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# Medical Adjuvant Therapy in Reducing Thrombosis With Arteriovenous Grafts and Fistulae Use: A Meta-Analysis of Randomized Controlled Trials

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## Abstract

Hemodialysis is required for patients with end-stage renal disease (ESRD) that require arteriovenous (AV) grafts or fistulas for vascular access. These access points are prone to thrombosis. To determine the effect of medical adjuvant therapy on AV graft/fistula patency among patients with ESRD on hemodialysis. Adhering to the PRISMA 2020 statement, a systematic search was conducted until August 20, 2021, with keywords including arteriovenous graft, fistula, patency, thrombosis, hemodialysis, adjuvant treatment. The following databases were searched: PubMed, Scopus, Web of Science, CINAHL Plus, and Cochrane. A random-effects model was employed using Review Manager 5.4 for data analysis. The meta-analysis pooled in 1985 participants with 1000 (50.4%) in the medical adjuvant treatment group. At a snapshot, medical adjuvant therapy reduced the risk for graft thrombosis (RR = 0.64, $P = .02$). Notable medications included aspirin for graft thrombosis (RR = 0.36, $P = .006$) and ticlopidine for fistula thrombosis (RR = 0.53, $P = .01$). Certain antiplatelet therapies (aspirin and ticlopidine) reduced the number of patients with AV fistula/graft thrombosis among patients with high heterogeneity among the trials. Other therapies (fish oil, sulfinpyrazone, clopidogrel, and aspirin/dipyridamole) did not demonstrate significant improvement but may be promising once concrete evidence is available. Potential benefits of anti-platelet therapies may be explored to maintain the potency of AV grafts/fistulas through well-designed placebo-controlled trials and long-term follow-up.

## Keywords

arteriovenous graft, fistula, patency, thrombosis, hemodialysis, adjuvant treatment, meta-analysis

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## Introduction

Patients with end-stage renal disease (ESRD) have a high rate of premature death despite the various advances in dialysis techniques. ESRD affects more than 0.6 million people in the United States; the estimated global burden is 4.902 to 7.083 million people, which is subjective to the prevalence of diabetes mellitus, obesity, hypertension, and aging in the population.[1] Hemodialysis requires repeated access to the bloodstream with 3 main types: (1) surgically created arteriovenous communication is known as autologous arteriovenous fistula (AVF), (2) synthetic arteriovenous graft (AVG), and (3) central venous catheter (CVC).[2] The type of hemodialysis access

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chosen for the patient has different complication rates.[3] CVCs are considered if arteriovenous communication fails to mature for dialysis or is occluded by thrombosis.[4] AVFs are preferred for hemodialysis access due to their comparatively lower morbidity and mortality than AVGs.[3] Ideally, access sites need to have low rates of complications. The Fistula Breakthrough Initiative was established in 2003 by the Centers for Medicare & Medicaid Services and ESRD networks to increase the rates of AVFs, consequently improving hemodialysis access outcomes and reducing healthcare costs.[5]

Complications associated with hemodialysis access sites frequently result in hospitalizations and further surgical interventions, with autologous AVFs being the safest option.[6] Vascular access dysfunction is the most common cause of morbidity associated with hemodialysis.[7] Primary failure typically occurs in the first few weeks following surgical creation of access points due to thrombosis or inadequate maturation of the valve.[8] Evaluation of early fistula failure is ideal during the first 4 to 6 weeks.[9] AVF requires swift proliferation of endothelial cells as part of the vascular remodeling.[10] The fistula vein is subjected to a significant increase in blood flow that thickens the fistula vein wall and dilates the venous lumen which allows for effective delivery of blood.[10] The AVF then witnesses an increase in the transmural pressure which activates the smooth muscle cells, extracellular matrix elements, and cytokine production.[11] However, abnormal vascular remodeling triggered by turbulent flow, pro-inflammatory environment due to high shear stress, and regular needle insertion causes hemostatic activation and nonmaturation of AVF, with underlying neointimal hyperplasia and vascular constriction.[12,13]

Complications associated with hemodialysis occur frequently, nevertheless, adjuvant medical treatment may further reduce these complications.[14] There is accumulating evidence of additional benefits from adjuvant medications on graft patency rates, identified by graft or fistula thrombosis.[15,16] However, conclusive evidence regarding pharmacologic agents has not been extensively examined. This meta-analysis aims to assess the efficacy of adjuvant medical treatments in individuals at risk for the development of AVF or prosthetic AVG thrombosis among patients with ESRD who are on hemodialysis. The synthesis will only collate evidence from randomized trials of active medical intervention versus placebo groups.

