Omega-3 polyunsaturated fatty acid supplementation to prevent arteriovenous fistula and graft failure: Systematic review and meta-analysis of randomized controlled trials

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Short title: Fish oils for hemodialysis vascular access
Abstract

Background:
Arteriovenous access failure frequently occurs in people on hemodialysis and is associated with morbidity, mortality and healthcare expenditure. Omega-3 polyunsaturated fatty acids (omega-3 PUFA) may improve outcomes via pleiotropic effects on access maturation and function, but may cause bleeding complications.

Study Design:
Systematic review with meta-analysis.

Setting & Population:
Adults requiring hemodialysis via arteriovenous fistula, graft or shunt.

Selection Criteria:
Trials evaluating omega-3 PUFA for arteriovenous access outcomes identified by searches in CENTRAL, MEDLINE, and Embase to 24 January 2017.

Intervention:
Omega-3 PUFA.

Outcomes:
Primary patency loss, dialysis suitability failure, access abandonment, interventions to maintain patency or assist maturation, bleeding, gastrointestinal side-effects, all-cause and cardiovascular mortality, hospitalization, and treatment adherence. Treatment effects were summarized as relative risks (RR) and 95% confidence interval (CI). Evidence was assessed using GRADE.

Results:
Five eligible trials (833 participants) compared omega-3 PUFA supplementation with placebo, commenced perioperatively, with median follow-up of 12 months. One trial (n=567) evaluated treatment for fistulae and four (n=266) for grafts. Omega-3 PUFA supplementation prevented primary patency loss with moderate certainty (761 participants, RR 0.81, CI 0.68-0.98). Low quality evidence suggested, that omega-3
PUFA may have had little or no effect on dialysis suitability failure (536 participants, RR 0.95, CI 0.73-1.23), access abandonment (732 participants, RR 0.78, CI 0.59-1.03), need for interventions (732 participants, RR 0.82, CI 0.64-1.04), or all-cause mortality (799 participants, RR 0.99, CI 0.51-1.92). Bleeding risk (793 participants, RR 1.40, CI 0.78-2.49) or gastrointestinal side-effects (816 participants, RR 1.22, CI 0.64-2.34) were uncertain. There was no evidence of different treatment effects for grafts or fistulae.

Limitations:
Small number and methodological limitations of included trials.

Conclusions:
Omega-3 PUFA supplementation probably protects against primary loss of arteriovenous access patency, but may have little or no effect on dialysis suitability failure, access interventions or abandonment. Potential treatment harms are uncertain.

Index words: Fish oil, omega-3 polyunsaturated fatty acids, hemodialysis, arteriovenous vascular access, arteriovenous fistula, arteriovenous graft, outcomes, complications, trials, meta-analysis.

Nontechnical Summary
People who need hemodialysis for kidney failure require a surgically-created connection between their artery and vein (arteriovenous access) for a durable connection to the dialysis machine. This is challenging because newly-formed arteriovenous accesses often clot or fail to develop into a useable structure for dialysis. Patients require admissions to hospital, procedures, and central venous catheters while waiting for their access to become functional. Fish oil (omega-3 polyunsaturated fatty acids) supplements reduce clotting and assist with remodeling of blood vessels, but may cause bleeding. In this meta-analysis, fish oil probably
protects dialysis patients from experiencing loss of blood flow through their access, but it remains uncertain whether fish oil improves dialysis access usability, reduces the need for additional procedures or hospital admissions, or is safe. Given that patients, caregivers, and health professionals consider vascular access to be critically important, additional trials to find healthcare interventions that improve access outcomes are needed.
Introduction

Hemodialysis is the most common renal replacement therapy worldwide and ideally requires a functioning arteriovenous vascular access. Establishing and maintaining a functional arteriovenous access remains one of the greatest challenges for dialysis care. Arteriovenous fistula (AVF) and graft (AVG) dysfunction lead to prolonged use of central venous catheters and repeated hospitalization and procedures, which are associated with higher rates of complications and mortality. Patients, caregivers, and health care professionals consider vascular access outcomes a critical priority. Strategies to improve the usability of hemodialysis vascular access are required.

The pathogenesis of arteriovenous access failure is complex and not fully understood. Pathogenic processes that may contribute to patency loss, impaired maturation, and dialysis suitability failure include neointimal hyperplasia formation and impaired vascular remodeling with insufficient vasodilation and vessel wall thickening in response to the increased pressure, shear stress and oxygen tension resulting from redirected arterial inflow.

