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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36 **Short title:** Fish oils for hemodialysis vascular access

37

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

90 protects dialysis patients from experiencing loss of blood flow through their access, but it
91 remains uncertain whether fish oil improves dialysis access usability, reduces the need for
92 additional procedures or hospital admissions, or is safe. Given that patients, caregivers, and
93 health professionals consider vascular access to be critically important, additional trials to
94 find healthcare interventions that improve access outcomes are needed.

95

96 **Introduction**

97 Hemodialysis is the most common renal replacement therapy worldwide and ideally requires
 98 a functioning arteriovenous vascular access. Establishing and maintaining a functional
 99 arteriovenous access remains one of the greatest challenges for dialysis care¹⁻³. Arteriovenous
 100 fistula (AVF) and graft (AVG) dysfunction lead to prolonged use of central venous catheters
 101 and repeated hospitalization and procedures, which are associated with higher rates of
 102 complications and mortality⁴⁻⁶. Patients, caregivers, and health care professionals consider
 103 vascular access outcomes a critical priority.⁷ Strategies to improve the usability of
 104 hemodialysis vascular access are required.

105 The pathogenesis of arteriovenous access failure is complex and not fully understood⁸.
 106 Pathogenic processes that may contribute to patency loss, impaired maturation, and dialysis
 107 suitability failure include neointimal hyperplasia formation and impaired vascular remodeling
 108 with insufficient vasodilation and vessel wall thickening in response to the increased
 109 pressure, shear stress and oxygen tension resulting from redirected arterial inflow⁸⁻¹⁰.

110 Randomized controlled trials have evaluated various local and systemic therapies to improve
 111 arteriovenous access maturation and function¹⁰. Most trials have focused on anti-platelet
 112 agents to prevent access thrombosis and maintaining vascular access patency. While anti-
 113 platelet agents may be effective in reducing early arteriovenous access thrombosis¹¹⁻¹⁶, they
 114 have not been shown to improve long-term patency and dialysis suitability^{16,17}. Given the
 115 complexity of processes involved in dialysis vascular access failure, an agent with pleotropic
 116 vascular effects may provide a more durable and effective therapeutic strategy for favorably
 117 influencing vascular remodeling, neointimal hyperplasia formation, and thrombotic risk in
 118 newly formed vascular access. Omega-3 polyunsaturated fatty acids (omega-3 PUFA) show
 119 promise because they inhibit platelet aggregation¹⁸ and exert anti-inflammatory^{19,20}, anti-

proliferative^{21,22} and vasodilatory effects²³ 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^{24,25}, the anti-platelet effects of omega-3 PUFA may continue to pose a concern given the already increased bleeding diathesis in this population²⁶⁻²⁹.

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^{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)

framework³². 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 used³³.

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 methodology³⁴ 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)^{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 metric³⁷. An I^2 value >75% was considered to indicate substantial heterogeneity³⁷. 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 participants³⁸⁻⁴³ 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 12⁴⁰ to 52 weeks^{41,42} and the study follow-up time ranged between five⁴³ and 12 months⁴⁰⁻⁴² (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^{38,41}, two weeks after access creation in one trial⁴², and one day before access creation in one trial⁴⁰. The dose of omega-3 PUFA varied from 3 grams three times weekly³⁹ to 6 grams daily³⁸, 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^{38,39,41,42}, one on AVF outcomes⁴⁰, and one on shunt outcomes⁴³. 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 outcomes³³ were available from two studies^{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^{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 data³⁸ or numbers were well balanced between treatment groups⁴⁰⁻⁴², unclear for one³⁹ and high risk for the cross-over study without available outcome data at the end of the first study phase⁴³. 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)^{38,40,41}. 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)³⁹⁻⁴². 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 bleed³⁹.

Dialysis suitability failure

A single trial reported data on late dialysis suitability failure⁴⁰, 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 trial⁴⁰ reported on the need for interventions to restore patency or assist maturation in newly created AVF (536 people) and one trial⁴¹ in AVG (196 people). Low certainty evidence suggested, that omega-3 PUFA treatment (2.4⁴⁰ to 3.4³⁹ 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 (2.4⁴⁰ to 3.4³⁹ 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^{38,40-42} (816 people) reported gastrointestinal side-effects, including bloating, gas or “fishy” aftertaste. Based on low certainty evidence, omega-3 PUFA treatment (1.6³⁷ to 3.4³⁹ 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 mortality³⁸⁻⁴¹ (RR 0.98, 95% CI 0.51-1.86) (Figures 2 and S8). Cardiovascular mortality was reported in 4 trials³⁸⁻⁴¹ (22 events in 768 people). Omega-3 PUFA supplementation (3 grams of EPA 3 times weekly³⁸ to 3.4 grams of EPA and DHA daily³⁹) 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^{39,40} (574 people). Omega-3 PUFA treatment (3 grams of EPA 3 times weekly³⁸ to 3.4 grams of EPA and DHA daily³⁹) 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^{38,40-42}. Three studies⁴⁰⁻⁴² measured changes in the fatty acid composition of whole blood cells⁴¹, platelets⁴² or erythrocytes⁴⁰, 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 capsules⁴⁰, the number of people who did

