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Tam KW, Wu MY, Siddiqui FJ, Chan ESY, Zhu Y, Jafar TH

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[Intervention Review]

Omega-3 fatty acids for dialysis vascular access outcomes in patients with chronic kidney disease

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ABSTRACT

Background

Maintaining long-term vascular access patency is necessary for high quality haemodialysis (HD) treatment of patients with the terminal and most serious stage of chronic kidney disease (CKD) - end-stage kidney disease (ESKD). Oral supplementation with omega-3 fatty acids (ω -3FA) may help to prevent blockage of the vascular access by reducing the risk of thrombosis and stenosis.

Objectives

To evaluate the efficacy and safety of ω -3FA supplementation versus placebo or no treatment for maintaining vascular access patency in ESKD patients undergoing HD.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 23 July 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) of omega-3 fatty acids versus placebo that assessed the patency of arteriovenous fistula (AVF) or arteriovenous graft (AVG) types of vascular access in ESKD patients.

Data collection and analysis

We assessed the risk of bias of each eligible study using the Cochrane Risk of Bias tool and made separate overall risk of bias judgments for the efficacy and safety outcomes. The certainty of evidence was assessed using the GRADE approach. The primary efficacy outcome was loss of vascular patency and the primary safety outcomes were occurrences of serious adverse events (e.g. death, hospitalisation, cardiovascular events, major bleeding). Secondary outcomes were the occurrence of non-serious adverse events (e.g. minor bleeding,

gastrointestinal events and other adverse events). Efficacy effects were reported as risk ratios (RR) and safety effects as risk differences (RD) with 95% confidence intervals (CI). Studies were pooled separately by type of vascular access using a random-effects model.

Main results

Five studies (833 participants) were included; one was a very small pilot study of 7 participants. All studies compared oral ω -3FA supplements against placebo. Four studies enrolled participants with arteriovenous grafts (AVGs), and the other had participants with arteriovenous fistulas (AVFs). The risk of bias for both efficacy and safety outcomes was unclear for all studies, due mainly to incomplete reporting for allocation concealment and incompleteness of study follow-up.

In AVF patients, ω -3FA supplementation probably makes little or no difference to the 12-month risk of patency loss (1 study, 536 participants: RR 1.01, 95% CI 0.84 to 1.21; moderate certainty evidence), risk of death (1 study, 567 participants: RD 0.00, 95% CI -0.03 to 0.02; moderate certainty evidence) and risk of hospitalisation (1 study, 567 participants: RD 0.00, 95% CI -0.08 to 0.08; low certainty evidence). There was no information on cardiovascular events and major bleeding.

In AVG patients, it is very uncertain whether ω -3FA supplementation reduces the risk of patency loss within 6 months (2 studies, 41 participants: RR 0.91, 95% CI 0.36 to 2.28; very low certainty evidence) or 12 months (2 studies, 220 participants: RR 0.59, 95% CI 0.27 to 1.31; very low certainty evidence). ω -3FA supplementation may make little or no difference to the risk of death within 6 to 12 months in AVG patients (4 studies, 261 participants: RD 0.01, 95% CI -0.05 to 0.07; low certainty evidence). It is very uncertain if ω -3FA supplementation increases the risk of hospitalisation (3 studies, 65 participants: RD 0.08, 95% CI -0.11 to 0.28; very low certainty evidence), changes the risk of cardiovascular events (4 studies, 261 participants: RD -0.02, 95% CI -0.11 to 0.07; very low certainty evidence), or increases the risk of major bleeding (3 studies, 65 participants: RD 0.08, 95% CI -0.11 to 0.28; very low certainty evidence) within 6 to 12 months in AVG patients. There may be an increase in the risk of mild gastrointestinal adverse reactions (3 studies, 65 participants: RD 0.25, 95% CI 0.07 to 0.43; low certainty evidence) such as a sensation of bloatedness, gas or a fishy aftertaste.

Authors' conclusions

In CKD patients with an AVF, there is moderate certainty that ω -3FA supplementation makes little or no difference to preventing patency loss; and in patients with an AVG, it is very uncertain that ω -3FA supplementation prevents patency loss within 12 months.

PLAIN LANGUAGE SUMMARY

Fish oil for preventing blockage of haemodialysis vascular access in patients with kidney failure

What is the issue?

Patients requiring long-term haemodialysis (HD) because of poorly functioning kidneys need a reliable and efficient method of circulating blood at high flow rates between their bodies and the HD machine. Arteriovenous fistulas (AVFs) and grafts (AVGs) are the two main methods of achieving such long-term vascular access. An AVF is a surgically constructed direct connection (fistula) between a patient's artery and vein. An AVG is a synthetic flexible hollow tubing (graft) that indirectly connects a patient's artery and vein and is usually used when a fistula cannot be created. During HD, the fistula or graft is pierced by needles (cannulated) connected to the dialysis machine. The patency of these artificial connections may be blocked by blood clots (thrombosis) or by a narrowing (stenosis) of the vein. The risk of this occurring is lower for AVFs, making it the method of choice. When a blockage does occur, HD cannot be performed and surgical or radiological salvage procedures will be urgently required. Omega-3 fatty acid fish oils can reduce blood viscosity and might conceivably reduce the risk of blood clots and blood vessel narrowing, hence improving long-term vascular access and quality of HD.

What did we do?

We collected data from studies that tested HD patients with supplements of omega-3 fatty acid fish oils against placebo and that reported results for preventing vascular access blockage and for the following side-effects - death, hospitalisation, cardiovascular events, major bleeding, minor bleeding, gastrointestinal events, and other adverse events. We analysed and reported the results separately for patients with AVFs and AVGs.

What did we find?

We found five randomised controlled trials (RCTs) that studied a total of 833 participants; one was a very small pilot study of seven participants. Four studies involved patients with AVGs; there was only one study of AVFs. The outcomes were measured over a period of six or 12 months. There were reservations about the overall quality of all the studies, making us moderately to highly uncertain about the evidence. In AVF patients, we are moderately certain that fish oil supplements do not prevent blockage nor do they cause additional harm but the evidence only comes from one study. In AVG patients, we are very uncertain of the evidence for preventing blockage or causing serious harm, but there may be an increased risk of mild digestive side-effects such as a sensation of bloatedness, gas or a fishy aftertaste.