## Methods

### Search Strategy and Study Selection

Adhering to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement guidelines, a systematic search was conducted until August 2021, using a combination of the following keywords: AVG, fistula, patency, thrombosis, hemodialysis, adjuvant treatment. The following databases were searched: PubMed, Scopus, Web of Science, CINAHL Plus, and Cochrane. The inclusion criteria comprised of randomized controlled trials only that employed a medical adjuvant to note the outcomes of graft and/or fistulae thrombosis employing an interventional and a placebo group, with no time and language restrictions. Cohort studies, case series, case reports, systematic reviews, meta-analyses, and letters were omitted. The data was stored in EndNote X9 (Clarivate Analytics, USA) which is a software management tool. An umbrella review methodology was employed where the reference lists of all screened articles were additionally reviewed to locate any RCTs that met the inclusion criteria. The PRISMA flowchart for study selection can be seen in Figure 1.

All investigators screened the abstracts and titles before a consensus was reached for a full-text review of screened studies. Disagreements were resolved using active discussion among the investigators. An a-priori methodology was adopted using a Delphi process to ensure that the outcomes of interest and collated findings were listed.[17]

### Outcomes

The primary outcome was events of graft and fistulae thrombosis on the use of medical adjuvant treatment. The treatment comprised of the following alone or in combination across the RCTs: aspirin, ticlopidine, dipyridamole, warfarin, clopidogrel, sulfinpyrazone, glyceryl trinitrate, fish oil. The secondary outcome was to provide a risk estimate of every treatment alone with RR, 95% CI, P values, and the I2 index.

### Data Analysis

Dichotomous data was entered for the medications used (aspirin, ticlopidine, dipyridamole, warfarin, clopidogrel, sulfinpyrazone, glyceryl trinitrate, fish oil) for the outcomes of graft and fistulae thrombosis. The forest plots were generated for the 2 outcomes separately, using a random-effects model and 95% confidence intervals. These data were presented as a risk ratio (RR) with the I2 index used to assess the heterogeneity among the included studies. The *P*-value was considered statistically significant if the value was less than 0.05. the meta-analysis was conducted using Review Manager (RevMan 5.4; Cochrane). The funnel plot was also generated as more than 10 RCTs were pooled in this analysis, based on the Cochrane Handbook guidelines. An inverted funnel shape meant that minimum publication bias was expected with the meta-analytical findings.

### Role of Funding and Ethical Approval

No external funding was obtained for this study. Ethical approval was not required as only secondary clinical data was utilized for this meta-analysis.

## Results

This meta-analysis includes 13 randomized placebo-controlled trials pooling in 1985 participants. The treatment group (N = 1000) employed antithrombotic medications such as ticlopidine, dipyridamole, aspirin, and clopidogrel, whereas there