Randomized controlled trials have evaluated various local and systemic therapies to improve arteriovenous access maturation and function. Most trials have focused on anti-platelet agents to prevent access thrombosis and maintaining vascular access patency. While anti-platelet agents may be effective in reducing early arteriovenous access thrombosis, they have not been shown to improve long-term patency and dialysis suitability. Given the complexity of processes involved in dialysis vascular access failure, an agent with pleotropic vascular effects may provide a more durable and effective therapeutic strategy for favorably influencing vascular remodeling, neointimal hyperplasia formation, and thrombotic risk in newly formed vascular access. Omega-3 polyunsaturated fatty acids (omega-3 PUFA) show promise because they inhibit platelet aggregation and exert anti-inflammatory, anti-
proliferative\textsuperscript{21,22} and vasodilatory effects\textsuperscript{23} on vascular structures. These actions may improve maturation and function of a newly created arteriovenous access. Conversely, while previous small studies did not show an increased risk of bleeding in dialysis patients taking omega-3 PUFA\textsuperscript{24,25}, the anti-platelet effects of omega-3 PUFA may continue to pose a concern given the already increased bleeding diathesis in this population\textsuperscript{26-29}.

The aim of this systematic review and meta-analysis was to evaluate the benefits and harms of omega-3 PUFA supplementation for arteriovenous access complications in people with end-stage kidney disease requiring hemodialysis.

**Methods**

**Study Design**

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines for reporting of systematic reviews of interventions and a pre-specified, registered protocol\textsuperscript{30,31}. Research ethics committee approval was not required for this study.

**Search strategy and selection criteria**

We searched MEDLINE (1946 through January 24, 2017), Embase (1980 through January 24, 2017) and CENTRAL (through Issue 11 of 12, 2016) without language restriction using search strategies designed by a specialist information manager (Table S1). All randomized controlled and quasi-randomized controlled trials comparing omega-3 PUFA with placebo or no treatment for prevention of AVF or AVG failure were eligible. Adults with end-stage kidney disease receiving or planning to receive hemodialysis via an AVF, AVG or arteriovenous shunt in the upper or lower limb were included.

**Study selection and data extraction**

Two authors (AV, SP) independently screened the titles and abstracts of all retrieved citations and reviewed the full text of potentially relevant records to identify trials that fulfilled the review eligibility criteria using the Population, Intervention, Comparison, Outcomes (PICO)
Baseline characteristics, study design, interventions, and outcome definitions were extracted independently by the same authors (AV, SP).

**Outcomes**

Standardized definitions for outcomes related to hemodialysis vascular access were used\(^3\). The primary efficacy outcome was loss of primary vascular access patency (first thrombosis or need for surgical or endovascular intervention to restore patency) and the primary safety outcome was bleeding. Secondary outcomes included: need for surgical or radiological intervention(s) to maintain dialysis vascular access patency or to assist maturation, dialysis vascular access abandonment (defined as an AVF/AVG that could no longer be used for hemodialysis and the associated access problem was not correctable by any further intervention), early dialysis suitability failure (defined as an access that, despite radiological or surgical interventions, could not be used successfully for dialysis by three months following access creation), late dialysis suitability failure (defined as an access that, despite radiological or surgical interventions, could not be used successfully for dialysis by six months following access creation), gastrointestinal side-effects, all-cause mortality, cardiovascular mortality, hospitalization, and treatment adherence. For each outcome, the number of events and number of people at risk in each treatment arm of included studies were extracted to calculate an individual study relative risk (RR) and 95% confidence interval (CI).

To reduce heterogeneity and increase certainty in the review findings, outcome measures from contributing studies were only used in meta-analyses, if consistent with the pre-specified outcome definitions reported in the protocol for this systematic review. Additional outcome data consistent with the outcome definitions in the protocol were requested from study investigators in writing (including re-analyses of patient-level data) and included in meta-analyses when provided.
Evidence quality assessment

Risks of bias in included studies were adjudicated independently by two review authors (AV, SP) using Cochrane methodology\(^\text{34}\) for: random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, attrition, selective reporting of outcomes, and other sources of bias. Discrepancies were resolved by discussion.

The certainty of the overall evidence related to each main outcome was assessed by two authors (AV and SP) using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008)\(^\text{35,36}\) to ensure accurate interpretation of effect estimates taking into consideration the certainty of available evidence (i.e. a non-significant effect estimate may be interpreted as “uncertain” if the certainty of available evidence is very low and a significant effect estimate as “probable” if the available evidence is moderate).