Conclusions

There is limited high quality data on the benefits of omega-3 fish oil supplementation for preventing HD blockage in kidney failure patients. We did not find strong evidence that omega-3 fish oil supplements could prevent blockage of HD vascular access or that it increases the risk of serious and non-serious side-effects. All the evidence for preventing blockages come from just one or two studies, so more and better quality studies are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Omega-3 fatty acids versus placebo for dialysis vascular access outcomes in AVF patients with ESKD

Omega-3 fatty acids versus placebo for dialysis vascular access outcomes in AVF patients with ESKD

Patient or population: Dialysis vascular access outcomes in AVF patients with ESKD

Setting: chronic outpatient haemodialysis

Intervention: omega-3 fatty acids (ω -3FA)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ω -3FA				
Loss of patency: assessed with clinical absence of bruit or need of rescue intervention Follow up: mean 12 months	470 per 1,000	475 per 1,000 (395 to 569)	RR 1.01 (0.84 to 1.21)	536 (1)	⊕⊕⊕⊖ MODERATE ¹	-
Serious adverse events: death Follow-up: mean 12 months	32 per 1,000	32 per 1,000 (2 to 52)	RD 0.00 (-0.03 to 0.02)	567 (1)	⊕⊕⊕⊖ MODERATE ²	-
Serious adverse events: hospitalisation Follow up: mean 12 months	385 per 1,000	385 per 1,000 (305 to 465)	RD 0.00 (-0.08 to 0.08)	567 (1)	⊕⊕⊖⊖ LOW ^{1 2}	-
Serious adverse events: cardiovascular events	-	-	-	-	-	Not reported
Serious adverse events: major bleeding	-	-	-	-	-	Not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RD:** Risk difference; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- ¹ 95% CI is wide and consistent with both important harm or benefit
² Unclear risk of bias - attrition bias

Summary of findings 2. Omega-3 fatty acids compared to Placebo for dialysis vascular access outcomes in AVG patients with ESKD

Omega-3 fatty acids compared to Placebo for dialysis vascular access outcomes in AVG patients with ESKD

Patient or population: dialysis vascular access outcomes in AVG patients with ESKD

Setting: chronic outpatient haemodialysis

Intervention: omega-3 fatty acids (ω -3FA)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ω-3FA				
Loss of patency by 6 months as-sessed with Fistulagram or duplex ultrasonography Follow up: range 6 to 8 months	Study population		RR 0.91 (0.36 to 2.28)	41 (2)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}	-
	400 per 1,000	364 per 1,000 (144 to 912)				
	Low					
	350 per 1,000	318 per 1,000 (126 to 798)				
	High					
	667 per 1,000	607 per 1,000 (240 to 1,000)				
Loss of patency by 12 months as-sessed with angiography Follow up: mean 12 months	Study population		RR 0.59 (0.27 to 1.31)	220 (2)	⊕⊕⊕⊕ VERY LOW ^{1 3 4}	-
	633 per 1,000	373 per 1,000 (171 to 829)				
	Low					
	620 per 1,000	366 per 1,000 (167 to 812)				
	High					

	750 per 1,000	443 per 1,000 (203 to 983)				
Serious adverse events: death Follow up: range 6 to 12 months	Study population		RD 0.01 (-0.05 to 0.07)	261 (4)	⊕⊕⊕⊕ LOW ^{1 5}	-
	62 per 1,000	72 per 1,000 (12 to 132)				
	Low					
	0 per 1,000	10 per 1,000 (0 to 70)				
	High					
	82 per 1,000	92 per 1,000 (32 to 152)				
Serious adverse events: hospitali- sation Follow up: mean 6 to 12 months	Study population		RD 0.08 (-0.11 to 0.28)	65 (3)	⊕⊕⊕⊕ VERY LOW ^{1 3 4}	-
	0 per 1,000	80 per 1,000 (0 to 280)				
Serious adverse events: cardiovas- cular events Follow up: range 6 to 12 months	Study population		RD -0.02 (-0.11 to 0.07)	261 (4)	⊕⊕⊕⊕ VERY LOW ^{1 2 3}	-
	170 per 1,000	150 per 1,000 (60 to 240)				
	Low					
	0 per 1,000	0 per 1,000 (0 to 70)				
	High					
	175 per 1,000	155 per 1,000 (65 to 245)				
Serious adverse events: major bleeding Follow up: range 6 to 12 months	0 per 1,000	80 per 1,000 (0 to 280)	RD 0.08 (-0.11 to 0.28)	65 (3)	⊕⊕⊕⊕ VERY LOW ^{1 3 4}	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RD:** Risk difference; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Unclear risk of bias - selection and attrition bias

² Point estimates favour different interventions

³ 95% CI is wide and consistent with both important harm and benefit

⁴ Point estimates are widely differing and $I^2 > 50\%$

⁵ 95% CI is wide and consistent with both moderate harm and benefit

BACKGROUND

Description of the condition

Patients with end-stage kidney disease (ESKD) on long-term haemodialysis (HD) require either an arteriovenous fistula (AVF) or an arteriovenous graft (AVG) to provide long-term vascular access to and from the dialysis machine. While central venous catheters are commonly inserted when urgent vascular access is required, they are associated with high rates of infection and stenosis. An AVF is a deliberate connection between an artery and a vein constructed from an end-to-side vein to artery anastomosis, typically in the forearm or upper arm. An AVG is a synthetic graft (generally made of expanded polytetrafluoroethylene) interposed between an artery and a vein. From 1996 to 2007, AVF use rose from 24% to 47% and increased further to 63% by 2010 in the USA (Ethier 2008; Pisoni 2015). Moreover, AVG use fell by 50% in the USA from 58% in 1996 to 28% by 2007 (Ethier 2008). An AVF is generally preferred over an AVG because of the higher chance of long-term patency, but the drawback is a longer waiting time from construction to first-use (maturation) and a higher maturation failure rate (Hayashi 2006). AVGs can be cannulated within 2 to 6 weeks, in contrast the median time to cannulate AVFs in the USA and UK is 3 months, and in Japan it is 30 days (Ravani 2004). Hence AVG placement remains an important alternative for patients (i) requiring early vascular access, (ii) with small or weak veins, or (iii) whose AVF have failed to mature (Lee 2013). However, AVG patency declines at a faster rate becoming worse than AVF in the long term (Munda 1983).

