodological quality of the studies was moderate due to incomplete reporting.

BACKGROUND

Description of the condition

End-stage renal disease (ESRD) patients continue to die prematurely despite continuing advances in our knowledge on dialysis. Renal patients on long-term haemodialysis require either an autologous (using the individual's own tissue) arteriovenous (AV) fistula (when an artery is connected to a vein) or an AV interposition prosthetic shunt (when an artery is connected to a vein through an artificial graft) for access. These access sites should ideally have a long life and a low rate of complications (for example thrombosis, infection, stenosis, aneurysm formation and distal limb ischaemia). Currently, there is no access type that fulfils all these criteria. However, long-term (up to four or five years) patency rates demonstrate that autologous AV fistulae have the best outcomes with fewer surgical interventions (Churchill 1992; Metha 1991; Pisoni 2002). Complications from haemodialysis access result in frequent hospitalisation of patients with ESRD and often require further intervention.

Why it is important to do this review

Although some of the complications may be unavoidable, any adjuvant technique or medical treatment aimed at decreasing complications would be welcome. It is recognised that up to 85% of cases of vascular access failure may be due to thrombosis caused by myointimal hyperplasia (proliferation of the cells lining the blood vessel), particularly in prosthetic grafts (Kanterman 1995). There is already some evidence suggesting that the formation of an autologous AV fistula may be preferable to prosthetic material and that graft surveillance programmes lead to improvements in long-term graft patency rates (National Kidney Foundation Dialysis Outcome Quality Initiative) (DOQI 1997). However, there is also some accumulating evidence that drug manipulation for patients with ESRD and autologous AV fistula (Dember 2008; Ghorbani 2009), and those with prosthetic interposition AV shunts (Lok 2012; Schmitz 2002), may confer additional benefits in terms of long-term patency and fewer complications.

OBJECTIVES

To assess the effects of adjuvant drug treatment in ESRD patients on haemodialysis via autologous AV fistulae or prosthetic interposition AV shunts.

The primary outcome measure was long-term graft patency rate, as outlined by life tables or Kaplan-Meier survival curves (Kaplan 1958). Secondary outcome measures included complications such as infection, aneurysm formation, distal limb ischaemia and need for surgical or radiological intervention.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials of active drug versus placebo in people with ESRD who were undergoing haemodialysis via an AV fistula or prosthetic interposition AV shunt. Any method of randomisation was accepted and differences in quality were taken into account in the analysis. Trials that were not analysed on an intention-to-treat basis were included provided that all randomised participants were accounted for.

Types of participants

People with ESRD and receiving haemodialysis through an AV fistula or a prosthetic AV shunt. All types of AV fistulae or AV prosthetic shunts positioned in the upper or lower limb, or at special sites (for example axillary artery to axillary vein), were considered. People on peritoneal dialysis, although they may have a patent AV fistula or interposition prosthetic AV shunt, were not included.

Types of interventions

Any drug therapy given to people with ESRD with the aim of improving the patency of AV fistulae or prosthetic grafts, compared with placebo. Examples included aspirin in AV fistulae (Andrassy 1974); and dipyridamole in AV prosthetic grafts (Sreedhara 1994).

We excluded studies investigating medical adjuvant therapy versus no treatment or intervention.

Types of outcome measures

Primary outcomes

The primary outcome measure considered was graft patency. It was intended to measure graft patency rates using life tables or Kaplan-Meier survival curves but the trials did not provide sufficient data to be pooled (Kaplan 1958). Future updates of this review will incorporate these measures if sufficient data become available.

Secondary outcomes

Secondary outcome measures included duration of hospital stay; complications such as infection, aneurysm formation, stenosis and distal limb ischaemia; and the number of related surgical or radiological interventions.

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases (PVD) Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched March 2015) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2015, Issue 2, part of the *Cochrane Library*, (www.cochranelibrary.com). See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in the *Cochrane Library* (www.cochranelibrary.com).

Searching other resources

The reference lists of all included and excluded studies were cross-checked for additional publications which may have been suitable.

Data collection and analysis

Selection of studies

For this update, one of the review authors (NCT) identified possible trials and the other review author (ADS) independently assessed the unblinded reports to confirm eligibility for inclusion in the review. Any disagreement was resolved by discussion.

Data extraction and management

Data were extracted independently by NCT using proformas designed by the Cochrane PVD Group. Discrepancies were discussed and reviewed by ADS. Data were extracted from the published reference papers directly. No attempt was made to obtain additional unpublished data. All analyses were based on endpoint data from the individual clinical trials. If several trials assessed the effect of the same adjuvant therapy (even if dosage was different) then results were amalgamated.

Assessment of risk of bias in included studies

The methodological quality of included trials was assessed independently by two review authors (NCT, ADS). Discrepancies were resolved by discussion. Quality was assessed using the 'Risk of bias' tool as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This assesses various domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and 'other bias') and determines the level of bias for each domain, namely 'low', 'high' or 'unclear' risk of bias. These assessments were reported for each individual study in the Risk of bias in included studies tables.

Measures of treatment effect

Statistical analysis was performed according to the statistical guidelines for authors in the Cochrane PVD Group information. Odds ratio (OR) with 95% confidence intervals (CI) were used as the measure of effect for each dichotomous outcome.

Unit of analysis issues

The participant was the unit of analysis.

Three trials had unit of analysis issues which required further evaluation by the review authors.

The Grontoft 1998 study had a non-standard design as it allowed people who had an initial failed AV fistula formation to re-enter the study after a three week 'washout period'. In addition, the published results had to be carefully interpreted as there was confusion between the number of participants within the study compared to the number of operations (i.e. AV fistulae formed), and participants who died were excluded from the published analysis.

Overall analysis for this review was undertaken using the number of operations performed on an 'intention-to-treat' basis.

The results of the Ghorbani 2009 study had to be carefully assessed by the review authors as the original data were not analysed on an 'intention-to-treat' basis, but analysed by the number of participants who completed the trial.

Grontoft 1985 also published their analysed results based on the number of participants who completed the trial, not an 'intention-to-treat' basis. It was not possible to use the intention-to-treat numbers because insufficient data regarding the original randomisation groups were provided. We therefore used the numbers of participants who completed the trial.

Dealing with missing data

Analysis was performed on a complete case basis and no attempt was made to contact study authors for further follow-up data. It was not necessary to contact authors for additional data.

Assessment of heterogeneity

Chi^2 tests were used to assess for heterogeneity between grouped trials, with P values lower than 0.2 being used as an indication of the possibility of the presence of significant heterogeneity. Some trials contained low participant numbers and therefore the power of this test is likely to be low if a small P value was used (Higgins 2011).

Assessment of reporting biases

There were insufficient studies identified to create funnel plots to assess reporting bias.

Data synthesis

Where there were sufficient data from more than one trial, a meta-analysis using a Mantel-Haenszel fixed-effect model was used. Where heterogeneity was identified (Chi^2 tests with P values lower than 0.2) we used a random-effects model. Review Manager 5 software was used for data synthesis (Review Manager 5).

Subgroup analysis and investigation of heterogeneity

No subgroup analysis was performed as insufficient data were available to perform additional subgroup analyses on infection, aneurysm formation and distal limb ischaemia.

Sensitivity analysis

Sensitivity analysis was not performed due to insufficient data.

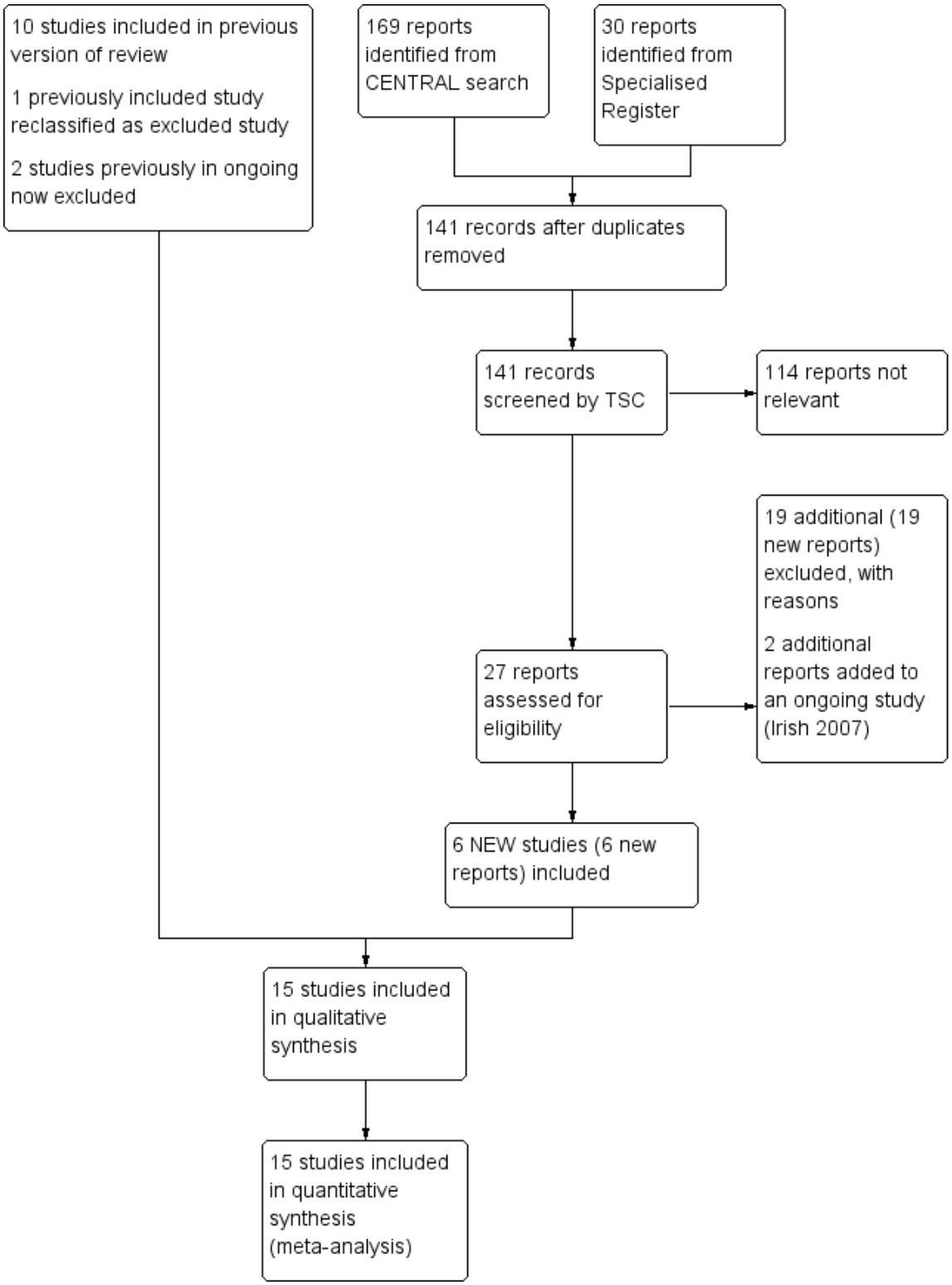
RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Fifteen randomised controlled trials fulfilled the criteria for consideration in the review (Andrassy 1974; Crowther 2002; Dember 2008; Dwivedi 2014; Fiskerstrand 1984; Ghorbani 2009; Grontoft 1985; Grontoft 1998; Harter 1979; Hye 2014; Lok 2012; Michie 1977; Peden 2013; Schmitz 2002; Sreedhara 1994). Twenty-six studies were excluded (Albert 1978; Alexopoulos 2011; Bhomi 2008; Chen 2013; D'Ayala 2008; De Fijter 1995; Dixon 2009; Dulude 2001; Fuster 2001; Janicki 2003; Kaegi 1975; Kaufman 2003; Kooistra 1994; Krasinski 2004; Lee 2009; Lin 2007; Lin 2013; Malovrh 2009; Mileti 1995; Radmilovic 1998; Rouzrokh 2009; Taber 1992; Trimarchi

2006; Wang 2010; Wasse 2014; Yuto 2012). One ongoing study was identified (Irish 2007).