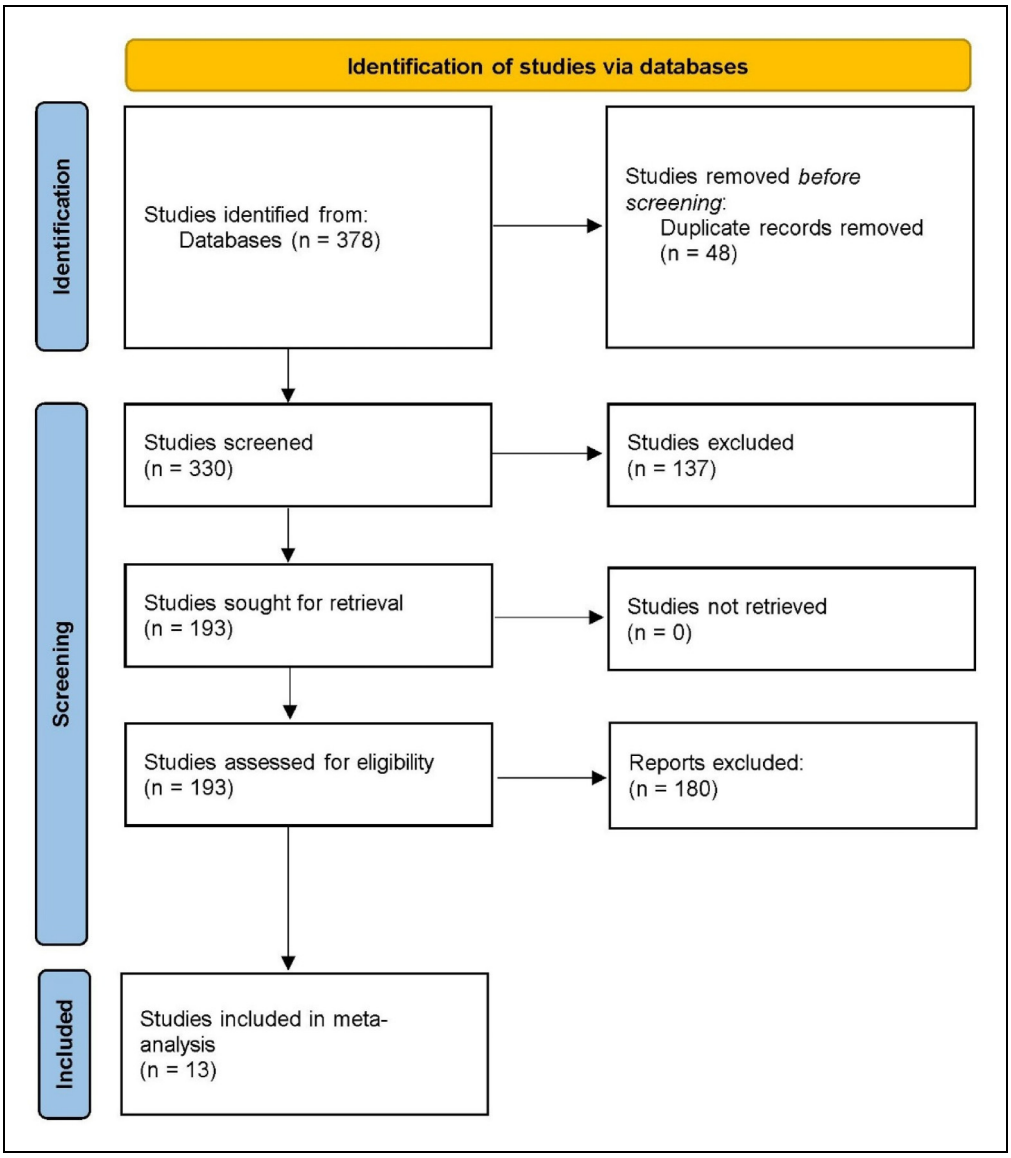


**Figure 1.** PRISMA flowchart.

were no antithrombotic medications utilized to prevent blockages in the artery or vein access points for dialysis in the placebo group (N = 985). The trials comprised of individuals who had advanced kidney disease receiving dialysis through AVFs or AVGs in the legs, arms, or other special sites. The characteristics of included studies are listed in Table 1.

Ten of the 13 trials listed outcomes for graft/fistulae thrombosis, as enlisted in Table 1. In total, 829 patients were pooled in the treatment group, whereas 817 patients were pooled in the placebo group. At a snapshot, the use of medical adjuvant therapy reduced the risk of graft thrombosis by 36% (RR = 0.64, 95% CI = 0.45-0.92, $P = .02$). There was moderately high heterogeneity present among the included studies (I2 = 70%) (Figure 2).

On conducting the subgroup analysis, the following results were obtained. Aspirin alone led to a reduction in graft thrombosis by 64% (RR = 0.36, 95% CI = 0.18-0.75, $P = .006$, I2 = 12%). Dipyridamole and Aspirin in combination led to relatively lower risk reduction when compared to aspirin alone (RR = 0.72, 95% CI = 0.26-1.99, $P = .53$), but with no statistical significance. Warfarin alone led to a higher risk of graft thrombosis compared to placebo (RR = 1.2, 95% CI = 0.92-1.58, $P = .18$), the results of which were statistically insignificant. The use of fish oils alone reduced the risk of graft thrombosis by 53%, but no significance was found (RR = 0.47, 95% CI = 0.16- 1.44, $P = .19$, I2 = 66%). Clopidogrel alone as compared to placebo led to a statistically insignificant reduction in graft thrombosis by 55% (RR = 0.45, 95% CI = 0.17-1.22, $P = .12$, I2 = 53%). Sulfinpyrazone alone reduced the risk of graft thrombosis by 50%, which was statistically insignificant (RR = 0.5, 95% CI = 0.06-4.47, $P = .54$). Glyceryl Trinitrate alone increased the risk of graft thrombosis, although the findings were insignificant (RR = 1.19, 95% CI = 0.71-2, $P = .51$].