not take the study treatment (as reported by study coordinators or evident from returned capsules)⁴¹ or people who were ‘noncompliant’ based on pill counts³⁸ (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^{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 hemodialysis⁴⁵: Random-effects pairwise meta-analysis of two trials (220

people)^{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 hemodialysis⁴⁶: 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.⁴⁶ including graft infection⁴⁷ and angioplasty for significant stenosis³⁸. Reduction in thrombosis and patency loss may be explained by inhibitory effects on platelet aggregation¹⁸, smooth muscle cell proliferation²¹ and inflammation¹⁹, reduction in serum viscosity⁴⁸ and promotion of vasodilation²³.

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 colleagues⁴⁶ 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 334 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^{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 hemodialysis⁵¹.

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^{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 professionals⁷. 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 definitions³³. 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^{40,41}. 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 colleagues⁴¹, 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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Contributions: research idea and study design: AV, AI, CH, DJ, EP, SP; data acquisition: AV, CL, EP, SP; data analysis/interpretation: AV, CL, CH, DJ, EP, GS, KP, SP, TM; statistical analysis: AV, CL, EP; supervision or mentorship: AI, CH, DJ, EP, KP, SP, TM.

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

1. Al-Jaishi AA, Liu AR, Lok CE, Zhang JC, Moist LM. Complications of the Arteriovenous Fistula: A Systematic Review. *J. Am. Soc. Nephrol.* 2016;28:12.
2. Al-Jaishi AA, Oliver MJ, Thomas SM, et al. Patency rates of the arteriovenous fistula for hemodialysis: a systematic review and meta-analysis. *Am. J. Kidney Dis.* 2014;63(3):464-478.
3. Malas MB, Canner JK, Hicks CW, et al. Trends in incident hemodialysis access and mortality. *JAMA Surg.* 2015;150(5):441-448.
4. Polkinghorne KR, McDonald SP, Atkins RC, Kerr PG. Vascular access and all-cause mortality: a propensity score analysis. *J. Am. Soc. Nephrol.* 2004;15(2):477-486.
5. Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J. Am. Soc. Nephrol.* 2013;24(3):465-473.
6. Ravani P, Gillespie BW, Quinn RR, et al. Temporal risk profile for infectious and noninfectious complications of hemodialysis access. *J. Am. Soc. Nephrol.* 2013;24(10):1668-1677.
7. Tong A, Manns B, Hemmelgarn B, et al. Establishing Core Outcome Domains in Hemodialysis: Report of the Standardized Outcomes in Nephrology-Hemodialysis (SONG-HD) Consensus Workshop. *Am. J. Kidney Dis.* 2017;69(1):97-107.
8. Lee T, Misra S. New Insights into Dialysis Vascular Access: Molecular Targets in Arteriovenous Fistula and Arteriovenous Graft Failure and Their Potential to Improve Vascular Access Outcomes. *Clin. J. Am. Soc. Nephrol.* 2016;11(8):1504-1512.
9. Lu DY, Chen EY, Wong DJ, et al. Vein graft adaptation and fistula maturation in the arterial environment. *J. Surg. Res.* 2014;188(1):162-173.
10. Riella MC, Roy-Chaudhury P. Vascular access in haemodialysis: strengthening the Achilles' heel. *Nat Rev Nephrol.* 2013;9(6):348-357.
11. Kaufman JS. Antithrombotic agents and the prevention of access thrombosis. *Semin Dial.* 2000;13(1):40-46.