Problems of establishing and maintaining a vascular access (e.g. maturation failure, infection, stenosis, thrombosis, aneurysm, limb ischaemia) accounts for much of the mortality, morbidity and diminished dialysis quality in patients receiving HD (Annuk 2001; Locatelli 2012; Roy-Chaudhury 2002). Vascular access dysfunction results in frequent hospitalisation for salvage surgical or endovascular operations (Feldman 1993). Because the number of patients needing HD is increasing, the burden of complications due to vascular access and related hospitalisation is expected to rise. Therefore therapies to prevent vascular access dysfunction are of significant interest.

Several strategies have specifically targeted prolonging vascular access patency by preventing stenosis and thrombosis, including advanced pre-operative planning, newer graft materials and design and use of specific drugs with anticoagulant, antiplatelet, or vascular-remodelling properties (Hung 2010; Mihmanli 2001; Saran 2002). In his review of the role of ω -3FAs in the treatment of kidney disease, Fassett 2010 reviews evidence for several biochemical and physiological effects that suggest that fish oil may also be useful for preventing vascular access failure.

Description of the intervention

Omega-3 fatty acids (ω -3FA) are polyunsaturated fatty acids that are essential dietary nutrients as the human body cannot synthesize it *de novo*. There are three major forms, alpha-linolenic acid is found in plants such as nuts and seeds, the other two forms - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as algae, phytoplankton and fish. In this review only the EPA and DHA forms of ω -3FAs were evaluated in the included studies, so we use the term "fish oil" interchangeably with ω -3FA to refer to the intervention.

How the intervention might work

Damage to the endothelial cells due to shear stress from turbulent blood flow or mechanical trauma from external compression, repeated venipunctures and angioplasties are thought to be the main reasons leading to smooth muscle proliferation, neointimal hyperplasia and stenosis, which in turn increases the risk of thrombosis (MacRae 2016). There are *in vitro* kidney tissue studies and *in vivo* kidney disease model studies that demonstrate ω -3FA could disrupt this pathogenic sequence by its anti-inflammatory and antithrombotic effects (Fassett 2010), inhibitory effects on smooth muscle proliferation, platelet aggregation, polypeptide growth factors, cytokine release and positive haemodynamic effects on blood viscosity and red blood cell flexibility (Cahill 1988; Friedman 2006; Lorente-Cebrián 2013; Mozaffarian 2011).

Why it is important to do this review

The high prevalence of ESKD means that maintenance of adequate vascular access will become a significant burden for many individuals and clinicians. Vascular access failure is associated with increased morbidity and mortality, therefore an effective way to prevent it is important. This review summarises the evidence for benefit and harm of ω -3FA supplementation in ESKD patients undergoing HD. Another Cochrane review has reviewed the evidence of adjuvant medical therapy in ESKD patients with HD (Tanner 2015).

OBJECTIVES

To evaluate the efficacy and safety of ω -3FA supplementation versus placebo or no treatment for maintaining vascular access patency in ESKD patients undergoing HD.

METHODS

Criteria for considering studies for this review

Types of studies

All parallel group randomised controlled trials (RCTs) comparing any dose or form of ω -3FAs compared to placebo or no treatment in ESKD patients.

Types of participants

Inclusion criteria

1. Adult patients (aged ≥ 18 years) currently on HD or in whom HD was planned to start within 6 months because of stage 4 or 5 chronic kidney disease (CKD)
2. An existing or planned first or subsequent vascular access (either AVF or AVG) in the upper or lower arm
3. Not experiencing an early loss of vascular access patency due to technical reasons.

Exclusion criteria

Patients requiring HD because of an acute kidney injury.

Types of interventions

Experimental intervention

Any form or dose of ω -3FA given by any route with intervention starting immediately or shortly after creation of the vascular access.

Control intervention

Placebo or no intervention.

Types of outcome measures

Primary outcomes

Loss of patency

The primary efficacy outcome was loss of patency (inability to use the vascular access without salvage radiological or surgical intervention to restore patency) measured either as a dichotomous outcome occurring between 3 to 12 months or as a time-to-event outcome. Early loss of patency due to technical reasons was excluded.

Serious adverse events

The primary safety outcome was occurrence of any serious adverse event such as death, hospitalisation, major bleeding (e.g. haemorrhage requiring hospital admission or transfusion), cardiovascular event or other life-threatening or severely disabling event.

Secondary outcomes

Non-serious adverse events

Non-life-threatening adverse events such as minor bleeding, gastrointestinal symptoms, or infection.

Search methods for identification of studies

Electronic searches

We searched the [Cochrane Kidney and Transplant Specialised Register](#) up to 23 July 2018 through the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about [Cochrane Kidney and Transplant](#).

See [Appendix 1](#) for search terms used in this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.

2. Contact with investigators known to be involved in previous studies seeking information about unpublished or ongoing studies.

Data collection and analysis

Selection of studies

Titles and abstracts were screened independently by two authors, who also independently assessed the retrieved full text for inclusion.

Data extraction and management

Data extraction was carried out independently by three authors using a standard data extraction template. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. When relevant data was only published in earlier versions, these data were used. Any disagreements were resolved by consensus involving all authors.

Assessment of risk of bias in included studies

The following domains were independently assessed by three authors using the Cochrane Risk of Bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Adequacy of sequence generation (selection bias)
- Adequacy of allocation concealment (selection bias)
- Adequacy of blinding of participants and care-givers (performance bias)
- Adequacy of blinding of outcome assessment (detection bias)
- Incompleteness of outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias
 - * inappropriate per protocol analysis
 - * potential inappropriate influence from commercial sponsors

Separate risk of bias judgments were made for the efficacy outcome (loss of patency) and the safety outcomes (serious adverse events, non-serious adverse events). These judgments were used in the assessment of the Risk of Bias domain for the GRADE Certainty of Evidence rating.