Statistical Analysis

Random-effects pairwise meta-analysis was used to estimate treatment effects. Summary effect estimates were expressed as relative risks (RR) and the associated 95% confidence intervals. Statistical heterogeneity was quantified using the Cochran Q test and the \(I^2\) metric\(^\text{37}\). An \(P\) value >75% was considered to indicate substantial heterogeneity\(^\text{37}\). Pre-specified subgroup analyses were planned to explore potential sources of heterogeneity: age (<65 years versus ≥65 years), gender, diabetes mellitus, peripheral vascular disease, risk of bias, vascular access type, vascular access location, and duration of intervention. Funnel plots to assess the potential existence of small study bias were planned if more than ten studies were included. Statistical analyses were performed using Review Manager 5, Version 5.3 (The Cochrane Collaboration, http://ims.cochrane.org/revman).

Results

Study characteristics
Description of included studies

Six trials involving 865 participants\textsuperscript{38-43} met eligibility criteria (Figure 1 and Table 1). The number of participants allocated to treatment in each study ranged between 7 and 567. Treatment was administered for 12\textsuperscript{40} to 52 weeks\textsuperscript{41,42} and the study follow-up time ranged between five\textsuperscript{43} and 12 months\textsuperscript{40-42} (median 10 months [interquartile range 6.5 to 12 months]).

The timing of treatment initiation was reported in four studies: within seven days of access creation in two trials\textsuperscript{38,41}, two weeks after access creation in one trial\textsuperscript{42}, and one day before access creation in one trial\textsuperscript{40}. The dose of omega-3 PUFA varied from 3 grams three times weekly\textsuperscript{39} to 6 grams daily\textsuperscript{38}, and varied in contents of the two main biologically active components (eicosapentaenoic acid, EPA [0.96-3 grams] and docosahexaenoic acid, DHA [0.6-1.52 grams]). Four studies investigated the effect of omega-3 PUFA on arteriovenous graft outcomes\textsuperscript{38,39,41,42}, one on AVF outcomes\textsuperscript{40}, and one on shunt outcomes\textsuperscript{43}. The latter study was a crossover trial without extractable outcome data reported at the end of the first study phase and it was therefore not possible to include data in meta-analyses. The definitions of the trial outcomes varied across trials (Table S2). Re-analyses of individual patient level data to conform with standardized definitions for outcomes\textsuperscript{33} were available from two studies\textsuperscript{40,41} (Table S3).

Risk of bias

Studies were at low risk of bias for most domains (Figure S1). Reported methods for generating the randomization sequence were low risk in 3 studies and unclear in the remainder. Allocation concealment was low risk in 2 studies and methods were unclear in 4 studies. Participants and investigators were masked to treatment allocation in 5 studies while outcome assessment was blinded in 2 trials for the primary outcome and was unclear in 3 trials. Three of the included RCTs were not strictly conducted by intention-to-treat principle\textsuperscript{38,40,41}, however, risks of bias from attrition were considered to be low in these studies as the numbers of participants and the reasons for exclusion were well balanced.
between treatment groups. Incomplete outcome data reporting was adjudicated as low risk for four studies because there were either no missing data or numbers were well balanced between treatment groups, unclear for one and high risk for the cross-over study without available outcome data at the end of the first study phase. Selective reporting was low risk for the two studies that reported all the major efficacy and safety outcomes as outlined in the published study protocol and unclear for those without available protocols. None of the studies appeared to have other sources of bias.

**Outcomes**

A summary of the findings is shown in Table 2. The outcome definitions that were used in meta-analyses are described in Table S3. Treatment estimates for trials evaluating omega-3 PUFA for AVF and AVG were combined when there was no evidence of statistical heterogeneity between subgroups (Figure 2).

**Primary patency loss**

Overall, 265 people experienced primary patency loss due to thrombosis or requiring an intervention to restore patency in three trials (761 people at risk). Moderate certainty evidence suggested that omega-3 PUFA treatment prevented primary patency loss (RR 0.81, 95% CI 0.68 - 0.98) using 1.6 to 3.4 grams of EPA and DHA for 12 to 52 weeks (Table 2, Figures 2 and S2). There was no evidence of significant heterogeneity in treatment effects. Treatment effects on vascular access patency loss did not differ significantly between access type (p [for subgroup difference] = 0.87).