**Table 1.** Characteristics of Included Studies.

| No. | Author, Year | Adjuvant medical treatment | Dose | Follow-up duration | Type of AVF or AVG | Graft/fistula thrombosis in treatment versus placebo |
|---|---|---|---|---|---|---|
| 1 | Andrassy et al, 1974 | Aspirin | 500 mg once daily | 28 days | AVFs | 2(4.4%) versus 11(23.4%) |
| 2 | Harter et al, 1979 | Aspirin | 160 mg once daily | 5 months | AV shunt formation between the radial artery and the cephalic vein with a Teflon adapter and straight Silastic arteriovenous-shunt material | 6(31.6%) versus 18(72%) |
| 3 | Sreedhara et al, 1994 | Dipyridamole and Aspirin | 75 mg and 325 mg, respectively, once daily | 18 months | Prosthetic Arteriovenous Expanded PTFE Grafts | 5(22.7%) versus 6(31.6%) |
| 4 | Crowther et al, 2002 | Warfarin | Varied dose to achieve INR for prothrombin time 1.4 to 1.9 | 37 months | PTFE grafts | 41(73.2%) versus 31(60.8%) |
| 5 | Lok et al, 2012 | Fish Oil | 4000 mg daily | 12 months | Synthetic AVGs | 33(33.3%) versus 45(46.4%) |
| 6 | Schmitz et al, 2002 | Fish Oil | 4000 mg daily | 12 months | PTFE Grafts | 2(16.7%) versus 9(75%) |
| 7 | Ghorbani et al, 2009 | Clopidogrel | 75 mg daily | 6 weeks | AVFs | 2(4.4%) versus 10(21.3%) |
| 8 | Dember et al, 2008 | Clopidogrel | 300 mg on post-op day 1 followed by 75 mg daily | 6 weeks | AVFs | 53(12.2%) versus 84(19.5%) |
| 9 | Michie et al, 1977 | Sulfinpyrazone | 200 mg 4 times daily | 3 months | Combination of AVFs, bovine grafts, and shunt | 1(12.5%) versus 2(25%) |
| 10 | Field et al, 2016 | Glyceryl Trinitrate | Transdermal patch | 6 weeks | AVFs | 24(27.9%) versus 19(23.5%) |
| 11 | Fiskerstrand et al, 1985 | Ticlopidine | 250 mg twice daily | One month | AVFs | 2(25%) versus 5(50%) |
| 12 | Grontoft (1) et al, 1985 | Ticlopidine | 250 mg twice daily | One month | AVFs | 2(10.5%) versus 8(47.1%) |
| 13 | Grontoft (2) et al, 1998 | Ticlopidine | 250 mg twice daily | One month | Most had native, distal arm AVFs with 16 artificial grafts and 9 who had free vein grafts | 16(11.1%) versus 25(17.7%) |

Three of the 13 trials listed outcomes for fistulae thrombosis, pooling in 171 patients in the treatment group and 168 in the placebo group. On the use of Ticlopidine alone, the risk of fistulae thrombosis was reduced by 47% (RR = 0.53, 95% CI = 0.32-0.88, $P = .01$). No heterogeneity was found in this subgroup of patients ($I2 = 0\%$) (Figure 2).

On visually inspecting the funnel plot, it may be stated that the demarcations of the 13 included studies tend to fit the criteria for an inverted funnel shape on the top, with one apparent deviation on the bottom (Michie et al, 1977) from the symmetrical shape. Based on these findings, it may be inferred that there was minimal publication bias present in this meta-analysis (Figure 3).

## Discussion

We explored potentially effective therapies that may prevent the development of thrombosis and improve the maintenance of hemodialysis among patients with ESRD. All of the included studies reported the AV patency by documenting graft thrombosis or fistulae thrombosis. Primary failure or failure to mature have been used interchangeably, despite major differences in underlying mechanisms. Only 2 pharmacologic interventions had beneficial effects on AV patency, namely aspirin and ticlopidine, both anti-platelets with different mechanisms. Our findings were observed to have publication bias and heterogeneity among the clinical trials. The results favor anti-platelet therapy clinically but one of the agents, ticlopidine, is not in currently clinical use for its unfavorable side effect profile.