- 477 **12.** Andrassy K, Malluche H, Bornefeld H, et al. Prevention of p.o. clotting of av. cimino fistulae
478 with acetylsalicyl acid. Results of a prospective double blind study. *Klin. Wochenschr.*
479 1974;52(7):348-349.
- 480 **13.** Grontoft KC, Mulec H, Gutierrez A, Olander R. Thromboprophylactic effect of ticlopidine in
481 arteriovenous fistulas for haemodialysis. *Scand. J. Urol. Nephrol.* 1985;19(1):55-57.
- 482 **14.** Grontoft KC, Larsson R, Mulec H, Weiss LG, Dickinson JP. Effects of ticlopidine in AV-
483 fistula surgery in uremia. Fistula Study Group. *Scand. J. Urol. Nephrol.* 1998;32(4):276-283.
- 484 **15.** Fiskerstrand CE, Thompson IW, Burnet ME, Williams P, Anderton JL. Double-blind
485 randomized trial of the effect of ticlopidine in arteriovenous fistulas for hemodialysis. *Artif.*
486 *Organs.* 1985;9(1):61-63.
- 487 **16.** Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous
488 fistulas for hemodialysis: a randomized controlled trial. *JAMA.* 2008;299(18):2164-2171.
- 489 **17.** Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet therapy to prevent hemodialysis
490 vascular access failure: systematic review and meta-analysis. *Am. J. Kidney Dis.*
491 2013;61(1):112-122.
- 492 **18.** Rylance PB, Gordge MP, Saynor R, Parsons V, Weston MJ. Fish oil modifies lipids and
493 reduces platelet aggregability in haemodialysis patients. *Nephron.* 1986;43(3):196-202.
- 494 **19.** Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or
495 pharmacology? *Br. J. Clin. Pharmacol.* 2013;75(3):645-662.
- 496 **20.** Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3
497 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by
498 mononuclear cells. *N. Engl. J. Med.* 1989;320(5):265-271.
- 499 **21.** Fox PL, DiCorleto PE. Fish oils inhibit endothelial cell production of platelet-derived growth
500 factor-like protein. *Science.* 1988;241(4864):453-456.
- 501 **22.** Shiina T, Terano T, Saito J, Tamura Y, Yoshida S. Eicosapentaenoic acid and
502 docosahexaenoic acid suppress the proliferation of vascular smooth muscle cells.
503 *Atherosclerosis.* 1993;104(1-2):95-103.

- 504 **23.** Wang Q, Liang X, Wang L, et al. Effect of omega-3 fatty acids supplementation on
505 endothelial function: a meta-analysis of randomized controlled trials. *Atherosclerosis*.
506 2012;221(2):536-543.
- 507 **24.** Donnelly SM, Ali MA, Churchill DN. Effect of n-3 fatty acids from fish oil on hemostasis,
508 blood pressure, and lipid profile of dialysis patients. *J. Am. Soc. Nephrol.* 1992;2(11):1634-
509 1639.
- 510 **25.** Lempert KD, Rogers JS, 2nd, Albrink MJ. Effects of dietary fish oil on serum lipids and
511 blood coagulation in peritoneal dialysis patients. *Am. J. Kidney Dis.* 1988;11(2):170-175.
- 512 **26.** Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and
513 cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic
514 review and meta-analysis. *Ann. Intern. Med.* 2012;156(6):445-459.
- 515 **27.** Baigent C, Landray M, Leaper C, et al. First United Kingdom Heart and Renal Protection
516 (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose
517 aspirin in chronic kidney disease. *Am. J. Kidney Dis.* 2005;45(3):473-484.
- 518 **28.** Kaufman JS, O'Connor TZ, Zhang JH, et al. Randomized controlled trial of clopidogrel plus
519 aspirin to prevent hemodialysis access graft thrombosis. *J. Am. Soc. Nephrol.*
520 2003;14(9):2313-2321.
- 521 **29.** Crowther MA, Clase CM, Margetts PJ, et al. Low-intensity warfarin is ineffective for the
522 prevention of PTFE graft failure in patients on hemodialysis: a randomized controlled trial. *J.*
523 *Am. Soc. Nephrol.* 2002;13(9):2331-2337.
- 524 **30.** Viecelli AK, Irish AB, Polkinghorne K, et al. Systematic review and meta-analysis of omega-
525 3 polyunsaturated fatty acids (fish oil) to prevent arteriovenous fistula and graft failure 2016;
526 https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036308.
527 Accessed 13 January, 2017.
- 528 **31.** Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for
529 systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.*
530 2009;151(4):264-269, W264.