**Bleeding**

Forty-four people experienced at least one bleeding event (794 people at risk). Very low certainty evidence suggested an uncertain risk of bleeding associated with omega-3 PUFA supplementation (RR 1.40, 95% CI 0.78- 2.49) (Figures 2 and S3). No data were provided on the severity or nature of the bleeding episodes with the exception of one participant allocated...
to omega-3 PUFA treatment (3 grams of EPA three times weekly) who required hospitalization for a gastrointestinal bleed\textsuperscript{39}.

**Dialysis suitability failure**

A single trial reported data on late dialysis suitability failure\textsuperscript{40}, defined as an AVF that was unable to be cannulated for at least 8 of 12 consecutive dialysis sessions or abandoned within six months of access surgery (Table 2, Figures 2 and S4). Meta-analysis was not possible. In the single trial, the RR determined by log-binomial regression analysis and adjusted for aspirin use was not statistically different between the omega-3 PUFA (3.4 grams of EPA and DHA daily for 12 weeks) and placebo arm (78/270 [29\%] versus 81/266 [30\%], RR 0.95, 95\% CI 0.73-1.24).

**Surgical or radiological interventions to restore patency or assist maturation**

One trial\textsuperscript{40} reported on the need for interventions to restore patency or assist maturation in newly created AVF (536 people) and one trial\textsuperscript{41} in AVG (196 people). Low certainty evidence suggested, that omega-3 PUFA treatment (2.4\textsuperscript{40} to 3.4\textsuperscript{39} grams of EPA and DHA daily) may have had little or no effect on the need for access interventions, such as thrombolysis or thrombectomy, angioplasty, revision, stent insertion or ligation of tributaries (RR 0.82, 95\% CI 0.64-1.04) to maintain patency (Table 2, Figures 2 and S5). There was no evidence that treatment effects were different for AVF and AVG (p = 0.64, Figure S5).

**Vascular access abandonment**

Based on low certainty evidence, omega-3 PUFA supplementation (2.4\textsuperscript{40} to 3.4\textsuperscript{39} grams of EPA and DHA daily) may have had little or no effect on arteriovenous access abandonment (RR 0.78, 95\% CI 0.59-1.03) (Figures 2 and S6). There was no evidence of different treatment effects according to arteriovenous access type (p = 0.30).
Gastrointestinal side-effects

Four studies\textsuperscript{38,40-42} (816 people) reported gastrointestinal side-effects, including bloating, gas or “fishy” aftertaste. Based on low certainty evidence, omega-3 PUFA treatment (1.6\textsuperscript{37} to 3.4\textsuperscript{39} grams of EPA and DHA daily) had an uncertain risk of gastrointestinal symptoms (RR 1.22, 95% CI 0.64-2.34) (Table 2, Figures 2 and S7).

All-cause and cardiovascular mortality

Omega-3 PUFA had uncertain effects on all-cause mortality\textsuperscript{38-41} (RR 0.98, 95% CI 0.51-1.86) (Figures 2 and S8). Cardiovascular mortality was reported in 4 trials\textsuperscript{38-41} (22 events in 768 people). Omega-3 PUFA supplementation (3 grams of EPA 3 times weekly\textsuperscript{38} to 3.4 grams of EPA and DHA daily\textsuperscript{39}) may not have reduced risks of death due to cardiovascular causes (RR 0.55, 95% CI 0.22-1.35) (Figures 2 and S9). There was no evidence that this treatment effect differed according to whether people had an AVF or AVG (p for subgroup difference = 0.93 for cardiovascular- and 0.78 for all-cause mortality, Figures 3, S8 and S9).

Hospitalization

Data on hospitalization were provided in 2 studies\textsuperscript{39,40} (574 people). Omega-3 PUFA treatment (3 grams of EPA 3 times weekly\textsuperscript{38} to 3.4 grams of EPA and DHA daily\textsuperscript{39}) may have had little or no effect on risks of hospitalization (RR 0.99, 95% CI 0.81- 1.22). There was no evidence that treatment effects differed between people with an AVF or AVG (p = 0.55, Figures 2 and S10).

Treatment adherence

Treatment adherence was assessed in 4 trials using various methods\textsuperscript{38,40-42}. Three studies\textsuperscript{40-42} measured changes in the fatty acid composition of whole blood cells\textsuperscript{41}, platelets\textsuperscript{42} or erythrocytes\textsuperscript{40}, and confirmed adherence by showing a significant increase in DHA and EPA in people prescribed omega-3 PUFA. Omega-3 PUFA was not associated with treatment non-adherence based on the median number of returned capsules\textsuperscript{40}, the number of people who did
not take the study treatment (as reported by study coordinators or evident from returned capsules)\textsuperscript{41} or people who were ‘noncompliant’ based on pill counts\textsuperscript{38} (Figures 2 and S11).