Two clinical trials administered aspirin alone or placebo with a discrepancy in the dose (160 mg/daily or 500 mg/daily), and follow-up duration (28 days or 5 months). Interestingly, there was a significant reduction in graft thrombosis by 64% ($p = .006$) when administered aspirin but heterogeneity was noted with a random-effects meta-analysis. One clinical trial administered dipyridamole (75 mg/daily) and aspirin (325 mg/daily) with an insignificant reduction in graft thrombosis and moderate

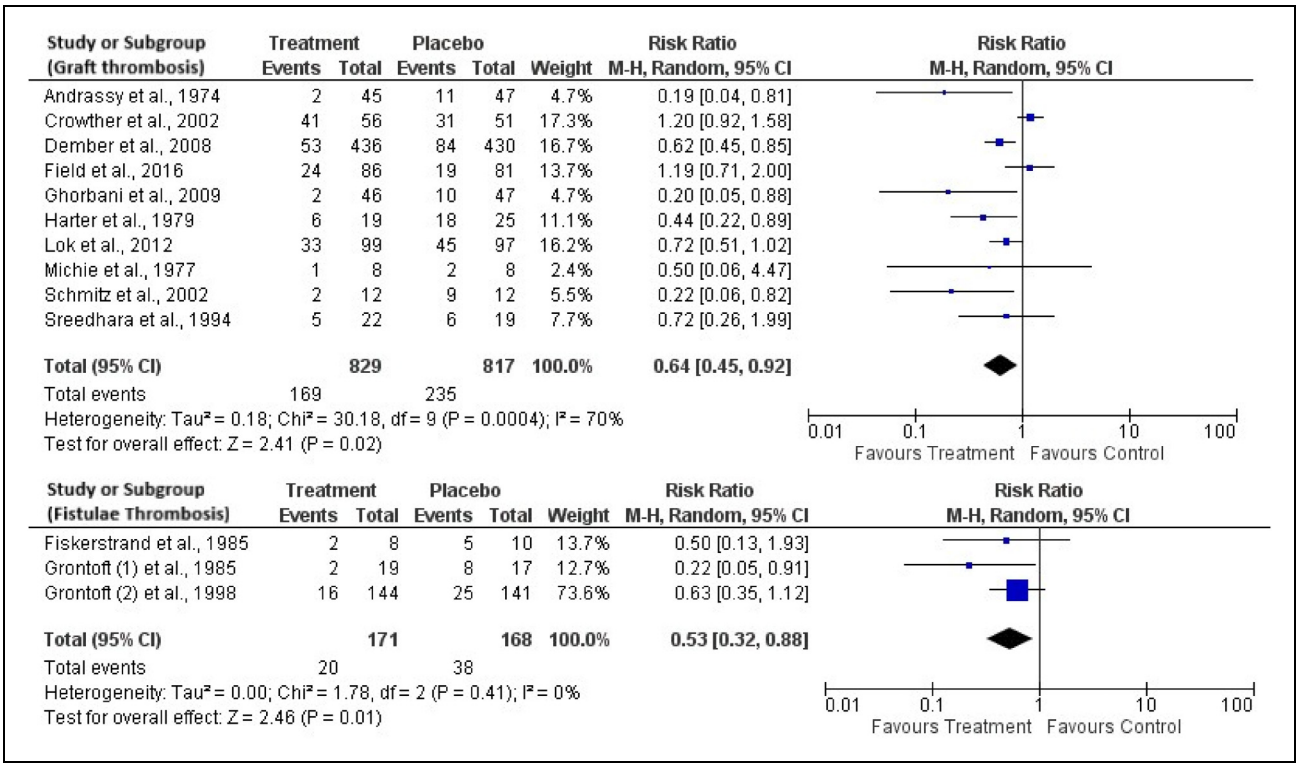


**Figure 2.** Forest plots displaying medications use (ie, Aspirin, Ticlopidine, Dipyridamole, Warfarin, Clopidogrel, Sulfinpyrazone, Glyceryl Trinitrate, Fish Oil) versus placebo in the outcomes of graft and fistulae thrombosis.

side effects (p = 0.53). All the aspirin trials were over 2 decades old and doses used varied across trials. However, the meta-analytical findings suggest the beneficial effect of aspirin on prolonged primary unassisted patency of the hemodialysis graft. It is expected that the action of aspirin is dose-dependent, warranting trials that focus on immediate and long-term outcomes with different dosing regimens for hemodialysis graft patency.[18] The combination of dipyridamole/aspirin compared to aspirin alone does not show significant benefits for graft thrombosis in our meta-analysis. A parallel-arm, randomized placebo-controlled trial employing a generalizable sample size, comparing dipyridamole/aspirin to aspirin for graft patency may be able to identify any additional benefits of dipyridamole.