Measures of treatment effect

The effect for loss of patency was expressed as a risk ratio (RR). Due to the presence of no events in both treatment arms of one study, the safety outcomes (serious adverse events and adverse events) were expressed as risk differences (RD) with 95% confidence intervals (CI) so that this study could be included in the meta-analyses. Where time-to-event data (e.g. time to loss of patency) was reported, the effect was expressed as a hazard ratio (HR).

Unit of analysis issues

The study participant was the unit of analysis. If multiple-arm studies were identified, all comparisons relevant to the review would be included. If the same control group was the common comparator in several intervention-control comparisons (e.g. a single placebo arm with two or more different ω -3FA arms), care would be taken not to double-count its outcomes should a meta-analysis be done.

Dealing with missing data

Wherever possible, the original authors were contacted for missing data. When attrition caused missing outcome data, various alternative intention-to-treat analysis (ITT) scenarios were performed (Table 1) and one of these was adopted as the default analysis for this review (see Table 2).

Table 3 describes the manner in which serious adverse events and adverse events outcome data were extracted or imputed in several ambiguous circumstances.

Assessment of heterogeneity

Clinical and design heterogeneity were described in the Characteristics of included studies and "Risk of bias" Tables. These were used to guide the decision to pool the data. Heterogeneity was quantified by the I^2 test (Higgins 2003) and incorporated in the assessment of the Inconsistency domain for the GRADE certainty of evidence rating.

Assessment of reporting biases

Vulnerability to reporting bias was indirectly assessed by documenting funding sources in the "Other bias" domain of the Risk of bias tables. We did not present funnel plots as any pattern would have been uninterpretable because we could not be certain that no other biases (no other than publication bias) were influencing the pattern and because there were insufficient number of studies to reliably define a pattern (Higgins 2011).

With regard to serious adverse events and adverse events, when any of our pre-specified adverse outcomes had not been explicitly reported (either as having or not having occurred) in the study report, we assumed that no events had occurred provided there was evidence of reporting of other serious adverse events and adverse events. We reasoned that current ethical trial conduct would require investigators to monitor for any adverse events and that a non-mention could be taken as equivalent to a non-occurrence. We only had to make this assumption for one study (Schmitz 2002) (see Table 3).

Data synthesis

Pooled effects were separately estimated for AVF and AVG access types and pooling was done using the random-effects model.

Subgroup analysis and investigation of heterogeneity

If data were available, we planned subgroup analyses to explore differences in treatment effectiveness (effect modification) by possible sources of heterogeneity such as patient characteristics (age, gender, comorbidities, smoking status), underlying renal pathology, location of vascular access (e.g. forearm, upper arm) and intervention dose.

Due to the lack of appropriate data these analyses were not performed.

Sensitivity analysis

We performed sensitivity analyses to explore the effect of assumptions about missing or ambiguous outcome data and its analysis (ITT analysis case scenarios, per-protocol analysis (Table 1)) on the robustness of the respective meta-analyses. The ITT "middle-case 1" or "middle-case 2" scenarios for the individual study results were used for most of the meta-analyses (see Table 2). The middle-case 1 scenario was the default scenario unless it was identical with the best-case scenario, in that situation the middle-case 2 scenario was used instead. For the FAVOURED 2009 study, we used the author's modified ITT imputation analysis of the loss of patency outcome.

'Summary of findings' tables

We presented the main results of the clinically important outcomes in two 'Summary of findings' (SoF) tables (Schünemann 2011a) - one for AVFs and the other for AVGs. The SoF tables also include a rating of the "Certainty of Evidence" for each outcome using the GRADE approach (GRADE 2008). The certainty of evidence is the extent to which one can be confident that the estimate of effect or association is close to the truth. It involves consideration of (GRADE) risk of bias (i.e. Cochrane overall risk of bias taken across studies), directness of evidence, heterogeneity of effects, precision of effect estimates and risk of publication bias (Schünemann 2011b). The certainty of evidence was rated for the following five outcomes:

- Loss of patency by 6 to 12 months
- Death
- Hospitalisation
- Cardiovascular events
- Major bleeding

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies

Results of the search

Our search of the Cochrane Kidney and Transplant's Specialised Register identified 36 records. Full-text assessment of these records resulted in the inclusion of five eligible studies (Bowden 2007; Diskin 1990; FAVOURED 2009; FISH 2007; Schmitz 2002). Seven studies were excluded (Bowden 2009; De Fijter 1995; Donnelly 1992a; Gharekhani 2014; Hung 2015; Saifullah 2007; Tumlin 2002a). Figure 1 depicts the study inclusion and exclusion process.

Figure 1. Study flow diagram.

Included studies

Five studies (833 participants) evaluating efficacy and safety of ω -3FA were included (Bowden 2007; Diskin 1990; FAVOURED 2009; FISH 2007; Schmitz 2002), see [Characteristics of included studies](#). The studies were published between 1990 and 2017, and had sample sizes ranging from 7 to 567. One was a very small "preliminary pilot study" (Diskin 1990) that recruited participants at high-risk of AVG patency failure (history of 3 or more thromboses in the past 12 months). The largest study (FAVOURED 2009) was also the only one to recruit AVF participants (stage 4 or 5 CKD, primary *de novo* vascular access). Bowden 2007 recruited participants with newly placed AVGs, while FISH 2007 and Schmitz 2002 involved both "first access" and "subsequent access" participants. Four studies excluded participants at high risk of bleeding (Bowden 2007; FAVOURED 2009; FISH 2007; Schmitz 2002).