**Subgroup analysis and assessment of small study effects**

Prespecified subgroup analyses and funnel plots could not be performed due to insufficient data observations.

**Discussion**

Moderate certainty evidence suggests that omega-3 PUFA therapy commenced around the time of dialysis vascular access surgery and continued for 12 to 52 weeks prevents primary patency loss. Based on an assumed event rate of 40 per 100 patients experiencing primary patency loss within one year\textsuperscript{2,44}, treatment of 100 patients with omega-3 PUFA started perioperatively might be expected to prevent 8 patients experiencing primary patency loss (95% CI 1 to 13) within 12 months of access creation, although effects of omega-3 PUFA treatment on dialysis suitability failure, access interventions, access abandonment or treatment harms (bleeding and gastrointestinal side-effects) are uncertain. There is no robust evidence that omega-3 PUFA supplementation lowers all-cause or cardiovascular mortality in people with end-stage kidney disease requiring hemodialysis as studies were not specifically designed to examine these outcomes.

This review adds to the existing literature by summarizing current evidence for the effects of omega-3 PUFA supplementation on a number of clinically important vascular access and safety outcomes, and by including the largest and only trial examining the effect of fish oil on AVF. The findings contrast with those of a well-conducted meta-analysis of medical adjuvant therapies to increase patency of arteriovenous dialysis access in people with end-stage kidney disease undergoing hemodialysis\textsuperscript{45}: Random-effects pairwise meta-analysis of two trials (220
people\textsuperscript{41,42} showed no significant treatment effect on the frequency of graft thrombosis (odds ratio 0.24, 95% CI 0.03 to 1.95). The lack of treatment benefit on graft thrombosis reported in this meta-analysis may be attributed to the low number of events resulting in imprecise treatment estimates or the difference in the chosen outcome (i.e. graft thrombosis as opposed to primary patency loss which additionally includes the need for interventions to restore patency). This assumption is supported by findings of a more recent meta-analysis of omega-3 PUFA examining a range of clinical outcomes (cardiovascular events, depression, protein malnutrition, dyslipidemia, secondary hyperparathyroidism, AVG thrombosis) in people on long-term hemodialysis\textsuperscript{46}: Significant treatment benefit of omega-3 PUFA (1.6 to 3.4 grams of EPA and DHA daily) on graft thrombosis was found using random-effects pairwise meta-analysis on data from four trials (n=287, RR 0.71, 95% CI 0.52 to 0.97). While this result accords with the protective effects of omega-3 PUFA on primary patency loss shown in the current study, it should be interpreted with caution because outcomes other than graft thrombosis were also included in the meta-analysis by He et al.\textsuperscript{46} including graft infection\textsuperscript{47} and angioplasty for significant stenosis\textsuperscript{38}. Reduction in thrombosis and patency loss may be explained by inhibitory effects on platelet aggregation\textsuperscript{18}, smooth muscle cell proliferation\textsuperscript{21} and inflammation\textsuperscript{19}, reduction in serum viscosity\textsuperscript{48} and promotion of vasodilation\textsuperscript{23}. There was no high certainty evidence that omega-3 PUFA treatment prevents all-cause mortality in the present study. This finding was consistent with the meta-analysis by He and colleagues\textsuperscript{46} that included 4 trials (n= 353) and showed a RR of 0.83 (95% CI 0.36 to 1.90) using fixed-effect meta-analysis. The same authors, however, reported a significant benefit of omega-3 PUFA supplementation on fatal and non-fatal cardiovascular events in participants of 5 studies (RR 0.41; 95% CI 0.26 to 0.66) which was not observed in the present study. The interpretability and meaningfulness of this result were limited by the inclusion of different composite outcome definitions. By restricting the definition to
cardiovascular death, a cardiovascular mortality benefit was not ascertained in the present meta-analysis. Thus far, cardiovascular benefits of omega-3 PUFA in people with chronic kidney disease have largely been shown by surrogate outcome measures, including lipid modulation, heart rate and blood pressure lowering effects\textsuperscript{49,50} which may not translate into patient-centered clinical outcomes, such as cardiovascular death. The latter outcome of omega-3 PUFA supplementation has not been addressed in adequately powered studies to date. However, a large international multicenter randomized controlled trial (Protection against Incidences of Serious Cardiovascular Events Study with daily fish oil supplementation in dialysis patients [PISCES]) is ongoing to assess the effect of omega-3 PUFA supplementation on serious fatal and non-fatal cardiovascular events in people on long-term hemodialysis\textsuperscript{51}.