Included studies

For this update an additional six studies were included (Dember 2008; Dwivedi 2014; Ghorbani 2009; Hye 2014; Lok 2012; Peden 2013), making a total of 15 included studies (Andrassy 1974; Crowther 2002; Dember 2008; Dwivedi 2014; Fiskerstrand 1984; Ghorbani 2009; Grontoft 1985; Grontoft 1998; Harter 1979; Hye 2014; Lok 2012; Michie 1977; Peden 2013; Schmitz 2002; Sreedhara 1994).

Three of the trials compared the effect of aspirin versus placebo and included a total of 175 participants (Andrassy 1974; Harter 1979; Sreedhara 1994). The follow-up time and the dosage of aspirin given were different in each of the trials. In Sreedhara 1994, 39 participants undergoing insertion of a new arteriovenous (AV) polytetrafluoroethylene (PTFE) graft were followed up for 18 months over a period of six years. Twenty participants received aspirin 325 mg once daily and the remainder received placebo. Andrassy 1974 included 92 participants undergoing Brescia-Cimino fistula formation. Of these, 45 participants received aspirin 500 mg once daily whereas the other 47 participants were given placebo. The total follow-up period was 28 days. Finally, the Harter trial included 44 participants undergoing AV shunt formation between the radial artery and the cephalic vein using silastic (silicone rubber) material with a Teflon adapter (Harter 1979). Nineteen participants received a single dose of 160 mg once-daily aspirin and 25 participants received placebo. The follow-up period was approximately five months.

Sreedhara 1994 also examined the effects of dipyridamole versus placebo with a total number of 42 participants in a parallel group trial over a six-year period. Twenty-three participants received dipyridamole at a dose of 75 mg three times a day; the other 19 received the equivalent placebo. All participants were followed up for 18 months.

In a separate arm of the trial, Sreedhara 1994 studied the effect a combination of dipyridamole and aspirin had versus placebo. Forty-one participants were involved (22 receiving dipyridamole 75 mg with 325 mg aspirin daily; 19 participants taking placebo).

Only type I participants (participants requiring a new AV expanded polytetrafluoroethylene (ePTFE) graft) were included in all analyses of this review. Additional data on type II participants (participants with an ePTFE graft which had thrombosed requiring thrombectomy or additional PTFE jump graft) was provided but not included for analysis as it was decided this cohort was high risk for thrombosis and did not meet our inclusion criteria.

Three trials compared ticlopidine with placebo, with a total number of 339 participants undergoing AV fistula formation or graft interposition (Fiskerstrand 1984; Grontoft 1985; Grontoft 1998). There were no separate data for participants undergoing either fistula formation or graft interposition. Each participant was given either 250 mg of ticlopidine twice daily or the equivalent placebo. All participants were followed up for one month in all three trials.

Two trials examined the effects of fish oil (4 g once daily) versus placebo, and included a total of 220 participants undergoing graft formation with a follow-up time of 12 months (Lok 2012; Schmitz 2002). In the Schmitz 2002 trial 24 participants were enrolled (12 participants received fish oil and 12 received an equivalent dose of a control oil). The primary outcome was graft thrombosis, but the authors did not state how patency was assessed. The Lok 2012 trial included 196 participants (99 participants received fish oil and 97 received a placebo oil capsule). The primary outcome was loss of native patency, which was defined as the graft having a primary event of thrombosis or requiring radiological or surgical intervention to maintain patency or promote maturation. However, they did provide separate data on graft thrombosis and this was included in the meta-analysis.

Crowther 2002 compared the effects of low intensity warfarin treatment (variable dose but a target international normalised ratio (INR) for prothrombin time of 1.4 to 1.9) with placebo. A total of 107 participants were randomised (56 to warfarin and 51 to placebo); all had newly placed PTFE grafts. How the authors assessed patency was not clear in that graft thrombosis was described as the "inability to dialyse or the need for immediate intervention to allow dialysis". This study was terminated early due a high rate of serious adverse events in the treatment arm.

Two trials compared the effects of clopidogrel versus placebo and included a total of 959 participants (Dember 2008; Ghorbani 2009). Dember 2008 assessed 866 participants for patency failure six weeks after native arteriovenous fistula formation. A total of 436 participants received a loading dose of 300 mg clopidogrel on postoperative day one followed by 75 mg daily; and 430 received matching placebo daily. Ghorbani 2009 compared 46 participants who received 75 mg clopidogrel daily with 47 who received placebo. Treatment was initiated 7 to 10 days prior to formation of a native arteriovenous fistula and continued for six weeks postoperatively. The primary outcome was fistula failure at eight weeks.

Michie 1977 compared the uricosuric drug sulphinpyrazone (200 mg four times daily) with placebo. Sixteen participants were randomised (eight to each group). There was heterogeneity across the treatment groups (six participants had AV fistulae and two had bovine interposition grafts in both groups). Participants were followed up for approximately three months or until 33 dialysis sessions had been undertaken.

Two trials from the same investigational group assessed the effect of a recombinant type I pancreatic elastase (PRT-201) applied directly to the adventitia of the inflow and outflow blood vessels of newly-created radiocephalic or brachiocephalic fistulae (Hye 2014; Peden 2013). The phase 1 trial compared 45 participants who received a variety of different doses of PRT-201 to 21 participants who received placebo (Peden 2013). The phase 2 trial compared 51 participants receiving placebo to 51 participants who received 10 µg, and 49 participants who received 30 µg, of PRT-201 (Hye 2014). All participants in both trials were followed up for 12 months. Dwivedi 2014 also investigated the effect of PRT-201 on AV grafts. This compared 28 participants who received placebo compared to 61 participants who received varying doses of PRT-201 applied directly to the vein-graft anastomosis and the adjacent outflow vein at the time of AV graft construction. All participants were followed up for 12 months.

In most studies, patency of AV shunts and grafts was assessed by detecting the presence of fistula or graft thrombosis. In the Andrassy 1974, Dember 2008 and Ghorbani 2009 studies, fistula clotting was detected by palpation (touch) and auscultation (listening with a stethoscope). In addition to those parameters, Sreedhara 1994 also included the presence of thrombus that was

noticed during introduction of the dialysis needle into the graft, whereas the Dwivedi 2014, Grontoft 1998, Peden 2013 and Hye 2014 studies added the use of Doppler technique to confirm the presence or absence of blood flow. The Harter study documented thrombosis by physical removal of thrombi from either the venous or arterial limbs of the shunt when dialysis was initiated (Harter 1979). The Crowther 2002 study defined graft thrombosis as an inability to dialyze or a need for immediate intervention to allow dialysis; and the earlier Grontoft 1985 study documented patency by simply stating that each fistula was assessed at regular intervals. The Lok 2012 study monitored participants biweekly and performed an angiogram if decreasing dialysis flow rates indicated stenosis. Michie 1977 used Doppler, ease of cannulation, palpation and auscultation to assess patency; there was no documentation of how patency was assessed in the Fiskerstrand or Schmitz studies (Fiskerstrand 1984; Schmitz 2002).

See Characteristics of included studies for further details.

Excluded studies

See Characteristics of excluded studies

For this update an additional 19 studies were excluded (Alexopoulos 2011; Bhomi 2008; Chen 2013; D'Ayala 2008; De Fijter 1995; Dixon 2009; Fuster 2001; Kooistra 1994; Lee 2009; Lin 2007; Lin 2013; Malovrh 2009; Mileti 1995; Rouzrokh 2009; Taber 1992; Trimarchi 2006; Wang 2010; Wasse 2014; Yuto 2012). In total 26 studies were excluded (Albert 1978; Alexopoulos 2011; Bhomi 2008; Chen 2013; D'Ayala 2008; De Fijter 1995; Dixon 2009; Dulude 2001; Fuster 2001; Janicki 2003; Kaegi 1975; Kaufman 2003; Kooistra 1994; Krasinski 2004; Lee 2009; Lin 2007; Lin 2013; Malovrh 2009; Mileti 1995; Radmilovic 1998; Rouzrokh 2009; Taber 1992; Trimarchi 2006; Wang 2010; Wasse 2014; Yuto 2012).

Thirteen published studies were reviewed as they appeared to meet the review inclusion criteria, but the study designs did not incorporate a placebo-controlled group (Albert 1978; Bhomi 2008; Chen 2013; D'Ayala 2008; Dixon 2009; Fuster 2001; Lee 2009; Lin 2007; Lin 2013; Malovrh 2009; Trimarchi 2006; Wang 2010; Yuto 2012); or were not randomised (Janicki 2003). These were therefore not deemed suitable for inclusion in the review. Trimarchi 2006 had been included in previous editions of this Cochrane review but on repeat evaluation it was concluded that the study did not meet inclusion criteria as there was no placebo-controlled arm to the trial. Malovrh 2009, evaluating the effect of blood volume expansion during surgery, did not use a suitable randomisation method or have placebo-controlled groups, and was deemed not to meet review criteria. Rouzrokh 2009 presented unclear results which included an assessment of fistula patency, but the timeframe of treatment or assessment was not documented. These data could not therefore be included for analysis. Wasse 2014 provided data on the percentage of participants who were successfully using their AV fistula or AV graft at six months but did not provide data to calculate the number of thromboses and therefore patency. There are multiple reasons why a fistula may not be used after creation besides loss of patency, therefore this study was excluded. A Dutch randomised placebo-controlled trial examined the effect of fish oil and placebo (De Fijter 1995). However the trial outcomes did not include fistula patency and participants included both those on haemodialysis and peritoneal dialysis. A single study examining the effect of sulphinpyrazone versus placebo was also considered (Kaegi 1975). Some of the participants also received warfarin either at the start or during the trial and, as the method for randomisation was not clearly concealed, this study was not included in this review. We excluded the Kooistra 1994 trial because long-standing (more than 6 weeks old) AV fistulae were assessed, and concurrent initiation of recombinant human erythropoietin with antiplatelet agent was studied, which we deemed a confounding factor. Another considered study analysed the effects of clopidogrel and aspirin versus placebo on rates of thrombosis in PTFE grafts (Kaufman 2003). However, the total number of thrombotic episodes in each group could not be determined from the results and so the study was excluded. A further trial examined the effects of pentoxifylline versus placebo on rates of thrombosis in external AV fistulae (Radmilovic 1998). As this method of fistula formation is now obsolete, the authors felt that including this study would be inappropriate. One trial sought to assess the effects of CJC-1004 (a locally acting anti-thrombotic agent) on graft occlusion (Dulude 2001). However, this was published as an abstract and, despite a literature search, no follow-up paper could be found. Similarly, no relevant data were published by Alexopoulos 2011, Krasinski 2004 and Taber 1992. One further reference to a study that appeared to meet the inclusion criteria was retrieved (Mileti 1995). The reference described the rationale and design of an ongoing study. No results have been published.