- 531 **32.** O'Connor D, Green S, Higgins JPT. Chapter 5: Defining the review question and developing
532 criteria for including studies. In: Higgins JP, Green S (editors). . *Cochrane Handbook for*
533 *Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane
534 Collaboration, 2011.
- 535 **33.** Lee T, Mokrzycki M, Moist L, et al. Standardized definitions for hemodialysis vascular
536 access. *Semin Dial.* 2011;24(5):515-524.
- 537 **34.** Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing
538 risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
- 539 **35.** Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of
540 evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.
- 541 **36.** Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12:
542 Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). . *Cochrane*
543 *Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* :
544 The Cochrane Collaboration; 2011.
- 545 **37.** Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses.
546 *BMJ.* 2003;327(7414):557-560.
- 547 **38.** Bowden RG, Wilson RL, Gentile M, Ounpraseuth S, Moore P, Leutholtz BC. Effects of
548 omega-3 fatty acid supplementation on vascular access thrombosis in polytetrafluorethylene
549 grafts. *J. Ren. Nutr.* 2007;17(2):126-131.
- 550 **39.** Diskin CJ, Thomas CE, Zellner CP, Lock S, Tanja J. Fish oil to prevent intimal hyperplasia
551 and access thrombosis. *Nephron.* 1990;55(4):445-447.
- 552 **40.** Irish AB, Vieceilli AK, Hawley CM, et al. The omega-3 fatty acids (Fish oils) and Aspirin in
553 Vascular access OUTcomes in RENal Disease (FAVOURED) study – a randomized placebo-
554 controlled trial [published online ahead of print February 1, 2017]. *JAMA Internal Medicine.*
555 doi: 10.1001/jamainternmed.2016.8029.
- 556 **41.** Lok CE, Moist L, Hemmelgarn BR, et al. Effect of fish oil supplementation on graft patency
557 and cardiovascular events among patients with new synthetic arteriovenous hemodialysis
558 grafts: a randomized controlled trial. *JAMA.* 2012;307(17):1809-1816.

- 559 **42.** Schmitz PG, McCloud LK, Reikes ST, Leonard CL, Gellens ME. Prophylaxis of
560 hemodialysis graft thrombosis with fish oil: double-blind, randomized, prospective trial. *J.*
561 *Am. Soc. Nephrol.* 2002;13(1):184-190.
- 562 **43.** de Fijter CW, Popp-Snijders C, Oe LP, Tran DD, van der Meulen J, Donker AJ. Does
563 additional treatment with fish oil mitigate the side effects of recombinant human
564 erythropoietin in dialysis patients? *Haematologica.* 1995;80(4):332-334.
- 565 **44.** Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and
566 polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic
567 review. *J. Vasc. Surg.* 2003;38(5):1005-1011.
- 568 **45.** Tanner NC, Da Silva A. Medical adjuvant treatment to increase patency of arteriovenous
569 fistulae and grafts. *Cochrane Database Syst Rev.* 2015;7:CD002786.
- 570 **46.** He L, Li MS, Lin M, Zhao TY, Gao P. Effect of fish oil supplement in maintenance
571 hemodialysis patients: a systematic review and meta-analysis of published randomized
572 controlled trials. *Eur. J. Clin. Pharmacol.* 2016;72(2):129-139.
- 573 **47.** Hung AM, Booker C, Ellis CD, et al. Omega-3 fatty acids inhibit the up-regulation of
574 endothelial chemokines in maintenance hemodialysis patients. *Nephrol. Dial. Transplant.*
575 2015;30(2):266-274.
- 576 **48.** van Acker BA, Bilo HJ, Popp-Snijders C, van Bronswijk H, Oe PL, Donker AJ. The effect of
577 fish oil on lipid profile and viscosity of erythrocyte suspensions in CAPD patients. *Nephrol.*
578 *Dial. Transplant.* 1987;2(6):557-561.
- 579 **49.** Mori TA, Burke V, Puddey I, et al. The effects of [omega]3 fatty acids and coenzyme Q10 on
580 blood pressure and heart rate in chronic kidney disease: a randomized controlled trial. *J.*
581 *Hypertens.* 2009;27(9):1863-1872.
- 582 **50.** Zhu W, Dong C, Du H, et al. Effects of fish oil on serum lipid profile in dialysis patients: a
583 systematic review and meta-analysis of randomized controlled trials. *Lipids Health Dis.*
584 2014;13:127.
- 585 **51.** Lok C. Protection against Incidences of Serious Cardiovascular Events Study (PISCES).
586 2013; <http://www.isrctn.com/ISRCTN00691795>. Accessed 18 January, 2017.