Ticlopidine and clopidogrel are both structurally related thienopyridine derivatives that permanently inhibit ADP-induced platelet activation and aggregation.[19] The meta-analysis demonstrated the protective effect of ticlopidine, an anti-platelet, which was observed across 3 trials, and the risk of fistula thrombosis was reduced by 47% ($P = .01$). Patients received either 250 mg of ticlopidine twice daily or placebo and followed for 1 month with no heterogeneity found across these trials. The pooled analysis did not statistically favor a reduction of graft thrombosis (55%) with clopidogrel, at a dose of 75 mg daily for 6 weeks across 2 trials, with high heterogeneity noted within the trials ($P = .12$). We identified significant risk reduction of thrombosis with ticlopidine which was not demonstrated with clopidogrel. Ticlopidine, the first member of thienopyridines, results in severe but reversible hematological disorders during the first 3 months of use; Clopidogrel, however, produces fewer side effects.[19,20] Clopidogrel has replaced ticlopidine, its predecessor, as it has a faster onset of action and improved safety profile, thereby presenting as a more attractive option for patients requiring anti-thrombotic therapy as prevention to increase the patency of AVFs and AVGs.[20] Our results did not demonstrate conclusive evidence for clopidogrel efficacy despite similar drug-specific mechanisms of ticlopidine.[21]

While many of the 13 included studies included patients with AVGs placed using polytetrafluoroethylene (PTFE) or other materials, current materials used for AVG include heparin-bonded expanded PTFE grafts such as Propaten, Acuseal, and Flixine.[22] Newer techniques have been observed to reduce complications, and our findings may not entirely apply to modern-day AVG materials used for dialysis access.[23] It is necessary to highlight that dialysis access thrombosis is multifaceted with a major component being abnormal vessel wall shear stress resulting in endothelial dysfunction.[24] In AVGs, there is no endothelium present, and the risk increases by 4 times for thrombosis when compared to AVFs.[24] The goal of monitoring dialysis access sites is to intervene before thrombosis development. Systemic anticoagulants/anti-platelet therapy has been used as the patients with ESRD are in an overall pro-thrombotic state; however, there has been variable success potentially due to the multifactorial etiology of AV access failure such as individual thrombophilic conditions.[25,26] We recommend large, placebo-controlled trials are conducted using AVG and AVF with long-term follow-up to identify the efficacy and safety of clopidogrel to optimize the use of this agent alone or in combination with other new anti-platelets