Risk of bias in included studies

The summarised data are included in the Characteristics of included studies table and Figure 2; Figure 3

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

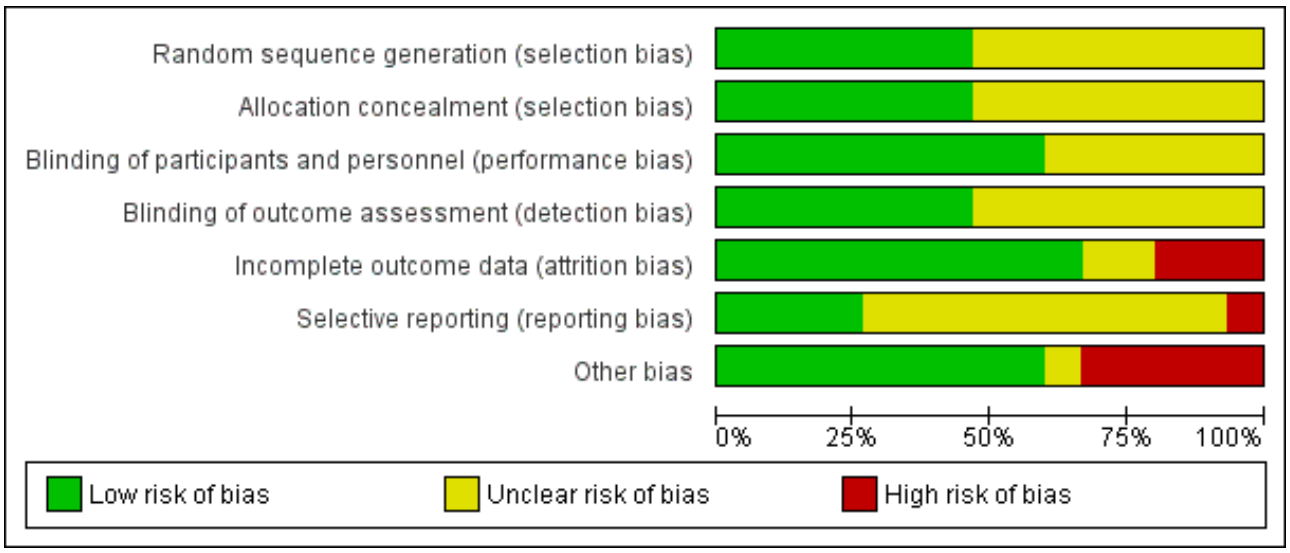
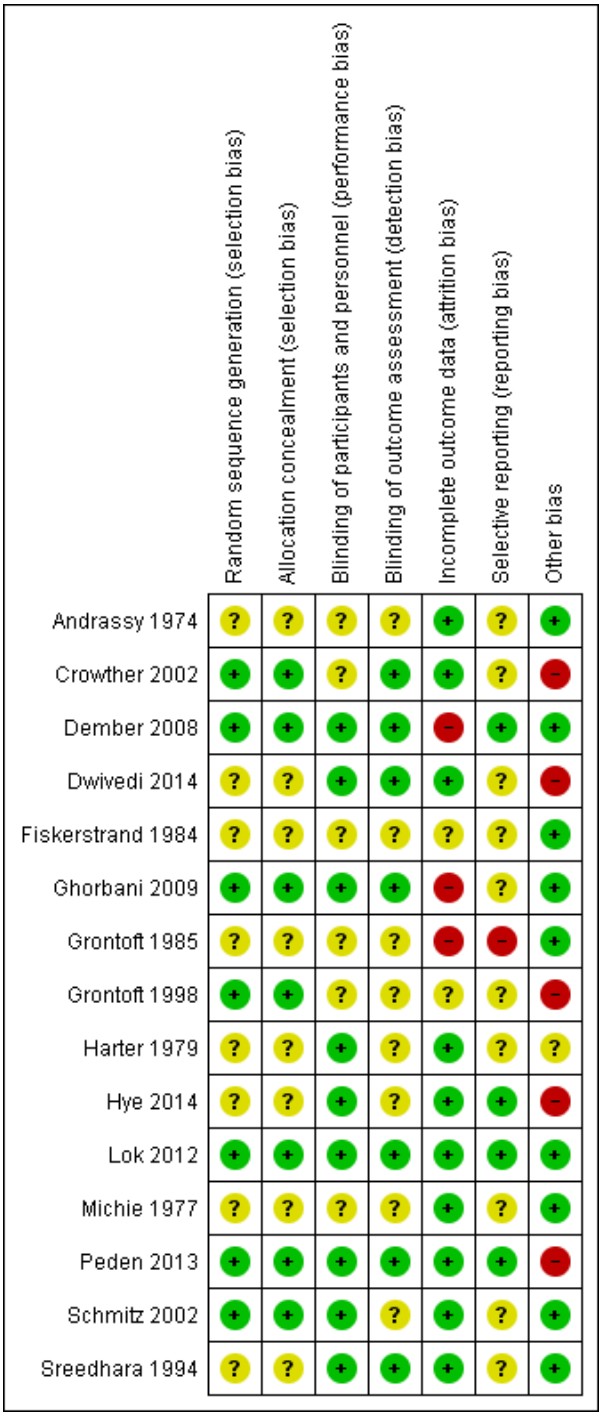


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Crowther 2002, Dember 2008, Ghorbani 2009, Lok 2012, Peden 2013, and Schmitz 2002 all utilised a permuted block randomisation schedule performed via an independent operator and so were deemed to have low risk of allocation bias. The Grontoft 1998 study used an independent statistician and a minimisation scheme based on four weighted stratification variables, implying that allocation concealment was acceptable.

Andrassy 1974 used an independent statistician but the precise method of randomisation was not stated, and Sreedhara 1994 stated a pre-determined schedule was used for randomisation but exact details were not provided. These were classed as having an unclear risk of selection bias.

Dwivedi 2014, Fiskerstrand 1984, Grontoft 1985, Harter 1979, Hye 2014, and Michie 1977 did not provide sufficient data to allow a judgement of bias.

Blinding

Dember 2008, Dwivedi 2014, Ghorbani 2009, Lok 2012, Peden 2013, and Sreedhara 1994 had thorough blinding of participants and assessors, providing a low risk of performance and detection bias.

Participants who developed a short-term indication for warfarin therapy were not excluded from analysis in the Crowther 2002 study and it is therefore unclear if there may have been a element of performance bias. However it is clear that detection bias was low risk as the clinical staff who assessed graft thrombosis were blinded to allocation assignment.

Harter 1979, Hye 2014, and Schmitz 2002 clearly stated that participants were blinded to treatment allocation, indicating a low risk of performance bias, but did not provide sufficient data on outcome assessment to allow a judgement of detection bias.

The Grontoft 1998 study allowed re-entry of participants into the study after secondary randomisation, and this may have lead to unblinding of the participants.

Andrassy 1974, Fiskerstrand 1984, Grontoft 1985, and Michie 1977 did not provide sufficient data to allow a judgement of bias.

Incomplete outcome data

Andrassy 1974, Harter 1979, Hye 2014, Lok 2012, Michie 1977, and Peden 2013 had no missing data and a low risk of attrition bias.

In the Schmitz 2002 study only one participant (out of 24) was lost to follow-up; and 12 (out of 107 randomised) within the Sreedhara 1994 study were lost to follow-up or did not complete the study. Both of these were deemed to have a low risk of attrition bias.

Crowther 2002 followed up all participants and ascertained the outcome for all participants, indicating a low risk of attrition bias. When data were analysed, participants who had a renal transplant, developed a clinical indication for the active treatment in this study (i.e. warfarin) or had their AV graft removed were censored.

Dember 2008 did not assess patency in 11 participants at six weeks and Ghorbani 2009 required re-analysis of the published data as the study authors did not perform analysis on an intention-to-treat basis but no participants were lost to follow-up. Eighteen participants did not complete the study protocol.

Dwivedi 2014 analysed all participants on an 'as-treated' basis although 50% of participants did not complete the study (45 out of 89). Reasons for non-completion included losses to follow-up, participant death, AV graft abandonment and recovery of renal function.

Grontoft 1985 performed analysis on the number of participants who completed the trial. As data were not provided within the publication of the initial randomisation groups it was therefore not possible to determine if, and how many, participants did not complete the trial.

In the Grontoft 1998 study, data were missing on one participant but an additional 17 participants could not have the AV fistulae or grafts evaluated. These were included in the data analysis though.

Fiskerstrand 1984 did not provide sufficient data to allow a judgement of bias.

Selective reporting

A pre-study protocol was not available in 10 studies and therefore it is not possible to determine if outcome reporting was selective (Andrassy 1974; Crowther 2002; Dwivedi 2014; Fiskerstrand 1984; Ghorbani 2009; Grontoft 1998; Harter 1979; Michie 1977; Schmitz 2002; Sreedhara 1994).

Dember 2008, Hye 2014, and Lok 2012 did not deviate from pre-study protocol-determined outcomes and have a low risk of reporting bias.

The authors of the Grontoft 1985 study provide an 'as treated' analysis, and additional data to permit an 'intention-to-treat' analysis was not provided.

Other potential sources of bias

Dwivedi 2014, Hye 2014 and Peden 2013 had a high risk of other bias as they were financially supported by Proteon Therapeutics who presumably supplied the recombinant human pancreatic elastase used.

The Crowther 2002 study protocol was changed after an interim analysis with regards to the dosing of warfarin, and 40% of participants also received additional antiplatelet therapy during the study period. This could have potentially influenced the study outcomes, including the high rate of bleeding reported in this study, and so was it judged to be at high risk of bias.

Other potential bias within studies include the re-entry of participants into randomisation after a washout period of three weeks if their first operation failed, which was permitted in the Grontoft 1998 study protocol. Harter 1979 did not have a pre-specified enrolment value, and protocol stated that enrolment would continue until 24 thrombi were observed so was judged as having an unclear risk of bias.

Andrassy 1974, Dember 2008, Fiskerstrand 1984, Ghorbani 2009, Grontoft 1985, Lok 2012, Michie 1977, Schmitz 2002, and Sreedhara 1994 had no obvious other source of bias and so were at low risk of bias.

Effects of interventions

Primary outcomes

Graft patency

For the primary outcome 'graft patency' the numbers recorded for analyses were the number of grafts that occluded during the specified time period as reported by the study authors. This should be kept in mind when interpreting the presented data.

Graft patency rates as outlined by life tables or Kaplan-Meier survival curves were not carried out as the description of the trials did not provide sufficient data (Kaplan 1958).