All studies evaluated either a combination of DHA-EPA (Bowden 2007; FAVOURED 2009; FISH 2007; Schmitz 2002) or EPA alone (Diskin 1990) as the ω -3FA fish oil supplement. Treatment was initiated at a range of different times - the day before scheduled AVF placement (FAVOURED 2009), at the start of dialysis (Diskin 1990), seven days after AVG placement (Bowden 2007; FISH 2007) and within two weeks of AVG placement (Schmitz 2002). Treatment duration was only clearly reported by three studies - Diskin 1990 (6 months), FAVOURED 2009 (12 weeks) and FISH 2007 (12 months). Dosages ranged from 3 to 6 g/day. Four studies described methods to assess compliance - three used lipid analysis of cell or platelet membranes (FAVOURED 2009; FISH 2007; Schmitz 2002) and one used dietician-support and pill counting (Bowden 2007).

All studies reported some version of vascular access failure as their primary outcome.

- Thrombosis or stenosis > 50% requiring salvage angioplasty at 6 months (Bowden 2007)
- Outflow stenosis by duplex ultrasound at 6 months (Diskin 1990)
- Thrombosis or stenosis requiring salvage at 12 months (FISH 2007)

- Thrombosis, access abandonment or cannulation failure at 12 months (FAVOURED 2009)
- Thrombosis at 12 months (Schmitz 2002).

Results for the following serious adverse events could be directly extracted or reasonably inferred from what was reported (see [Table 3](#)).

- Death: five studies (Bowden 2007; Diskin 1990; FAVOURED 2009; FISH 2007; Schmitz 2002)
- Hospitalisation: four studies (Bowden 2007; Diskin 1990; FAVOURED 2009; Schmitz 2002)
- Cardiovascular events: four studies (Bowden 2007; Diskin 1990; FAVOURED 2009; Schmitz 2002) e.g. stroke, peripheral vascular disease, myocardial infarction, congestive heart-failure, cardiac-related death
- Major bleeding: three studies (Bowden 2007; Diskin 1990) e.g. gastrointestinal bleeding requiring hospitalisation.

Results for the following non-serious adverse events could be directly extracted or reasonably inferred from what was reported (see [Table 3](#)).

- Minor bleeding: four studies (Bowden 2007; Diskin 1990; FAVOURED 2009)
- Gastrointestinal events: four studies (Bowden 2007; Diskin 1990; FAVOURED 2009; Schmitz 2002) e.g. bloating, gas, "fish" aftertaste
- Other adverse events: four studies (Bowden 2007; Diskin 1990; FAVOURED 2009; Schmitz 2002).

Excluded studies

Seven studies were excluded (see [Characteristics of excluded studies](#)). Six studies included no primary outcomes of interest (Bowden 2009; Donnelly 1992a; Gharekhani 2014; Hung 2015; Saifullah 2007; Tumlin 2002a) and one study was a cross-over study (De Fijter 1995).

Risk of bias in included studies

The risk of bias is summarised in [Figure 2](#) and in the [Characteristics of included studies](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Loss of patency	Blinding of outcome assessment (detection bias): All adverse outcomes	Incomplete outcome data (attrition bias): Loss of patency	Incomplete outcome data (attrition bias): All adverse outcomes	Selective reporting (reporting bias)	Other bias
Bowden 2007	+	?	+	+	+	?	?	?	?
Diskin 1990	?	?	+	?	?	?	?	+	?
FAVOURED 2009	+	+	+	+	+	?	?	+	?
FISH 2007	+	+	+	+	+	?	?	?	+
Schmitz 2002	?	?	+	+	+	?	?	+	+

Allocation

Random sequence generation

Random sequence generation was judged as low risk in three studies ([Bowden 2007](#); [FAVOURED 2009](#); [FISH 2007](#)), all documented computer-generated randomisation. Although described as randomised, [Diskin 1990](#) was judged as having unclear risk because the randomisation method was not reported.

Allocation concealment

Allocation concealment was judged as low risk in two studies ([FAVOURED 2009](#); [FISH 2007](#)), which reported central, independent randomisation facilities. The other studies ([Bowden 2007](#); [Diskin 1990](#); [Schmitz 2002](#)) were judged as unclear risk because they did not report the method.

Blinding

Blinding of participants and personnel (performance bias) and blinding of outcome assessors (detection bias) were judged as low risk in all studies due to the use of placebo controls and the objective nature of the outcome measurements.

Incomplete outcome data

Loss to follow-up and analysis drop-out rates in the other four studies ranged from 0% to 25% in the fish oil group and 0% to 11.8% in the placebo group (see [Table 4](#); [Table 5](#); [Table 6](#); [Table 7](#); [Table 8](#)). These were comparable or greater than the outcome event risks observed, so for all outcomes, all studies were judged as unclear risk because the effect estimates could be sensitive to assumptions made about the outcome status of the drop-outs i.e. the method of missing data analysis.

Selective reporting

Selective reporting was judged as low risk in three studies ([Diskin 1990](#); [FAVOURED 2009](#); [Schmitz 2002](#)), where pre-specified outcomes of interest to this review were all reported. Two studies were judged as unclear risk of bias - [Bowden 2007](#) did not report the efficacy outcomes for five patients who completed follow-up but were deemed as non-compliant and also only reported adverse events judged as related to ω -3FA supplementation, and [FISH 2007](#) did not report hospitalisation events and also did not differentiate between major and minor bleeding events. We performed a sensitivity analysis with [FISH 2007](#) by assuming all the bleeding events reported were either major or minor bleeds.

Other potential sources of bias

Two other potential sources of bias were considered - the funding source and the method of imputing missing outcome data. Three studies were judged as unclear risk of bias: two studies ([Bowden 2007](#); [Diskin 1990](#)) did not report their funding sources; one study ([FAVOURED 2009](#)) did not provide the method of imputation for missing outcome data and it had a pharmaceutical industry funder for the ω -3FA supplement. No other potential sources of bias were identified in two studies ([FISH 2007](#); [Schmitz 2002](#)).

Effects of interventions

See: [Summary of findings for the main comparison Omega-3 fatty acids versus placebo for dialysis vascular access outcomes in AVF patients with ESKD](#); [Summary of findings 2 Omega-3 fatty](#)

[acids compared to Placebo for dialysis vascular access outcomes in AVG patients with ESKD](#)

The effects of fish oil are reported separately for AVF and AVG studies. As the risk of patency loss is known to differ between AVFs and AVGs, the effectiveness of fish oil could also differ between them. See [Summary of findings for the main comparison](#) for the effects in AVF patients and [Summary of findings 2](#) for the effects in AVG patients.