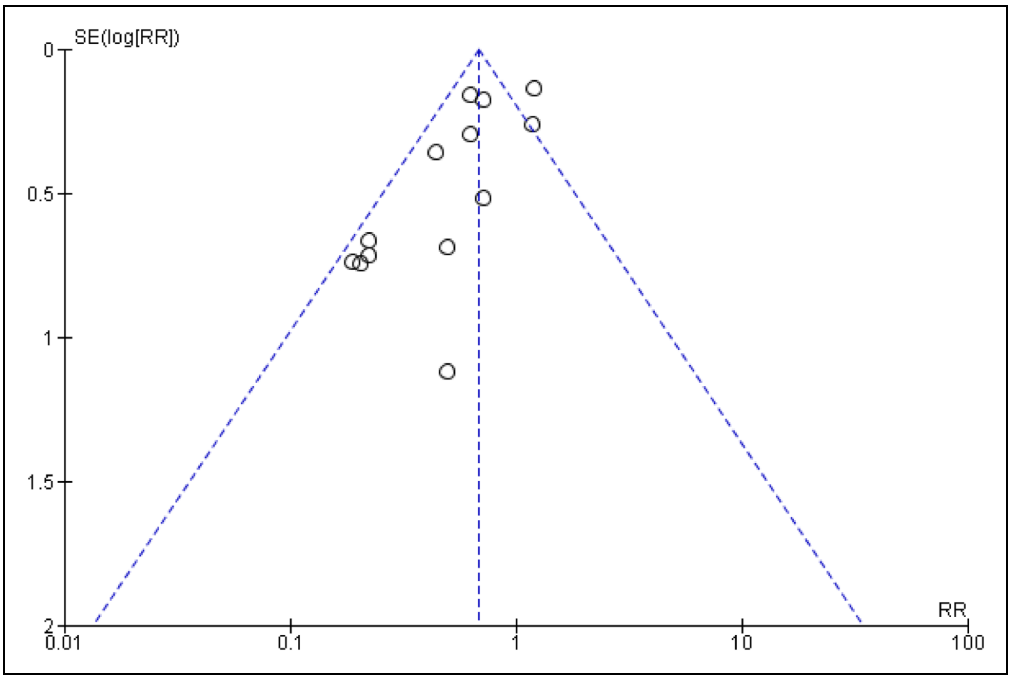


**Figure 3.** Funnel plot to assess for publication bias.

(eg, aspirin) as well as assess clinical implications for medical management of hemodialysis patients.

Two trials explored the impact of fish oil at a dose of 4000 mg daily and followed the patients for development graft thrombosis until 12 months. Overall, the meta-analysis favored treatment (RR 0.47, 95% CI 0.16-1.44) but the results remained insignificant ($P = .19$). Theoretically, fish oil has anti-proliferative, anti-oxidant, and vasodilatory effects with potential protection against loss of AV access patency.[27] Fish oil has also been used to reduce cardiovascular morbidity and mortality.[28] It is worth exploring if fish oil has a significant reduction in graft thrombosis as a consistent trend of benefit is being reported, albeit insignificant.[29] One trial observed the efficacy of sulfinpyrazone at a dose of 200 mg 4 times daily for 3 months with a 50% risk reduction (95% CI 0.06-4.47) of graft thrombosis yet the findings were insignificant ($P = .54$). Sulfinpyrazone has an antithrombotic effect that is not elucidated and observed among patients with gout, recurrent venous thrombosis, and prosthetic valve replacements.[30] It is well-tolerated and may provide concomitant efficacy for graft thrombosis reduction with larger, placebo-controlled trials in patients with ESRD at risk for thrombosis of AV grafts/fistulas.

Only one trial compared warfarin versus placebo but was observed to worsen patency rates and increase complications. Therefore, the trial was terminated after 37 months of follow-up with risk identified with the use of warfarin in renal patients with AVGs or AVFs. Similarly, glyceryl trinitrate alone also increased the risk of graft thrombosis (RR: 1.19, 95% CI 0.71-2) when administered for 6 weeks via a transdermal patch in one trial. There is little favorable evidence of locally applied glyceryl trinitrate transdermal patch with supporting evidence from small observational studies.[31] However, our findings demonstrate no benefit of glyceryl trinitrate in supporting AVF maturation.

## Limitations

There are a few limitations of our meta-analysis that deserve consideration. Many of the trials had a wide range of dosing, time to start intervention, and follow-up periods. This resulted in heterogeneity among the included trials. As with the differences in primary failure versus failure to mature, the duration of follow-up may have missed AV grafts/fistulas that were functional initially but thrombosed later. Therefore, it is essential to plan well-designed and homogenous placebo-controlled trials with long-term follow-ups. Another limitation was the lack of recent data observing medical adjuvant therapy as some of the included trials were conducted over 2 decades ago. Finally, there may be a wide variation in hemodialysis access experiences by surgeons that may result in insignificant evidence of medical adjuvant therapy.[3]

## Conclusion

To summarize, certain anti-platelets (aspirin and ticlopidine) resulted in a significant reduction of graft/fistula thrombosis among ESRD patients, associated with heterogeneity among the trials. Similarly, fish oil therapies may also confer some additional protective benefits and are worth exploring in this subset of patients. Other therapies such as sulfinpyrazone, clopidogrel, and aspirin/dipyridamole have so far not demonstrated favorable outcomes given the paucity of data. We recommend the designing of robust, well-designed placebo-controlled trials for both AVG and AVF, paying attention to anti-platelets

such as aspirin and clopidogrel due to their favorable side effect profiles.

## Declaration of Conflicting Interests

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