Aspirin versus placebo - Analysis 1.1

Andrassy 1974 reported that 2 out of 45 in the aspirin group developed a graft thrombosis compared with 11 out of 47 who received placebo (odds ratio (OR) 0.15, 95% confidence interval (CI) 0.03 to 0.73). In the Harter 1979 study, 6 out of 19 in the aspirin group developed a graft thrombosis compared with 18 out of 25 in the placebo group (OR 0.18, 95% CI 0.05 to 0.66). In the Sreedhara

1994 study, 10 out of 20 who received aspirin developed a graft thrombosis compared with 6 out of 19 on placebo (OR 2.17, 95% CI 0.59 to 7.99).

Due to evidence of heterogeneity (Chi^2 9.31, P = 0.01) we used a random-effects model meta-analysis. The overall results showed no differences between the treatments (OR 0.40, 95% CI 0.07 to 2.25). The overall P value was 0.30.

Ticlopidine versus placebo - Analysis 2.1

All three trials comparing ticlopidine with placebo favoured treatment (Fiskerstrand 1984; Grontoft 1985; Grontoft 1998). In the Fiskerstrand 1984 study, 2 out of 8 participants in the ticlopidine group compared with 5 out of 10 in the placebo group developed fistulae thromboses at one month (OR 0.33, 95% CI 0.04 to 2.52). In the earlier Grontoft study, only 2 out of 19 who received treatment developed fistulae thromboses compared to 8 out of 17 on placebo (OR 0.13, 95% CI 0.02 to 0.76) (Grontoft 1985). In Grontoft 1998, 16 out of 144 participants who received ticlopidine developed thromboses in their fistulae compared with 25 out of 141 in the placebo group (OR 0.58, 95% CI 0.30 to 1.14).

The overall result of the meta-analysis also favoured treatment (OR 0.45, 95% CI 0.25 to 0.82). The overall P value was 0.009.

Dipyridamole versus placebo - Analysis 3.1

The single trial that examined the effect of dipyridamole versus placebo followed participants for up to 18 months (Sreedhara 1994). Four out of 23 participants taking dipyridamole developed thrombosis compared to six out of 19 taking placebo. The overall result also favoured treatment (OR 0.46, 95% CI 0.11 to 1.94).

Dipyridamole + Aspirin versus placebo - Analysis 4.1

The Sreedhara trial also used a parallel group design to examine the effect of dipyridamole plus aspirin versus placebo (Sreedhara 1994). Five out of 22 participants who received a combination of dipyridamole and aspirin developed a graft thrombosis compared to 6 out of 19 who received placebo (OR 0.64, CI 0.16 to 2.56).

Warfarin versus placebo - Analysis 5.1

The single trial that examined the effect of low-intensity warfarin treatment versus placebo followed up participants for 37 months (before the trial was terminated prematurely due to a significant increase in bleeding seen in the treatment group) (Crowther 2002). The overall result favoured placebo (OR 1.76, CI 0.78 to 3.99) but this was not statistically significant (P = 0.17).

Fish oil versus placebo - Analysis 6.1

The Schmitz 2002 trial examined the effects of fish oil versus placebo on graft thrombosis. Two out of 12 participants taking fish oil developed a thrombosis compared with 9 out of 12 who received placebo. The overall result favoured fish oil (OR 0.07, 95% CI 0.01 to 0.49). In the Lok 2012 study 33 out of 99 participants taking fish oil had graft thrombosis at 12 months compared with 45 out of 97 who received placebo. (OR 0.58, 95% CI 0.32 to 1.03).

Due to evidence of heterogeneity (Chi^2 4.13, P = 0.04) we used a random-effects model meta-analysis. The overall results showed no differences between the treatments (OR 0.24, 95% CI 0.03 to 1.95). The overall P value was 0.18.

Clopidogrel versus placebo - Analysis 7.1

Dember 2008 reported that 53 out of 436 participants in the treatment group and 84 out of 430 in the placebo arm developed fistula thrombosis at six weeks (OR 0.57, 95% CI 0.39 to 0.83). In the Ghorbani study 2 out of the 46 participants in the clopidogrel group compared with 10 out of 47 in the placebo group had AVF failure at eight weeks (OR 0.17, 95% CI 0.03 to 0.82) (Ghorbani 2009).

Due to evidence of heterogeneity (Chi^2 2.18, P = 0.14) we used a random-effects model meta-analysis. The overall results showed no differences between the treatments (OR 0.40, 95% CI 0.13 to 1.19). The overall P value was 0.10.

Sulphinpyrazone versus placebo - Analysis 8.1

The Michie 1977 trial examined the effects of sulphinpyrazone versus placebo on native fistulae or bovine graft thrombosis. One out of eight participants taking sulphinpyrazone developed a graft thrombosis compared with two of eight taking placebo (although two participants in the placebo group did not complete the study protocol). The overall result favoured sulphinpyrazone (OR 0.43, 95% CI 0.03 to 5.98).

PRT-201 versus placebo – Analysis 9.1

Peden 2013 reported that 8 out of 45 participants in the treatment group (all doses of PRT-201 combined) and 3 out of 21 in the placebo arm developed fistula thrombosis at 12 months (OR 1.30, 95% CI 0.31 to 5.48). In the Hye 2014 study 14 out of the 100 participants in the treatment group (all doses of PRT-201 combined) compared with 12 out of 51 in the placebo group had AVF thrombosis within 12 months (OR 0.53, 95% CI 0.22 to 1.25). In the Dwivedi 2014 study looking at AV grafts, 26 out of 61 participants in the treatment group (all doses of PRT-201 combined) and 13 out of 28 in the placebo arm developed AV graft thrombosis at 12 months (OR 0.86, 95% CI 0.35 to 2.11).

The overall results of the meta-analysis favoured treatment (OR 0.75, 95% CI 0.42 to 1.32) but this was not statistically significant (P = 0.31).

Secondary outcomes

Data on the secondary outcome measures outlined in the 'Criteria for considering studies for this review' section were not specific enough to allow pooled analysis.

Duration of hospital stay

None of the studies included data on length of hospital stay.

Complications

The later Grontoft study reported data on a total of 45 complications, including hepatic, haematological, haemostatic, cutaneous, gastrointestinal, cardiovascular, and other miscellaneous complications affecting 30 participants on ticlopidine (Grontoft 1998). A total number of 39 complications were recorded in participants taking placebo. There were four deaths in the placebo group and two in the ticlopidine group.

The Crowther study also included information on bleeding complications for participants receiving warfarin (Crowther 2002). Six major bleeds occurred in five participants: three upper gastrointestinal (GI) bleeds, one cerebral haematoma after a road

traffic accident, and one femoral artery injury after coronary angiography. All five of the participants were also taking anti-platelet therapy at the time of the bleeding event. A further 18 participants (7 allocated to placebo) experienced a minor bleeding event, however according to the study authors there was no significant difference between the two groups (P = 0.30). There were five deaths in the treatment group and seven in the placebo group.

Dember 2008 also reported data on bleeding complications and mortality occurring within 30 days of completion of study medications for participants taking clopidogrel and placebo. Overall, bleeding events were similar for both groups (2.9% versus 2.8% respectively, P = 0.84) as was all-cause mortality (0.9 in both groups) as reported by the study authors.

The Ghorbani study evaluating the effects of clopidogrel included information on bleeding and mortality (Ghorbani 2009). GI bleeding was reported in 2.1% of the treatment group and 3.2% of the placebo group (P = 0.31), and non-GI tract bleeding in 5.3% and 4.3% respectively (P = 0.63). There were two mortalities in both groups. There was no severe bleeding during the active treatment period and no deaths were attributable to bleeding.

Sreedhara 1994 stated that 34 participants experienced adverse events which resulted in discontinuation of study medication (combination of dipyridamole, aspirin or placebo). These participants were considered to have completed the study protocol however. The most common adverse events were GI bleeding and nausea across all study groups. There were also seven mortalities during the study.

Lok 2012 did include data on mortality, reporting that 16 participants died (8 in each group) after starting the study medication but before 12 months of follow-up were completed.

The only adverse event reported by Fiskerstrand 1984 was the development of a rash in a single participant treated with ticlopidine. No data on mortality were stated.

The Andrassy study comparing aspirin and placebo reported a greater risk of gastric pain and epistaxis (11% aspirin: 4% placebo) for participants but the risk of GI bleeding or wound hematoma was the same in both groups (4% in both arms) (Andrassy 1974).

Dwivedi 2014, Peden 2013 and Hye 2014 listed several adverse events including local symptoms secondary to the creation of a new AV fistula but according to the study authors there were no significant differences between placebo and PRT-201-treated participants.

Number of related radiological or surgical interventions

The Lok study comparing fish oil and placebo reported data on several complications, including a reduced number of radiological/surgical interventions in the intervention group but this was not significant (38 out of 99 versus 48 out of 97) (OR 0.64, 95% CI 0.36 to 1.12; P = 0.12) (Lok 2012).

Also, Dember 2008 studied clopidogrel versus placebo and reported the frequency of additional interventions required to maintain patency in AV fistulae but this was not statistically significant (7 out of 436 participants taking clopidogrel and 10 out of 430 taking placebo) (OR 0.69, 95% CI 0.26 to 1.82; P = 0.45).

The Dwivedi 2014 study comparing various doses of PRT-201 versus placebo calculated the rate of all procedures required to restore or maintain patency as a mean number per participant per year. There was no statistically significant difference between groups according to the study authors (4.4 for the placebo group versus 3.3 for all doses of PRT-201).

Subgroup and sensitivity analyses

No subgroup or sensitivity analyses were undertaken due to insufficient data.

DISCUSSION

Summary of main results

All but three (Crowther 2002; Peden 2013; Sreedhara 1994) of the 14 included studies revealed a beneficial effect with the active drug. However, there may be an element of bias due to clinical heterogeneity with the dose and length of follow-up in the aspirin trials. In addition, one of the aspirin trials was conducted over 40 years ago with a relatively high dose of aspirin (500 mg/once daily) (Andrassy 1974). It should be noted that there was a marked discrepancy between results in the aspirin versus placebo trials, with Sreedhara 1994 favouring placebo and the Andrassy 1974 and Harter 1979 studies favouring treatment. The authors in the Sreedhara study postulate several possible biochemical and pharmacological actions of aspirin that may have worsened its results.

The results in the ticlopidine trials clearly favoured anti-platelet treatment, using a dose of 250 mg twice daily, although the follow-up time was only one month (Fiskerstrand 1984; Grontoft 1985; Grontoft 1998).

The Crowther study, comparing warfarin against placebo, had the longest follow-up at 37 months (Crowther 2002). Despite this, there was no beneficial effect on the group of participants treated with warfarin. This study was stopped prematurely due to serious side effects. Therefore, the risk-benefit does not favour anticoagulation unless there is another established indication.

Schmitz 2002 and Lok 2012 studied the effect of fish oil on graft patency and both trials favoured treatment. However, there was statistically significant heterogeneity between the trials (despite the same dose and length of follow-up) and the random-effects meta-analysis showed no difference between the treatments.

Michie 1977 appears to show a benefit in terms of reducing graft thrombosis in participants treated with sulphinpyrazone. However, this study was conducted over 30 years ago with relatively small participant numbers and over a short follow-up period (three months). Again, there is insufficient evidence from a single trial to recommend its use.