AVF

Primary outcomes

Loss of patency by 12 months

ω -3FA probably makes little or no difference to the risk of loss of patency within 12 months in AVF patients ([Analysis 1.2.1](#) (1 study, 536 participants): RR 1.01, 95% CI 0.84 to 1.21; moderate certainty evidence).

Serious adverse events

Death

ω -3FA probably makes little or no difference to the risk of death within 12 months in AVF patients ([Analysis 1.4.1](#) (1 study, 567 participants): RD 0.00, 95% CI -0.03 to 0.02; moderate certainty evidence).

Hospitalisation

ω -3FA may make little or no difference to the risk of hospitalisation within 12 months in AVF patients ([Analysis 1.5.1](#) (1 study, 567 participants): RD 0.00, 95% CI -0.08 to 0.08; low certainty evidence).

Cardiovascular events and major bleeding

Cardiovascular events and major bleeding were not reported.

Secondary outcomes

Non-serious adverse events

Minor bleeding

ω -3FA probably makes little or no difference to the risk of minor bleeding within 12 months in AVF patients ([Analysis 1.8.1](#) (1 study, 567 participants): RD 0.02, 95% CI -0.01 to 0.06; moderate certainty evidence).

Gastrointestinal events

ω -3FA probably makes little or no difference to the risk of gastrointestinal events within 12 months in AVF patients ([Analysis 1.9.1](#) (1 study, 567 participants): RD 0.00, 95% CI -0.03 to 0.04; moderate certainty evidence).

Other adverse events

ω -3FA probably makes little or no difference to the risk of other adverse events within 12 months in AVF patients ([Analysis 1.10.1](#) (1 study, 567 participants): RD 0.01, 95% CI -0.02 to 0.03; moderate certainty evidence).

AVG

Primary outcomes

Loss of patency by 6 months

It is very uncertain whether ω -3FA slightly reduces the risk of loss of patency within 6 months in AVG patients ([Analysis 1.1](#) (2 studies, 41 participants): RR 0.91, 95% CI 0.36 to 2.28; very low certainty evidence).

- Sensitivity analysis: See [Analysis 1.11](#). The pooled scenario RRs range from 0.61 (in favour of ω -3FA) to 1.02. The two middle case scenarios have RRs of 0.66 and 0.95. There is a moderate degree of heterogeneity in any particular scenario (I^2 from 30% to 52%); the point estimates of the two studies in the meta-analysis are highly discordant. If the pilot study ([Diskin 1990](#)) is excluded, four of the five point estimates in the scenario analysis favour placebo, so evidence for direction of effect is highly sensitive to inclusion of the pilot study.

Loss of patency by 12 months

It is very uncertain whether ω -3FA reduces the risk of loss of patency within 12 months in AVG patients ([Analysis 1.2.2](#) (2 studies, 220 participants): RR 0.59, 95% CI 0.27 to 1.31; very low certainty evidence).

- Sensitivity analysis: See [Analysis 1.12](#). The pooled scenario RRs range from 0.45 to 0.66, all in favour of ω -3FA. The two middle case scenarios have RRs of 0.49 and 0.60. There is a moderate to high degree of heterogeneity in any particular scenario (I^2 from 58% to 79%); the point estimates of the two studies in the meta-analysis are highly discordant.

Serious adverse events

Death

ω -3FA may make little or no difference to the risk of death within 6 to 12 months in AVG patients ([Analysis 1.4.2](#) (4 studies, 261 participants): RD 0.01, 95% CI -0.05 to 0.07; low certainty evidence).

- Sensitivity analysis: See [Analysis 1.13](#). The pooled scenario RDs range from -0.03 to 0.10. The two middle case scenarios have RDs of 0 and 0.03. There is a very low degree of heterogeneity in any particular scenario (I^2 close to 0%).

Hospitalisation

It is very uncertain whether ω -3FA increases the risk of hospitalisation within 6 months to 12 months in AVG patients ([Analysis 1.5.2](#) (3 studies, 65 participants): RD 0.08, 95% CI -0.11 to 0.28; very low certainty evidence).

- Sensitivity analysis: See [Analysis 1.14](#). The pooled scenario RDs range from -0.03 to 0.01. The two middle case scenarios have RDs of 0.01 and 0.11. There is a low degree of heterogeneity in any particular scenario (I^2 from 0% to 10%). If the pilot study was excluded, the risk of hospitalisation changes to little or no difference (RD 0.02, 95% CI -0.08 to 0.11); the 95% CI is consistent with both moderate harm and benefit.

Cardiovascular events

It is very uncertain whether ω -3FA increases or decreases the risk of cardiovascular events within 6 to 12 months in AVG patients

([Analysis 1.6](#) (four studies, 261 participants): RD -0.02, 95% CI -0.11 to 0.07; very low certainty evidence).

- Sensitivity analysis: See [Analysis 1.15](#). The pooled scenario RDs range from -0.09 to 0.10. The two middle case scenarios have RDs of -0.03 and 0.01. There is a low to high degree of heterogeneity in any particular scenario (I^2 from 0% to 73%).

Major bleeding

It is very uncertain whether ω -3FA increases the risk of major bleeding within 6 to 12 months in AVG patients ([Analysis 1.7](#) (3 studies, 65 participants): RD 0.08, 95% CI -0.11 to 0.28; very low certainty evidence).

- Sensitivity analysis 1: See [Analysis 1.16](#). The pooled scenario RDs range from -0.03 to 0.16. The two middle case scenarios have RDs of 0.01 and 0.11. There is a low degree of heterogeneity in any particular scenario (I^2 from 0% to 10%). If the pilot study was excluded, the risk of major bleeding reduces to little or no difference (RD 0.02, 95% CI -0.08 to 0.11); the 95% CI is consistent with both moderate harm and benefit.
- Sensitivity analysis 2: See [Analysis 1.7](#). After inclusion of [FISH 2007](#) by assuming all the reported bleeding events were major, the estimate of effect reduces to little or no difference (RD 0.02, 95% CI -0.05 to 0.10); the 95% CI is consistent with both moderate important harm and benefit.