People treated with hemodialysis are at increased risk of bleeding due to uremia-induced platelet dysfunction and requirements for anticoagulation during dialysis. The addition of low intensity anticoagulation with warfarin or antiplatelet agents exacerbates bleeding\textsuperscript{28,29}, yet the safety profile of omega-3 PUFA therapy in this population is uncertain. This systematic review observed few bleeding events (among 44 participants) leading to imprecise treatment estimates. In addition, the frequencies of minor (i.e. bleeding that ceases without intervention other than compression) versus major bleeding events (i.e. bleeding that requires blood products, hospital admission and/or interventions) were not specified.

Effective treatments to reduce arteriovenous access complications are highly valued by patients and mandate the need for larger, adequately powered RCTs addressing patient-centered, clinically important outcomes, such as dialysis suitability, need for interventions, mortality and risk of severe bleeding events to improve our confidence in the effectiveness and safety of omega-3 PUFA supplementation in dialysis patients. In addition,
implementation of standardized outcome definitions for vascular access outcomes would facilitate meta-analysis of treatment effects arising from new trials. An international, multi-stakeholder initiative (Standardized Outcomes in NephroloGy [SONG]) is currently underway to establish core outcome measures for vascular access complications based on shared priorities of patients and health professionals. This initiative will enhance the quality and relevance of outcome reporting of interventional trials in hemodialysis.

The present review was conducted according to methods outlined by Cochrane, including a systematic search designed by a specialist trial information manager, and data extraction and assessments of risks of bias and evidence certainty using the GRADE approach by two independent authors. Patient-level data analysis was performed by the original authors where possible to ensure reliable comparison and meta-analysis of outcomes aligned with previously published standardized outcome definitions. Although this review included a broad range of clinically relevant efficacy and safety outcomes, the key findings were limited by several factors. First, risk estimates were imprecise and the certainty of evidence was low for most outcomes due to the small numbers of trials and events. Only one trial was conducted in people undergoing AVF creation, which limited the generalizability of its results to this clinical setting. Moreover, data for vascular access suitability for dialysis, access abandonment and need for interventions were limited to the two most recently conducted trials. Second, the ability to detect a significant treatment effect difference between AVG and AVF may have been limited by the small number of trials and potential confounding due to differences in patient and access characteristics could not be excluded. Third, the findings are based on dichotomous outcomes and may not be applicable to more sensitive metrics such as rate or time to event as evident from the trial by Lok and colleagues, whereby the rate of access interventions but not the number of participants requiring AVG intervention was reduced by omega-3 PUFA supplementation. Fourth, the
dose effects of omega-3 PUFA treatment were unable to be determined due to large variations in the dosages, the compositions of omega-3 PUFA and different methods used to assess adherence. Fifth, the optimal timing and duration of omega-3 PUFA supplementation could not be determined due to differences in study designs. Finally, unpublished studies may have been missed despite a highly sensitive search that included hand-searching and conference abstracts.

In conclusion, omega-3 PUFA supplementation started at the time of arteriovenous access surgery probably prevents primary patency loss within 12 months but may have little or no effect on access interventions, dialysis suitability failure or access abandonment and treatment harms are uncertain. Larger RCTs are required to determine the efficacy and safety of omega-3 PUFA supplementation in patients requiring hemodialysis and to assess novel putative interventions to improve dialysis vascular outcomes. Based on the available evidence, recommendations on the routine use of omega-3 PUFA for safely preventing arteriovenous access complications cannot be made.

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Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. AV takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
Supplementary Tables and Figures

Table S1. Search terms

Table S2. Published primary and secondary outcomes and narrative conclusions reported in included studies

Table S3. Definitions provided by included studies for outcomes included in the meta-analyses

Figure S1. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

Figures S2 to S11 show the meta-analysis for each outcome.