The clopidogrel versus placebo trials showed a beneficial effect in favour of 75 mg/day clopidogrel but the random-effects meta-analysis showed no difference between treatment (Dember 2008; Ghorbani 2009). There was statistical heterogeneity and the weighting of the meta-analysis was biased towards the much larger Dember trial (Dember 2008).

Finally, Peden 2013, Hye 2014 and Dwivedi 2014 studied the effect of PRT-201 versus placebo. The Peden 2013 and Hye 2014 studies

were phase 1 and phase 2 trials using a variety of active treatment doses (range 3.3 µg to 9000 µg) on AV fistulae. The follow-up for both trials was 12 months. Peden 2013 and Hye 2014 did not find a difference between treatment and placebo. Dwivedi 2014 looked at AV grafts but again used a variety of treatment doses (0.01 mg to 9.0 mg). Outcomes were reported after 12 months, and showed a non-significant benefit in favour of treatment. The overall meta-analysis of the three studies showed there was insufficient evidence of, and effect on, graft patency between PRT-201 and placebo.

It appears, therefore, that at least in the short term anti-platelet drugs such as ticlopidine may have some clinical advantages compared with placebo. No trials with follow-up longer than 36 months demonstrated a beneficial effect of anti-thrombotic or anti-platelet treatment to increase patency of arteriovenous fistulae and grafts, thus their long-term effect remains unclear.

Overall completeness and applicability of evidence

Many of the comparisons included only one or two studies while data on the secondary outcome measures outlined in the 'Criteria for considering studies for this review' section were not specific enough to allow pooled analysis.

As mentioned above, no trials with follow-up longer than 36 months demonstrated a beneficial effect of anti-thrombotic or anti-platelet treatment to increase patency of arteriovenous fistulae and grafts, thus their long-term effect remains unclear.

Quality of the evidence

The limitations of this meta-analysis deserve to be mentioned. Firstly, some of the trials are not recent (the most recent was from 2014 but three are 30 or more years old). Additionally, most of the trials had a short period of follow-up and many of the comparisons included only one or two studies. The methodological quality of the trials was moderate mainly due to the variation in detail provided in the study reports. Finally, there is evidence of heterogeneity in the aspirin, fish oil and clopidogrel trials. Therefore the overall quality of the evidence within this review is classed as low.

Potential biases in the review process

A thorough search for potential studies was performed.

For three trials unit of analysis issues were identified (Ghorbani 2009; Grontoft 1985; Grontoft 1998.

The Grontoft 1998 study had a non-standard design as it allowed participants who had an initial failed AV fistula formation to re-enter the study after a three week 'washout period'. According to the study authors 25 participants re-entered the trial (12 in placebo and 13 in ticlopidine group). In addition the published results had to be carefully interpreted as there was confusion between the number of participants within the study compared to the number of operations (i.e. AV fistulae formed), and participants who died were excluded from the published analysis. Overall analysis for this review was undertaken using the number of operations performed on an 'intention-to-treat' basis. In total 258 participants were randomised with a total of 285 operations.

The results of the Ghorbani 2009 study had to be carefully assessed by the review authors as the original data was not analysed on an 'intention-to-treat' basis, but analysed by the number of participants who completed the trial.

Grontoft 1985 also published their analysed results based on the number of participants who completed the trial, not on an 'intention-to-treat' basis. As review authors it was not possible to use the intention-to-treat numbers because insufficient data regarding the original randomisation groups were provided. We therefore used the numbers of participants who completed the trial.

For the primary outcome 'graft patency', the numbers recorded for analyses were the number of grafts that occluded during the specified time period as reported by the study authors. This should be kept in mind when interpreting the presented data.

Agreements and disagreements with other studies or reviews

A meta-analysis published by Coleman 2010 found a beneficial effect of antiplatelet agents in reducing thrombosis in arteriovenous fistulae but not with grafts. There is significant cross-over with our review however, as Coleman 2010 included 10 studies in total in their meta-analysis, and 8 of these studies are also included within our review. For our review Dixon 2009 was deemed not suitable for inclusion as there was cross-over between participants who were prescribed aspirin prior to the trial; and Kooistra 1994 assessed participants who had concurrent administration of recombinant human erythropoietin and aspirin, so this was deemed to be confounding.

AUTHORS' CONCLUSIONS

Implications for practice

The meta-analyses of three studies for ticlopidine (an anti-platelet treatment) which all used the same dose of treatment but with a short follow-up of only one month, suggest ticlopidine may have a beneficial effect as an adjuvant treatment to increase the patency of AV fistulae and grafts in the short term. There was insufficient evidence to determine if there was a difference in graft patency between placebo and other treatments such as aspirin, fish oil, clopidogrel, PRT-201, dipyridamole, dipyridamole plus aspirin, warfarin, and sulphinpyrazone. However, the quality of the evidence was low due to short follow-up periods, the small number of studies for each comparison, heterogeneity between trials, and moderate methodological quality of the studies due to incomplete reporting. It therefore appears reasonable to suggest further prospective studies be undertaken to assess the use of these anti-platelet drugs in renal patients with an arteriovenous fistula or graft.

Implications for research

Clearly there is a lack of evidence confirming the long-term effects of anti-platelet and anti-thrombotic drugs. Further randomised controlled trials with at least one or two years' follow-up are required to address these clinical issues.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andrassy 1974

Methods	Study design: randomised, double-blind clinical trial
Participants	Country: Germany No. of participants: 92 Age: not stated Gender: M = 50, F = 42 Inclusion criteria: end-stage renal failure Exclusion criteria: not stated
Interventions	Treatment: aspirin 500 mg daily (n = 45) Control: placebo (n = 47) Duration: started 1 day pre-operatively and continued for 28 days
Outcomes	Primary: fistula thrombosis, 28 days follow-up
Notes	Brescia-Cimino fistula formation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Independent statistician used but exact method not stated
Allocation concealment (selection bias)	Unclear risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided to assess
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	Low risk	Nil obvious

Crowther 2002

Methods	Study design: randomised, double-blind clinical trial
Participants	Country: Canada (2 university-based teaching hospitals & community dialysis unit) No. of participants: 107 Number of participants prematurely discontinuing: placebo: 11; warfarin: 12 Age: 20 to 85 years Gender: M = 61, F = 46 Inclusion criteria: haemodialysis-dependent or planned haemodialysis in near end-stage renal disease patients Exclusion criteria: recent major haemorrhage (within 6 months), allergy to warfarin, persistent thrombocytopenia, inability to take oral medications, already taking warfarin for other reasons at start of trial, expectation of recovery of renal function or life expectancy less than two months, lack of informed consent or inability to give informed consent
Interventions	Treatment: warfarin variable dose with target INR 1.4 to 1.9 Control: placebo Duration: 37 months. Initiation within 7 days of surgery
Outcomes	Primary: graft thrombosis
Notes	PTFE grafts Trial terminated November 2000 due to increased number of major bleeding events in treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Concealed computer-generated randomisation scheme in random permuted blocks of 4, with stratification by clinical centre, use of antiplatelet therapy and whether the graft was placed in a participant currently on haemodialysis or in anticipation of the need for haemodialysis
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants who developed a short-term indication for warfarin therapy (e.g. acute venous thrombosis) were not excluded from analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Graft thrombosis was determined by clinical staff blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who had a renal transplant or developed an indication for long-term warfarin therapy or if the graft was removed were censored. Complete follow-up and outcome ascertainment was achieved in all participants

Crowther 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	High risk	Protocol for warfarin dosing changed after interim analysis 40% of participants received antiplatelet therapy (ASA) during the study period

Dember 2008

Methods	Study design: multicenter, randomised, double-blind placebo-controlled clinical trial
Participants	Country: United States No. of participants randomised: 877 No. of participants who completed the trial: 799 (8 did not receive intervention as randomised, 70 discontinued study drug early) Age: mean age Treatment = 52.7 years; Placebo = 54.5 years Gender: M = 548 males, F = 329 females Inclusion criteria: individuals undergoing creation of a new upper extremity arteriovenous fistula Exclusion criteria: active bleeding or bleeding events requiring red blood cell transfusion within the previous 12 weeks, platelet count less than 75 x 10^3 µL, known coagulopathy, acute ulcer disease, systolic blood pressure > 200 mm Hg or diastolic blood pressure > 115 mm Hg, advanced liver disease, inability to discontinue antiplatelet or anticoagulant therapy including aspirin during the study drug period, pregnancy, and current substance abuse
Interventions	Treatment: loading dose of clopidogrel 300 mg on day 1 post-operation followed by 75 mg daily Control: placebo od Duration: 42 days total
Outcomes	Primary: thrombosis (patency failure) 6 weeks after fistula creation Secondary: failure to attain suitability for dialysis
Notes	Early termination of enrolment after fourth interim analysis, when study information fraction had reached 0.813

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated permuted block randomisation with stratification by location of fistula and by centre
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that participants and members of the study team were blinded to treatment assignment. Placebo and the study drug were provided by the same company

Dember 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was performed by trained study personnel who were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Results re-analysed by review authors
Selective reporting (reporting bias)	Low risk	Pre-study protocol available
Other bias	Low risk	Nil obvious

Dwivedi 2014

Methods	Study design: randomised, double-blind, placebo-controlled, phase 1-2, single-dose escalation study
Participants	Country: United States No. of participants randomised: 115 No. of participants who received allocated intervention: 89 Age: placebo 60 ± 13, all PRT-201 56 ± 12 Gender (%): placebo: 61% M, all PRT-201 48% M Inclusion criteria: at least 18 years of age with chronic kidney disease either receiving maintenance haemodialysis or expected to commence within 3 months Exclusion criteria: alpha 1-antitrypsin deficiency and suspected ipsilateral outflow vein or central vein lumen stenosis or occlusion
Interventions	Treatment: single application of: *Low dose* [0.01, 0.03 mg] PRT-201 (n = 24) *Medium dose* [0.1, 0.3, 1.0 mg] PRT-201 (n = 12) *High dose* [3.0, 6.0, 9.0 mg] PRT-201 (n = 25) Control: placebo (n = 28) Duration: 2.5 mL of solution or placebo were administered as a series of drops over a period of 10 minutes to the exposed graft-vein anastomosis and the adjacent outflow vein at the time of AVG creation. The wound was then lavaged with saline for one minute
Outcomes	Primary: proportion with > 25% intraoperative increase in diameter of AVG outflow vein Others: change and percentage change in diameter of AVG outflow vein, change and percentage change in the intraoperative blood flow volume, primary unassisted patency and secondary patency loss
Notes	Only arteriovenous grafts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Dwivedi 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States that investigator, clinical staff, participants and central readers of digital photographs were blinded. The research pharmacist who mixed the treatment solutions was the only unblinded personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assumed based on above
Incomplete outcome data (attrition bias) All outcomes	Low risk	45 participants did not complete the study, but analysis completed on all participants 'as treated'
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	High risk	1) There was a participant who crossed-over after being randomised from the placebo group to the treatment group due to pharmacist error 2) The study was supported financially by Proteon Therapeutics