Secondary outcomes

Non-serious adverse events

Minor bleeding

ω -3FA may slightly increase the risk of minor bleeding within 6 to 12 months in AVG patients ([Analysis 1.8.2](#) (3 studies, 65 participants): RD 0.03, 95% CI -0.07 to 0.12; low certainty evidence).

- Sensitivity analysis 1: See [Analysis 1.17](#). The pooled scenario RDs range from -0.05 to 0.14. The two middle case scenarios have RDs of 0 and 0.09. There is a very low degree of heterogeneity in any particular scenario (I^2 close to 0%).
- Sensitivity analysis 2: See [Analysis 1.8](#). After inclusion of [FISH 2007](#) by assuming all the reported bleeding events were minor, there is little impact on the estimate of effect (RD 0.02, 95% CI -0.04 to 0.08).

Gastrointestinal events

ω -3FA may increase the risk of gastrointestinal events within 6 to 12 months in AVG patients ([Analysis 1.9.2](#) (3 studies, 65 participants): RD 0.25, 95% CI 0.07 to 0.43; low certainty evidence).

- Sensitivity analysis: See [Analysis 1.18](#). The pooled scenario RDs range from 0.14 to 0.33. The two middle case scenarios have RDs of 0.18 and 0.28. There is a very low degree of heterogeneity in any particular scenario (I^2 close to 0%).

Other adverse events

ω -3FA may make little or no difference to the risk of other adverse events within 6 to 12 months in AVG patients ([Analysis 1.10.2](#) (3 studies, 65 participants): RD 0.02, 95% CI -0.08 to 0.11; low certainty evidence).

- Sensitivity analysis: See [Analysis 1.19](#). The pooled scenario RDs range from -0.07 to 0.12. The two middle case scenarios have RDs of -0.01 and 0.09. There is a low degree of heterogeneity in any particular scenario (I^2 from 0% to 18%).

DISCUSSION

Summary of main results

There is little evidence that ω -3FA fish oil supplementation can prevent blockage (patency loss) of HD vascular access compared to no supplementation. For AVF access, we are moderately certain that ω -3FAs make little or no difference to preventing patency loss within 12 months. This result is based on one large multicentre study that was terminated early ([FAVOURD 2009](#)). For AVG patency loss at both 6 and 12 months of follow-up, the best effect estimates are in favour of ω -3FA but with very low certainty and so despite the apparently sizable relative risk reduction the 95% CIs indicate that the intervention might make little or no difference.

There is little evidence that ω -3FA fish oil supplementation increases the risk of some serious adverse events compared to no supplementation. For AVF access, ω -3FA fish oil supplementation probably makes little or no difference to the risk of death (moderate certainty) or hospitalisation (low certainty). This result is based on one large multicentre study that was terminated early. There is no evidence from these studies on the risk of cardiovascular events or major bleeding. For AVG access, the certainty of evidence for increased serious adverse events risks is low or very low. ω -3FA fish oil supplementation may make little or no difference to the risk of death and cardiovascular events. The observed increased risks of hospitalisation and major bleeding are very uncertain results skewed by the single small pilot study of seven participants ([Diskin 1990](#)). The 95% CIs indicate the intervention might make little or no difference. In a sensitivity analysis with [Diskin 1990](#) excluded, there is little or no difference in the risk of hospitalisation or major bleeding. Of the non-serious adverse events, there may be an increased risk of minor gastrointestinal side-effects such as sensations of bloatedness, gas and a fishy aftertaste.

Overall completeness and applicability of evidence

This review gives a comprehensive review of the current best RCT evidence for the effect of omega-3 fish oil supplements for preventing HD vascular access blockage and for affecting the risk of serious and non-serious side-effects in CKD patients. Overall the evidence is limited as there are only five studies, one of which is a very small pilot study. Only polytetrafluoroethylene grafts were used, there were no studies of newer graft designs and materials. The longest follow-up time was one year. There is even more limited evidence and hence applicability to the following patient categories:

- Patients with AVF access - only one study ([FAVOURD 2009](#)) of patients with AVFs that terminated early with a large proportion (23%) of missing data requiring imputation
- Patients with a history of vascular access failure - only one very small pilot study ([Diskin 1990](#))
- Patients not at low risk of bleeding - only one very small pilot study ([Diskin 1990](#))
- Patients with other potential effect modifiers (e.g. elderly, diabetics, smokers) - non-randomised analysis reported in one study ([FAVOURD 2009](#))

Quality of the evidence

No study had a low overall risk of bias for either the efficacy or safety outcomes. Randomisation method but not allocation concealment was generally well reported. Blinding was convincing due to the employment of placebo supplements. Attrition bias due to a high proportion of losses to follow-up relative to the outcome event rate were of concern in all studies, and selective reporting of adverse events was a concern in two studies. Evidence for AVF patients comes from only a single study that terminated early with a large proportion of missing data (22.8%) requiring imputation in a modified ITT analysis. Another potential bias of concern was the non-declaration of the study funder.

Potential biases in the review process

We have not identified any major bias in our review process. Our literature search included several international databases and search criteria were intentionally broadened to identify as many potentially relevant articles as possible. We did not exclude studies published in languages other than English. We were not successful in contacting authors to clarify aspects of incomplete or selective reporting that were partially reported e.g. details on randomisation processes, allocation concealment, drop-outs, adverse events and funding sources.

In the AVG studies, the inclusion of the small pilot study ([Diskin 1990](#)) substantially affects the direction and/or magnitude of the pooled estimate for the efficacy, hospitalisation and major bleeding outcomes. This occurs because there are not many other studies or when the outcome event rate is generally low. Use of a conservative default ITT analysis has for two studies ([Diskin 1990](#); [Schmitz 2002](#)) meant using the worst-case scenario. We tried to mitigate these issues by exploring the impact with sensitivity analyses.