Figure S2. Effect of fish oil supplementation on primary patency loss of arteriovenous dialysis accesses

Figure S3. Effect of fish oil supplementation on bleeding

Figure S4. Effect of fish oil supplementation on late dialysis suitability failure

Figure S5. Effect of fish oil supplementation on the need for interventions to maintain patency or assist maturation of arteriovenous dialysis accesses

Figure S6. Effect of fish oil supplementation on arteriovenous dialysis access abandonment

Figure S7. Effect of fish oil supplementation on gastrointestinal side-effects

Figure S8. Effect of fish oil supplementation on all-cause mortality

Figure S9. Effect of fish oil supplementation on cardiovascular mortality

Figure S10. Effect of fish oil supplementation on hospitalization

Figure S11. Effect of fish oil supplementation on adherence
References


45. Tanner NC, Da Silva A. Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts. *Cochrane Database Syst Rev.* 2015;7:CD002786.


Table 1. Characteristics of populations and interventions in the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. of participants</th>
<th>Vascular access type</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Control</th>
<th>Study duration</th>
<th>Age (y)</th>
<th>Male n (%)</th>
<th>DM, n (%)</th>
<th>PVD, n (%)</th>
</tr>
</thead>
<tbody>
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<td>Bowden et al</td>
<td>North America</td>
<td>34</td>
<td>PTFE graft</td>
<td>Adult (≥ 18 y) long-term hemodialysis patients with new PTFE graft. And unable to have an AVF</td>
<td>Fish oil (0.96g EPA, 0.6g DHA) daily for 8 months, starting within 7 days following access creation</td>
<td>Placebo (canola oil)</td>
<td>8 months</td>
<td>62</td>
<td>13 (45)</td>
<td>20 (35)</td>
<td>NR</td>
</tr>
<tr>
<td>De Fijter et al</td>
<td>Netherlands</td>
<td>32</td>
<td>Shunt</td>
<td>Hemodialysis patients</td>
<td>Fish oil (3g EPA + DHA) daily for 5 months</td>
<td>Placebo</td>
<td>5 months</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Diskin et al</td>
<td>North America</td>
<td>7</td>
<td>PTFE graft</td>
<td>Chronic hemodialysis patients with &gt; 3 episodes of graft thrombosis within the 12 preceding months</td>
<td>Fish oil (3g EPA) trice weekly on hemodialysis</td>
<td>Placebo</td>
<td>6 months</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Irish et al</td>
<td>Australia, NZ, Malaysia, UK</td>
<td>567</td>
<td>AVF</td>
<td>Patients aged over 19 with stage 4 or 5 chronic kidney disease on dialysis or planned to start within 12 months. Planned de novo AVF of in the upper or lower arm is planned</td>
<td>Fish oil (1.84g EPA, 1.52g DHA) daily for 12 weeks starting 1 day prior to access creation</td>
<td>Placebo (olive oil)</td>
<td>12 months</td>
<td>55</td>
<td>359 (63)</td>
<td>264 (50)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Lok et al</td>
<td>North America, Canada</td>
<td>201</td>
<td>PTFE graft</td>
<td>Individuals aged ≥ 18 years with end-stage renal disease who require a new synthetic graft for chronic hemodialysis. The patient may or may not have initiated dialysis at the time of enrolment.</td>
<td>Fish oil (1.6g EPA, 0.8g DHA) daily for 12 months, starting 7 days after access creation</td>
<td>Placebo (corn oil)</td>
<td>12 months</td>
<td>63</td>
<td>49 (50)</td>
<td>103 (53)</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Schmitz et al</td>
<td>North America</td>
<td>24</td>
<td>PTFE graft</td>
<td>Patients close to the initiation of chronic hemodialysis or on chronic hemodialysis who required placement of a new PTFE graft.</td>
<td>Fish oil (1.76g EPA, 0.96g DHA) daily for 12 months, starting 2 weeks after access creation</td>
<td>Placebo (corn oil)</td>
<td>12 months</td>
<td>53</td>
<td>11 (46)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AVF – Arteriovenous fistula; DHA – Docosahexanoic acid; EPA – Eicosapentaenoic acid; n – number; NR – not reported; NZ – New Zealand; PTFE –Polytetrafluorethylene; UK – United Kingdom; y – years (mean). aNumber of randomized people; bStudy duration equals time of outcome assessment.
### Table 2: Summary of findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Illustrative comparative risks</th>
<th>Relative risk (95% CI)</th>
<th>No of people (studies)</th>
<th>Certainty of evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary patency failure</strong></td>
<td>Placebo 73 fewer (123 fewer to 8 fewer)</td>
<td>0.81 (0.68, 0.98)</td>
<td>761 (3)</td>
<td>⊕⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Directness: data derived from small number of studies in different settings which may not be generalizable (treatment duration variable, access type variable).</td>