Fiskerstrand 1984

Methods	Study design: randomised, double-blind, clinical trial
Participants	Country: United Kingdom No. of participants recruited: 18 No. of participants who completed the trial: 15 Age: not stated Gender: not stated Inclusion criteria: patients requiring access surgery for chronic haemodialysis Exclusion criteria: patients requiring anti-platelet or anticoagulant therapy; history of peptic ulcer; known bleeding disorder; platelet count < 100,000/mm^3
Interventions	Treatment: ticlopidine 250 mg bid Control: placebo bid Duration: medication started two days pre-operatively and continued for one month postoperation
Outcomes	Primary: fistula thrombosis
Notes	Brescia-Cimino AVF

Risk of bias

Bias	Authors' judgement	Support for judgement

Fiskerstrand 1984 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient data provided to assess
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient data provided to assess
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient data provided to assess
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data provided to assess
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	Low risk	Nil obvious

Ghorbani 2009

Methods	Study design: randomised, double-blind clinical trial
Participants	Country: Iran No. of participants randomised: 93 No. of participants who completed the trial: 75 (6 withdrew consent, 11 participants developed complications, 1 participant died) Age: mean age in years 45.03 ± 1.2 Gender: M = 48, F = 45 Inclusion criteria: individuals ≥ 18 years undergoing haemodialysis requiring a primary AVF or requiring a new AVF at a different site Exclusion criteria: history of gastrointestinal bleeding or previous bleeding episodes within six months prior to the initiation of the study; patients already receiving chronic anticoagulation therapy (antiplatelet agents or warfarin); terminal or life-threatening disease; pregnancy; malignant hypertension; platelet count of < 100,000/mm^3; and other demonstrated medical condition that would make antiplatelet therapy dangerous
Interventions	Treatment: clopidogrel 75 mg daily Control: matching placebo od Duration: initiated 7 to 10 days prior to scheduled surgery and continued for up to six weeks postoperatively Total follow-up: six months
Outcomes	Primary outcome: incidence of primary AVF failure eight weeks after fistula formation

Ghorbani 2009 *(Continued)*

	Secondary outcome: incidence of successful haemodialysis within six months of fistula formation
Notes	Autologous AV fistulae

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation schedule by central coordinating centre with stratification according to medical centre
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that participants and medical personnel were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Fistula failure was determined by either the study coordinator or site principal investigator who was blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Re-analysis of results performed as authors did not analyse on an intention-to-treat basis
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	Low risk	Nil obvious

Grontoft 1985

Methods	Study design: randomised, double-blind clinical trial
Participants	Country: Sweden No. of participants recruited: 42 No. of participants who completed the trial: 36 Losses to follow-up: 3 received artificial grafts, 1 received other form of anticoagulant and 2 serious side effects suspected Age: 24 to 72 years Gender: M = 28, F = 14 Inclusion criteria: patients undergoing fistula operation Exclusion criteria: patients with bleeding tendency; reduced platelet counts; receiving anticoagulants, anti-inflammatories or platelet aggregation inhibitors
Interventions	Treatment: ticlopidine 250 mg bid Control: placebo bid

Grontoft 1985 *(Continued)*

	Duration: 2 days pre- and 4 weeks postoperative
Outcomes	Fistula thrombosis Platelet aggregation
Notes	Native AV fistulae

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient data provided to assess
Allocation concealment (selection bias)	Unclear risk	Insufficient data provided to assess
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient data provided to assess
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient data provided to assess
Incomplete outcome data (attrition bias) All outcomes	High risk	Initial randomisation groups not stated prior to exclusions, therefore analysis completed on the number who completed the trial
Selective reporting (reporting bias)	High risk	Authors provide 'as treated' analysis, not on an 'intention-to-treat' basis
Other bias	Low risk	Nil obvious

Grontoft 1998

Methods	Study design: randomised, double-blind, multicentre, clinical trial
Participants	Country: Sweden and Finland (8 Swedish, 1 Finnish centre) No. of participants recruited: 258 (285 operations) Non-evaluability amongst randomised operations: consent withdrawn = 2, no medication taken = 4, no new anastomosis = 11, no data recovered = 1 Age: placebo 58 ± 15, ticlopidine 56 ± 15 Gender: placebo M = 77, F = 47; ticlopidine M = 75, F = 43 Inclusion criteria: patients with chronic renal failure predialysis or on dialysis; patients requiring AVF Patients in whom first operation failed could be re-entered after washout period Exclusion criteria: patients requiring anti-platelet or anticoagulant therapy; history of hepatic disease; severe or malignant hypertension; gastrointestinal ulcer; bleeding disorder; reduced white blood cells or platelets
Interventions	Treatment: ticlopidine 250 mg bid

Grontoft 1998 *(Continued)*

	Control: placebo bid Duration: aim to start 7 days (minimum 3 days) pre- and 28 days post-surgery
Outcomes	Primary: fistula thrombosis Secondary: Biochemical markers: urea, haemoglobin and cholesterol levels
Notes	Native AV fistulae, transposition grafts and synthetic grafts Recruitment interrupted for 4 months due to serious adverse event

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Minimisation scheme based on the 4 weighted stratification variables of the participating centre
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Potential risk due to the re-entry of certain participants into randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Potential risk due to the re-entry of certain participants into randomisation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data missing on 267 operations
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	High risk	Participants in whom the first operation failed could be re-entered after a 3-week washout period

Harter 1979

Methods	Study design: randomised, double-blind, clinical trial
Participants	Country: United States No. of participants: 44 Age: aspirin 53 ± 14 years, placebo 46 ± 16 years Gender: M = 20, F = 24 Inclusion criteria: patients undergoing chronic haemodialysis Exclusion criteria: recent gastrointestinal bleeding
Interventions	Treatment: aspirin 160 mg/day

Harter 1979 *(Continued)*

	Control: placebo Duration: aspirin or placebo started 1 month postoperation and continued for approximately 5 months
Outcomes	Primary: graft thrombosis
Notes	AV shunts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated Unequal group sizes
Allocation concealment (selection bias)	Unclear risk	Insufficient data to assess
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that participants and members of the study team were blinded to treatment assignment. Placebo and the study drug were provided by the same company
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient data to assess
Incomplete outcome data (attrition bias) All outcomes	Low risk	31 participants completed the study
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	Unclear risk	No pre-specified enrolment value. Enrolment would continue until 24 thrombi were observed.

Hye 2014

Methods	Study design: randomised, double-blind, placebo-controlled phase 2 clinical trial
Participants	Country: United States No. of participants randomised: 169 No. of participants who received allocated intervention: 151 Age: placebo 59 ± 15, *10 µg PRT-201* 59 ± 18, *30 µg PRT-201* 59 ± 15 Gender: placebo 63% M, *10 µg PRT-201* 55% M, *30 µg PRT-201* 55% M Inclusion criteria: at least 18 years of age with chronic kidney failure either receiving maintenance haemodialysis or expected to commence within 6 months and required creation of an AVF Exclusion criteria: not stated
Interventions	Treatment: single application of: *10 µg PRT-201* (n = 59)

Hye 2014 *(Continued)*

	30 µg PRT-201 (n = 53) Control: placebo (n = 57) Duration: 2.5 mL of solution or placebo were administered over a period of 10 minutes to the exposed inflow artery, anastomosis and outflow vein at the time of AVF creation. The wound was then lavaged with saline for one minute
Outcomes	Primary: primary patency Secondary: secondary patency, unassisted maturation, use for haemodialysis, lumen stenosis
Notes	Only radiocephalic or brachiocephalic autologous fistulae

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded to treatment received. Not stated if personnel were blinded but as study is reported as double blind, we assume a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessor of fistula patency not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	24 participants did not complete the study. 'Intention-to-treat' analysis performed
Selective reporting (reporting bias)	Low risk	Pre-study protocol available
Other bias	High risk	The study was supported financially by Proteon Therapeutics

Lok 2012

Methods	Study design: multicenter, randomised, placebo-controlled clinical trial
Participants	Country: 12 Canadian and 3 United States sites No. of participants randomised: 201 No. of participants who started the study intervention: 196 No. of participants who completed the trial: 164 (5 excluded prior to receiving treatment, 32 did not complete 12 months follow-up) Age: 27 to 88 years Gender: M = 98, F = 98

Lok 2012 *(Continued)*

	Inclusion criteria: adults (≥ 18 years) who required a synthetic arteriovenous graft for chronic haemodialysis. The graft could be either a 'first access' or a 'subsequent access' after a previously failed access Exclusion criteria: reversible renal failure; active malignancy; pregnancy; malignant hypertension; active major bleed in the prior month; receiving more than 2 antiplatelet agents or anticoagulants; life expectancy less than 6 months; surgical revision of a previous access; arteriovenous graft that failed prior to and including postoperative day 7; ingestion of any form of fish oil at time of randomisation; allergy to fish or fish products; enrolment in another interventional study of arteriovenous grafts
Interventions	Treatment: four 1 gram fish oil capsules per day. Each capsule was MEG-3 (Ocean Nutrition Canada Ltd), which contained 48% (400 mg/capsule) eicosapentaenoic acid (EPA) and 25% (200 mg/capsule) docosahexaenoic acid (DHA) Control: 4 placebo capsules per day containing 1% peppermint-flavoured corn oil Duration: 12 months
Outcomes	Primary: proportion with loss of native patency within 12 months Secondary: rate and proportion of graft thrombosis, proportion with radiological or surgical intervention, cumulative graft patency, cardiovascular outcomes
Notes	Synthetic arteriovenous grafts Premature termination due to slow recruitment and lack of additional funds decreased study power from 80% to 74%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Concealed allocation by central independent randomisation facility with stratification by site and first access or subsequent access
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that participants, study coordinators, care-givers and site pharmacists were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment undertaken by an independent assessor who was blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five participants excluded after randomisation, but before treatment initiated. All participants were included in the primary analysis, even if they didn't complete follow-up
Selective reporting (reporting bias)	Low risk	Pre-study protocol available
Other bias	Low risk	Nil obvious

Michie 1977

Methods	Study design: randomised, double-blind, parallel-group trial
Participants	Country: United States No. of participants: 16 No. of participants who completed the protocol = 14 (1 lost to FU, 1 died) Age: 31 to 64 years Gender: M = 10, F = 8 Race: Negro = 15, Caucasian = 1 Inclusion criteria: chronic renal failure scheduled to begin haemodialysis Exclusion criteria: not stated Paticipants were not allowed to take acetylsalicylic acid or products containing this drug or other drugs known to modify platelet functions during the experiment period
Interventions	Treatment: sulphinpyrazone 200 mg qds Control: placebo qds Duration: initiated 2 days prior to surgery and continued for nearly 3 months (33 dialysis sessions)
Outcomes	Primary: graft thrombosis Secondary: haematological variables
Notes	AV fistulae and bovine grafts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient data provided
Allocation concealment (selection bias)	Unclear risk	Insufficient data provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient data provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient data provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 participants completed the study. All randomised participants received the appropriate treatment
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available