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

Study	Country	No. of participants ^a	Vascular access type	Inclusion criteria	Intervention	Control	Study duration ^b	Age (y)	Male n (%)	DM, n (%)	PVD, n (%)
Bowden et al 2007	North America	34	PTFE graft	Adult (≥ 18 y) long-term hemodialysis patients with new PTFE graft. And unable to have an AVF	Fish oil (0.96g EPA, 0.6g DHA) daily for 8 months, starting within 7 days following access creation	Placebo (canola oil)	8 months	62	13 (45)	20 (35)	NR
De Fijter et al 1995	Netherlands	32	Shunt	Hemodialysis patients	Fish oil (3g EPA + DHA) daily for 5 months	Placebo	5 months	NR	NR	NR	NR
Diskin et al 1990	North America	7	PTFE graft	Chronic hemodialysis patients with > 3 episodes of graft thrombosis within the 12 preceding months	Fish oil (3g EPA) trice weekly on hemodialysis	Placebo	6 months	NR	NR	NR	NR
Irish et al 2017	Australia, NZ, Malaysia, UK	567	AVF	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	Fish oil (1.84g EPA, 1.52g DHA) daily for 12 weeks starting 1 day prior to access creation	Placebo (olive oil)	12 months	55	359 (63)	264 (50)	24 (5)
Lok et al 2012	North America, Canada	201	PTFE graft	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.	Fish oil (1.6g EPA, 0.8g DHA) daily for 12 months, starting 7 days after access creation	Placebo (corn oil)	12 months	63	49 (50)	103 (53)	29 (15)
Schmitz et al 2002	North America	24	PTFE graft	Patients close to the initiation of chronic hemodialysis or on chronic hemodialysis who required placement of a new PTFE graft.	Fish oil (1.76g EPA, 0.96g DHA) daily for 12 months, starting 2 weeks after access creation	Placebo (corn oil)	12 months	53	11 (46)	NR	NR

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

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591 **Table 2: Summary of findings**

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Outcome	Illustrative comparative risks		Relative risk (95% CI)	No of people (studies)	Certainty of evidence (GRADE) ^b	Comments
	Assumed risk per 1000 patients treated for 12 to 52 weeks	Corresponding risk per 1000 patients treated for 12 to 52 weeks (95% CI) ^a				
	Placebo	Omega-3 PUFA				
Primary patency failure	384	73 fewer (123 fewer to 8 fewer)	0.81 (0.68, 0.98)	761 (3)	⊕⊕⊕ ¹ moderate	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).
Bleeding	46	18 more (10 fewer to 68 more)	1.40 (0.78, 2.49)	794 (4)	⊕ ^{1,2} very low	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).
Dialysis suitability failure	305	15 fewer (82 fewer to 70 more)	0.95 (0.73, 1.23)	536 (1)	⊕⊕ ^{1,2} low	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).
Interventions to maintain patency or assist maturation	275	50 fewer (99 fewer to 11 more)	0.82 (0.64, 1.04)	732 (2)	⊕⊕ ^{1,2} low	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).
Access abandonment	256	56 fewer (105 fewer to 8 more)	0.78 (0.59, 1.03)	732 (2)	⊕⊕ ^{1,2} low	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)
Gastrointestinal side-effects	57	12 more (20 fewer to 76 more)	1.22 (0.64, 2.34)	816 (4)	⊕⊕ ¹ low	Evidence quality downgraded as follows: ¹ Severe imprecision (2 downgrades): risk estimates include null effect and estimate consistent with both appreciable benefit and harm.
All-cause mortality	43	1 fewer (21 fewer to 37 more)	0.98 (0.51, 1.86)	799 (4)	⊕ ^{1,2} very low	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).

Outcome	Illustrative comparative risks					
	Assumed risk per 1000 patients treated for 12 to 52 weeks	Corresponding risk per 1000 patients treated for 12 to 52 weeks (95% CI) ^a				
	Placebo	Omega-3 PUFA	Relative risk (95% CI)	No of people (studies)	Certainty of evidence (GRADE) ^b	Comments
Cardiovascular mortality	37	17 fewer (29 fewer to 13 more)	0.55 (0.22, 1.35)	768 (4)	⊕ ^{1,2} very low	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).
Hospitalization	381	4 fewer (72 fewer to 84 more)	0.99 (0.81, 1.22)	574 (2)	⊕⊕ ^{1,2} low	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)
^a 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). ^b 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 very 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.						

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Figure Legend

Figure 1: Identification process for eligible trials

Abbreviations: AVF – arteriovenous fistula; AVG – arteriovenous graft.

^ano 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