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<td></td>
<td>Omega-3 PUFA 18 more (10 fewer to 68 more)</td>
<td>1.40 (0.78, 2.49)</td>
<td>794 (4)</td>
<td>⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Severe Imprecision (2 downgrades): risk estimates include null effect and estimate consistent with both appreciable benefit and harm. 2. Directness: data derived from small number of studies in specific settings which may not be generalizable (treatment duration variable, dose variable, co-administration of anti-platelet agents variable).</td>
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<tr>
<td><strong>Bleeding</strong></td>
<td>Placebo 15 fewer (82 fewer to 70 more)</td>
<td>0.95 (0.73, 1.23)</td>
<td>536 (1)</td>
<td>⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Imprecision: risk estimate includes null effect 2. Directness: data derived from only 1 study in specific setting which may not be generalizable (AVF, 3 months of treatment).</td>
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<tr>
<td></td>
<td>Omega-3 PUFA 50 fewer (99 fewer to 11 more)</td>
<td>0.82 (0.64, 1.04)</td>
<td>732 (2)</td>
<td>⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Imprecision: risk estimate includes null effect 2. Directness: data derived from small number of studies in specific settings which may not be generalizable (treatment duration variable, access different – interventions may differ).</td>
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<tr>
<td><strong>Dialysis suitability failure</strong></td>
<td>Placebo 56 fewer (105 fewer to 8 more)</td>
<td>0.78 (0.59, 1.03)</td>
<td>732 (2)</td>
<td>⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Imprecision: risk estimate includes null effect 2. Directness: data derived from small number of studies in specific settings which may not be generalizable (treatment duration variable, access different – interventions may differ).</td>
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<td>Omega-3 PUFA 12 more (20 fewer to 76 more)</td>
<td>1.22 (0.64, 2.34)</td>
<td>816 (4)</td>
<td>⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Severe imprecision (2 downgrades): risk estimates include null effect and estimate consistent with both appreciable benefit and harm.</td>
</tr>
<tr>
<td><strong>Interventions to maintain patency or assist maturation</strong></td>
<td>Placebo 1 fewer (21 fewer to 37 more)</td>
<td>0.98 (0.51, 1.86)</td>
<td>799 (4)</td>
<td>⊕⊕</td>
<td>Evidence quality downgraded as follows: 1. Severe Imprecision (2 downgrades): risk estimates include null effect and estimate consistent with both appreciable benefit and harm. 2. Directness: data derived from small number of studies in specific settings which may not be generalizable (treatment duration variable, dose variable, co-administration of anti-platelet agents variable).</td>
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<tr>
<td>Outcome</td>
<td>Assumed risk per 1000 patients treated for 12 to 52 weeks</td>
<td>Corresponding risk per 1000 patients treated for 12 to 52 weeks (95% CI)*</td>
<td>Relative risk (95% CI)</td>
<td>No of people (studies)</td>
<td>Certainty of evidence (GRADE)*</td>
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<td>Cardiovascular mortality</td>
<td>Placebo</td>
<td>Omega-3 PUFA</td>
<td>0.55 (0.22, 1.35)</td>
<td>768 (4)</td>
<td>⊕¹, ⊥²  low</td>
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<td></td>
<td>37</td>
<td>17 fewer (29 fewer to 13 more)</td>
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<td></td>
<td>381</td>
<td>4 fewer (72 fewer to 84 more)</td>
<td>0.99 (0.81, 1.22)</td>
<td>574 (2)</td>
<td>⊥², ⊥²  low</td>
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*The basis for the assumed risk (e.g., the average control group risk across studies) was calculated from data in the meta-analyses. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative risk of the intervention (and its 95% CI).

It was not possible to assess or downgrade for small-study effects.

Abbreviations: CI - Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.
Figure Legend

Figure 1: Identification process for eligible trials
Abbreviations: AVF – arteriovenous fistula; AVG – arteriovenous graft.

a no non-English citations were identified.

Figure 2. Summary of overall treatment effects of omega-3 polyunsaturated fatty acids on arteriovenous vascular access outcomes and potential adverse events.
Abbreviations: AVF – arteriovenous fistula; AVG – arteriovenous graft; CI – confidence interval; NA – not assessable; PUFA – polyunsaturated fatty acids