Michie 1977 *(Continued)*

Other bias	Low risk	Nil obvious

Peden 2013

Methods	Study design: randomised, double-blind, placebo-controlled, phase 1-2, dose-escalation study
Participants	Country: United States No. of participants randomised: 66 Age: placebo 52 ± 17, all PRT-201 57 ± 15 Gender: placebo 71% M, all PRT-201 73% M Inclusion criteria: at least 18 years of age with chronic kidney failure either receiving maintenance haemodialysis or expected to commence within 6 months and required creation of an AVF Exclusion criteria: alpha 1-antitrypsin deficiency; cephalic vein lumen diameter by ultrasound < 2.0 mm with a tourniquet; lack of continuity of the cephalic vein with the subclavian vein; central venous stenosis or occlusion; and treatment with any investigational agent within 30 days or investigational antibody therapy within 90 days of signing the informed consent document
Interventions	Treatment: single application of: *Low dose* [0.0033, 0.01, 0.033 mg] PRT-201 (n = 16) *Medium dose* [0.1, 0.33, 1.0 mg] PRT-201 (n = 17) *High dose* [3.0, 6.0, 9.0 mg] PRT-201 (n = 12) Control: placebo (n = 21) Duration: 2.5 mL of solution or placebo were administered over a period of 10 minutes to the exposed inflow artery, anastomosis and outflow vein at the time of AVF creation. The wound was then lavaged with saline for one minute
Outcomes	Unassisted primary and secondary patency Others include: intra-operative increase in AVF outflow vein diameter or blood flow, AVF maturation, incidence of stenosis and time to use
Notes	Only radiocephalic or brachiocephalic autologous fistulae

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation sequence in blocks of 6 without stratification
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that participants, investigators, clinical staff and the central reader of photographs and ultrasound were all blinded. The research pharmacist who mixed the treatment solutions was the only unblinded person
Blinding of outcome assessment (detection bias)	Low risk	Assessor was blinded

Peden 2013 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants did not complete the study, but were included in the analysis
Selective reporting (reporting bias)	Low risk	An ad hoc subgroup analysis for early surgical failures was undertaken
Other bias	High risk	1) There was a participant who crossed-over after being randomised from the placebo group to the treatment group due to pharmacist error 2) The study was supported financially by Proteon Therapeutics

Schmitz 2002

Methods	Study design: randomised, double-blind clinical trial
Participants	Country: United States No. of participants: 24 Age: 46 to 58 years Gender: M = 11, F = 13 Inclusion criteria: newly placed PTFE graft Exclusion criteria: patients needing fistula revision; history of gastro-intestinal bleeding; already taking warfarin or an anti-platelet agent; terminal or life-threatening disease; pregnancy; or malignant hypertension
Interventions	Treatment: 4000 mg fish oil once daily Control: placebo od Duration: 12 months (medication started within 2 weeks of graft placement)
Outcomes	Primary: graft thrombosis
Notes	PTFE grafts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Permuted block randomisation scale
Allocation concealment (selection bias)	Low risk	No pre-allocation bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and treatment capsules manufactured by the same company

Schmitz 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to assess
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants received the appropriate treatment. Only one was lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	Low risk	Nil obvious

Sreedhara 1994

Methods	Study design: randomised, double-blind, parallel group study
Participants	Country: United States No. of participants recruited: 108 No. of participants randomised: 107 (1 participant excluded after receiving Brescia-Cimino fistula) Type I patients = 84 (patients who required a new AV ePTFE graft for chronic HD) Type II patients = 23 (patients on chronic HD with AV ePTFE with graft thrombosis requiring new graft) No. of participants who completed the protocol: 96 (2 lost to FU, 9 withdrew consent or had transplant - all Type I patients) Age: mean age 54.4 years, range 19 to 84 Gender: M = 45, F = 63 Inclusion criteria: type I patients: patients who required a new AV ePTFE graft for chronic HD; type II patients: patients on chronic HD with AV ePTFE with graft thrombosis requiring new graft Exclusion criteria: uncontrolled hypertension; history of peptic ulcer disease; haemophilia; von Willebrand's disease; other bleeding disorders; malignancy; hypersensitivity to the study drugs
Interventions	1. Dipyridamole 75 mg tid with aspirin placebo od 2. Dipyridamole placebo tid with aspirin 325 mg od 3. Dipyridamole 75 mg tid with aspirin 325 mg od 4. Dipyridamole placebo tid with aspirin placebo od Duration: aim to start 2 days pre-op and continue for 18 months or until graft thrombosis
Outcomes	Primary: graft thrombosis
Notes	PTFE grafts Type II patients not included in review meta-analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sreedhara 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Pre-determined schedule (not detailed)
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated that neither participants nor investigator could determine the specific treatment protocol
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Graft thrombosis assessed by an investigator who was blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants who were enrolled did not complete the study or were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Pre-study protocol not available
Other bias	Low risk	Nil obvious

AV: arteriovenous
AVF: arteriovenous fistula
AVG: arteriovenous graft
ePTFE: expanded polytetrafluoroethylene
F: females
FU: follow-up
HD: haemodialysis
M: males
od: once a day
bid: twice a day
tid: three times a day
qds: four times a day

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albert 1978	Study compares acetylsalicylic acid with sulphinpyrazone, no placebo group included so did not meet inclusion criteria
Alexopoulos 2011	No data on patency rates or secondary outcomes published
Bhomi 2008	Not a placebo-controlled trial
Chen 2013	This is a comparison of two different treatments versus no treatment, and no placebo was used for the trial. Therefore, did not meet inclusion criteria
D'Ayala 2008	Not a placebo-controlled trial
De Fijter 1995	No data published on patency rates or secondary outcomes. The study mixed participants on haemodialysis and peritoneal dialysis

Study	Reason for exclusion
Dixon 2009	Dipyridamole + aspirin combination was the treatment arm versus placebo; however if the participants were taking aspirin prior to the study initiation this was not stopped. Therefore, no true placebo was used for all participants
Dulude 2001	Only abstract available; not enough information presented to allow adequate data extraction of primary or secondary outcomes
Fuster 2001	Not a placebo-controlled trial. The paper described the rationale and design of an ongoing study. No results have been published
Janicki 2003	It was not a randomised trial as there is no mention of any randomisation process. There is no data on date of the study, thus the control group could have been a historical group. There is no information on how patency or thrombosis was assessed
Kaegi 1975	Some participants were on warfarin at the start of the study. Other participants were started on this drug during the trial
Kaufman 2003	Not able to elicit absolute number of thrombotic episodes from results, as only a table of cumulative incidence, hazard ratios and risk reduction figures. The average age of the dialysis access was 565 days (placebo) and 587 days (treatment)
Kooistra 1994	Long-standing (> 6 weeks old) AV fistulae assessed, and concurrent initiation of recombinant human erythropoietin with antiplatelet agent was studied, so was a confounding factor
Krasinski 2004	Abstract only available: not able to elicit absolute numbers of thrombotic episodes from results or secondary outcomes
Lee 2009	This randomised trial looked at the effect of different routes of administration of the study drug. It did not therefore include a true placebo
Lin 2007	Not placebo controlled. Study undertaken on AV fistulae which had been functional for at least 3 months
Lin 2013	Not placebo controlled. Study undertaken on AV fistulae which had been functional for at least 6 months
Malovrh 2009	Not placebo controlled. Not truly randomised (groups based on vessel quality, and if fistula was non-functional at the end of surgery)
Mileti 1995	The paper described the rationale and design of an ongoing study. No results have been published
Radmilovic 1998	The trial looked at external fistulae, a technique now not practised and numbers of thrombotic episodes could not be elicited from the results
Rouzrokh 2009	Unclear results with the time frame of assessment of patency not clear
Taber 1992	Abstract only available: no data published on patency rates or secondary outcomes
Trimarchi 2006	This is a comparison of treatment versus no treatment, and no placebo was used for trial. Therefore, excluded from review. *Note: this study was mistakenly included in previous versions of this review
Wang 2010	Not a placebo-controlled trial

Study	Reason for exclusion
Wasse 2014	Patency defined as AVF or AVG being successfully used at six months, therefore no data provided on actual thrombotic events as other factors could have precluded the AVF or AVG use
Yuto 2012	Not a placebo-controlled trial

AV: arteriovenous
AVF: arteriovenous fistula
AVG: arteriovenous graft

Characteristics of ongoing studies *[ordered by study ID]*

Irish 2007

Trial name or title	FAVOURED (Fish oil and aspirin in vascular access outcomes in renal disease)
Methods	Factorial-trial design. Medication commenced pre-operatively and continued for 3 months post surgery
Participants	Stage 4 or 5 chronic kidney disease patients with arteriovenous fistulae
Interventions	Low-dose aspirin and fish oil either alone or in combination
Outcomes	Primary outcome: fistula patency at 3 months Secondary outcomes: patency at 6 months, primary patency time, secondary (assisted) patency time, adverse events (e.g. bleeding)
Starting date	2007
Contact information	
Notes	

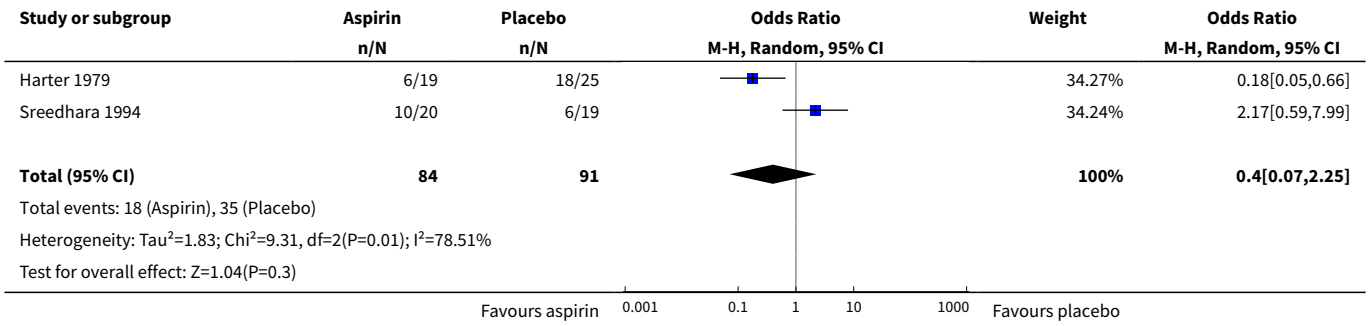
DATA AND ANALYSES

Comparison 1. Aspirin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	3	175	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.07, 2.25]

Analysis 1.1. Comparison 1 Aspirin versus placebo, Outcome 1 Graft thrombosis.

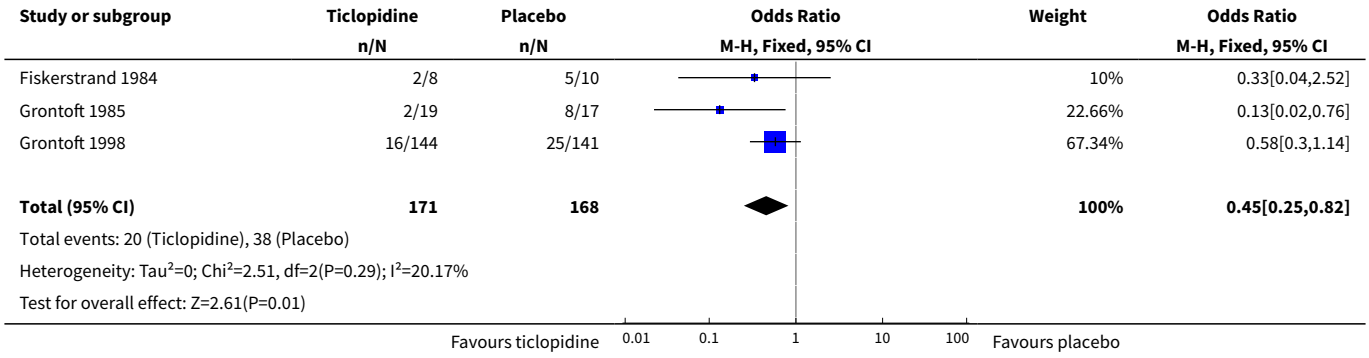
Study or subgroup	Aspirin n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Andrassy 1974	2/45	11/47		31.49%	0.15[0.03,0.73]



Comparison 2. Ticlopidine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fistulae thromboses at one month	3	339	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.25, 0.82]

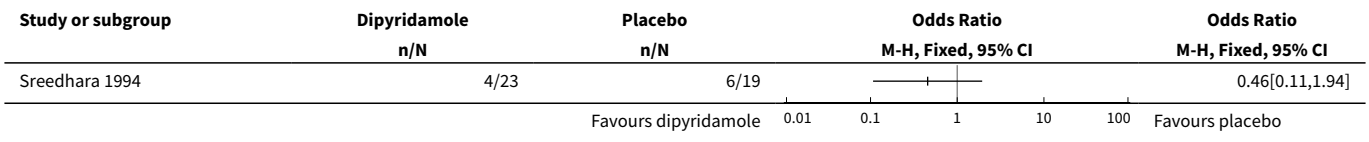
Analysis 2.1. Comparison 2 Ticlopidine versus placebo, Outcome 1 Fistulae thromboses at one month.



Comparison 3. Dipyridamole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Dipyridamole versus placebo, Outcome 1 Graft thrombosis.



Comparison 4. Dipyridamole + aspirin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Dipyridamole + aspirin versus placebo, Outcome 1 Graft thrombosis.

Study or subgroup	Dipyridamole+Aspirin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Sreedhara 1994	5/22	6/19		0.64[0.16,2.56]

Favours dipyrid+aspi 0.01 0.1 1 10 100 Favours placebo

Comparison 5. Warfarin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Warfarin versus placebo, Outcome 1 Graft thrombosis.

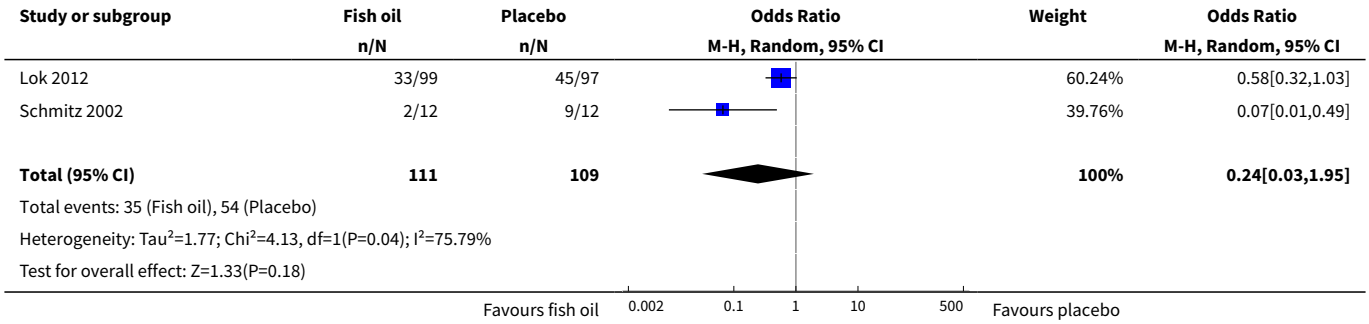
Study or subgroup	Warfarin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Crowther 2002	41/56	31/51		1.76[0.78,3.99]

Favours Warfarin 0.01 0.1 1 10 100 Favours placebo

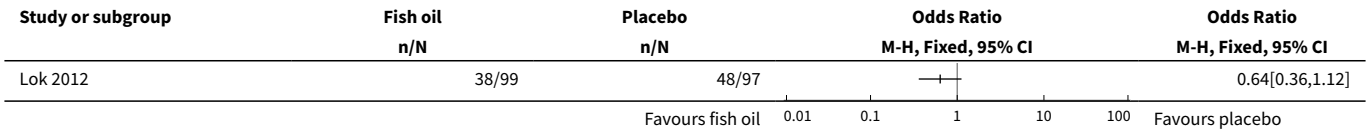
Comparison 6. Fish oil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	2	220	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.03, 1.95]
2 Radiological and/or surgical intervention	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Fish oil versus placebo, Outcome 1 Graft thrombosis.



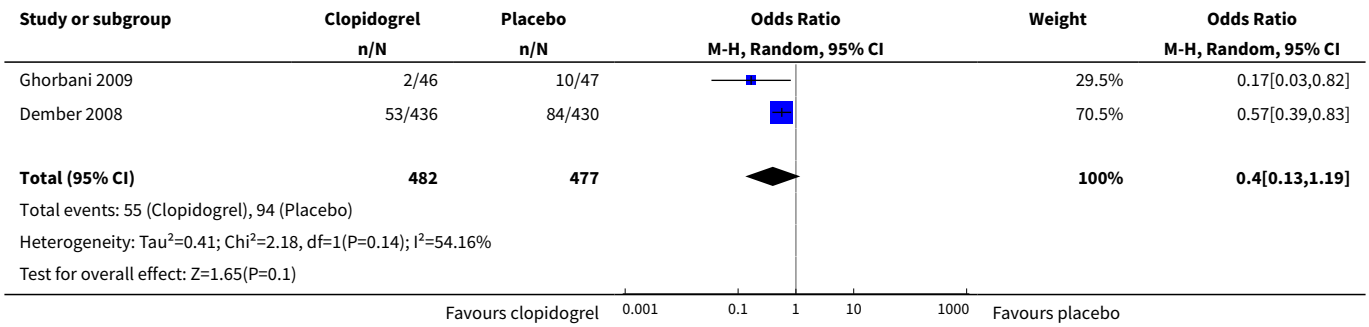
Analysis 6.2. Comparison 6 Fish oil versus placebo, Outcome 2 Radiological and/or surgical intervention.



Comparison 7. Clopidogrel versus placebo

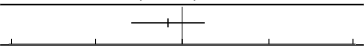
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	2	959	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.13, 1.19]
2 Radiological and/or surgical intervention	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Clopidogrel versus placebo, Outcome 1 Graft thrombosis.



Analysis 7.2. Comparison 7 Clopidogrel versus placebo, Outcome 2 Radiological and/or surgical intervention.

Study or subgroup	Clopidogrel n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Dember 2008	7/436	10/430		0.69[0.26,1.82]

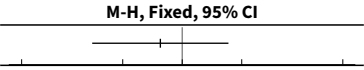


Comparison 8. Sulphinpyrazone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 Sulphinpyrazone versus placebo, Outcome 1 Graft thrombosis.

Study or subgroup	Sulphinpyrazone n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Michie 1977	1/8	2/8		0.43[0.03,5.98]

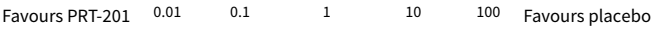


Comparison 9. PRT-201 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft thrombosis	3	306	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.42, 1.32]

Analysis 9.1. Comparison 9 PRT-201 versus placebo, Outcome 1 Graft thrombosis.

Study or subgroup	PRT-201 n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Dwivedi 2014	26/61	13/28		37.51%	0.86[0.35,2.11]
Hye 2014	14/100	12/51		50.15%	0.53[0.22,1.25]
Peden 2013	8/45	3/21		12.34%	1.3[0.31,5.48]
Total (95% CI)	**206**	**100**		**100%**	**0.75[0.42,1.32]**
Total events: 48 (PRT-201), 28 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.27, df=2(P=0.53); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					



APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Renal Dialysis] this term only	3343
#2	MeSH descriptor: [Hemodiafiltration] this term only	172
#3	MeSH descriptor: [Hemofiltration] this term only	318
#4	MeSH descriptor: [Hemodialysis, Home] this term only	51
#5	(hemodialysis or haemodialysis)	5378
#6	(hemofiltration or haemofiltration)	613
#7	(hemodiafiltration or haemodiafiltration)	371
#8	dialysis	9041
#9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)	10441
#10	MeSH descriptor: [Arteriovenous Fistula] this term only	32
#11	MeSH descriptor: [Arteriovenous Shunt, Surgical] this term only	222
#12	((vascular next access) or (venous next access))	806
#13	(fistula* or avf* or graft or shunt)	17642
#14	MeSH descriptor: [Blood Vessel Prosthesis] this term only	452
#15	#10 or #11 or #12 or #13 or #14	18366
#16	MeSH descriptor: [Graft Occlusion, Vascular] explode all trees	524
#17	(occlud* or occlusion or obstruct*):ti,ab,kw in Trials	18531
#18	stenos*:ti,ab,kw in Trials	4525
#19	restenos*:ti,ab,kw in Trials	1879
#20	#16 or #17 or #18 or #19	23080
#21	#9 and #15 and #20 in Trials	169

WHAT'S NEW

Date	Event	Description
13 June 2015	New citation required but conclusions have not changed	Searches re-run. Six new trials included and 19 new studies excluded, one study previously included reclassified as excluded study. New author added to review team. Risk of bias tables com-

Date	Event	Description
		pleted in keeping with current Cochrane policy. More evidence offered to support conclusions, conclusions not changed
13 June 2015	New search has been performed	Searches re-run. Six new trials included and 19 new studies excluded, one study previously included reclassified as excluded study

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 2, 2003

Date	Event	Description
19 May 2008	New citation required but conclusions have not changed	New citation: conclusions not changed. Review updated with the addition of an additional author.
19 May 2008	New search has been performed	Four new trials added to included studies, six trials added to excluded studies and five trials added to ongoing studies. More evidence offered to support conclusions.
19 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

NCT: assessed trials to confirm eligibility, quality and extracted data, updated the text of the review
ADS: assessed trials to confirm eligibility and quality, updated the text of the review

DECLARATIONS OF INTEREST

NCT: none known
ADS: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The Chief Scientist Office, Scottish Executive Health Directorates, the Scottish Government, UK.

  The PVD Group editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the previous published version of this review (Osborn 2008), the quality of trials was investigated using the methods of Jadad (Jadad 1996); and Schulz (Schultz 1995). In keeping with updated requirements of Cochrane, methodological quality has now been assessed using the 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Arteriovenous Shunt, Surgical [*adverse effects] [*methods]; Chemotherapy, Adjuvant; Kidney Failure, Chronic [*therapy]; Platelet Aggregation Inhibitors [*therapeutic use]; Randomized Controlled Trials as Topic; Renal Dialysis [methods]; Ticlopidine [therapeutic use]; Vascular Patency [*drug effects]

MeSH check words

Humans