Agreements and disagreements with other studies or reviews

[Palmer 2013a](#) reviewed antiplatelet agents for preventing HD access failure. They concluded that antiplatelet treatment protects AVFs from thrombosis or loss of patency (6 studies, 1242 participants: RR 0.49, 95% CI 0.30 to 0.81), no GRADE certainty of evidence was reported, however more detailed information found in a complementary Cochrane review ([Palmer 2013b](#)) reveals that five of the six studies would have been classified as having a high risk of bias, the remaining study would be classified as uncertain. With the (arguably) added concern about imprecision, it would be reasonable to grade the certainty of evidence as low. Nevertheless the potential benefit of antiplatelets for AVFs means that future AVF studies should seriously consider using antiplatelet agents as an active control.

In their updated Cochrane review on medical adjuvant treatments to increase HD vascular access patency rates, [Tanner 2015](#) included two of our included studies ([FISH 2007](#); [Schmitz 2002](#)) when evaluating fish oil interventions. The efficacy outcome they reported from the [FISH 2007](#) paper was the risk of "one or more thrombosis events", in contrast, we reported the risk of "loss of native patency", see Table 2 of [FISH 2007](#). The difference is that our outcome is a composite outcome ("... graft having a primary event thromboses or requiring radiological or surgical intervention to maintain patency following its creation.") that contains their outcome as a subset. The analysis they reported is what we regard as a middle-case 1 scenario ITT analysis (2 studies, 220 participants:

OR 0.24, 95% CI 0.03 to 1.95), when expressed in terms of the RR, it is equivalent to RR 0.72 (95% CI 0.16 to 1.44). They concluded that "there was insufficient evidence to determine if there was a difference in graft patency". Although they did not report a GRADE certainty of evidence, a reasonable conclusion based on their own risk of bias assessment and downgrading for inconsistency ($I^2 = 66\%$) and imprecision would be that there is low certainty evidence that fish oils may slightly reduce the risk of thrombosis, and the 95% CI indicates that the intervention might make little or no difference. This is consistent with our conclusion of very low level evidence for effect on risk of LOP at 12 months ([Summary of findings 2](#)). The difference in judgments is attributable to our harsher Risk of Bias appraisal. If our appraisal had been used instead, there would have been a further downgrading for risk of bias and hence the certainty of evidence judgments would have been identical regardless of the efficacy endpoint chosen. What further differentiates our review from theirs is the exclusive focus on ω -3FA supplements and incorporation of new evidence from three studies ([Bowden 2007](#); [Diskin 1990](#); [FAVOUR 2009](#)) which also include the only large study of AVF patients.

The systematic review of [He 2016](#) of ω -3FA versus placebo in HD patients reported a largely different set of outcomes than the ones in this review. Their meta-analysis of "arteriovenous graft events" most closely approximates our primary outcome (see Fig. 2 of [He 2016](#)). They included four studies; three were common to our review ([Bowden 2007](#); [FISH 2007](#); [Schmitz 2002](#)). The remaining study ([Hung 2015](#)), was excluded from our review because the event measured was graft infection and not explicitly loss of patency (see Table 4 of [Hung 2015](#)). The other differences between their meta-analysis and ours were:

- their analysis of [Bowden 2009](#) used a per protocol analysis - we used an ITT analysis;
- their analysis of [Schmitz 2002](#) is slightly wrong, because they used the wrong number of control group events - 7 instead of 9 (see page 186 of [Schmitz 2002](#));
- their analysis of Lok counted thrombosis events and not loss of native patency (see Table 2 of [FISH 2007](#));
- they pooled a study with 6 months follow-up [Bowden 2007](#) with two studies of 12 months follow-up;
- they used a fixed-effect rather than a random-effects model to pool the data, which we judged as inappropriate given the design heterogeneity - differences in length of follow-up and outcome definition;
- we have included two additional studies ([Diskin 1990](#); [FAVOUR 2009](#)).

AUTHORS' CONCLUSIONS

Implications for practice

There is no strong evidence that ω -3FA fish oil supplements reduces the risk of AVF or AVG access blockage in patients not currently consuming it. There is also no strong evidence of an increased risk in serious adverse effects; however there may be a moderately increased risk of bloatedness, gas or a fishy aftertaste. So for those currently consuming it, the decision to continue or not will also involve other considerations specific to the individual patient such as the tolerability of specific side-effects, the recurring cost of medication and the burden of polypharmacy.

Implications for research

In AVF patients, since the evidence comes from a single study that was flawed in important ways (e.g. change of primary outcome definition, large attrition rate, and early study termination), coupled with the importance of this mode of vascular access, further studies are recommended.

In AVG patients, there is a tantalizing but very weak signal of effect, again this comes from primarily one study. Since AVGs are at a higher risk of blockage than AVFs, and they continue to have an important role either as a first-line or second-line access, further studies are recommended.

In addition, future studies should consider (1) recruiting a more real-world population not specially selected for being at low bleeding risk, (2) stratified randomisation for suspected effect-modifiers, (3) use of an active anti-thrombotic control group, (4) standardized outcome definition and criteria of assessment, (5) follow-up of at least one year, and (6) systematic reporting of adverse events and reasons for losses to follow-up.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bowden 2007

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: July 2003 to October 2004 Study follow-up period: 6 months (primary outcome)
Participants	<ul style="list-style-type: none"> Country: USA Setting: multicentre (4 sites) Patients on long-term 4 HD with newly placed PTFE grafts who were unable to receive a native AVF Number (randomised/analysed): treatment group (17/14); control group (17/15) Mean age $\pm$ SD (years): treatment group (61 $\pm$ 13); control group (63 $\pm$ 11) Gender (M/F): treatment group (6/9); control group (7/7) Diabetes: treatment group (9/14); control group (11/15) Smokers: treatment group (4/14); control group (4/5) Forearm AVG: not reported Exclusion criteria: history of GI bleeding in the previous 6 months; earlier treatment with anticoagulation therapy and antiplatelet medication; life expectancy of less than 6 months; pregnancy; malignant hypertension; history of HD or previous medication noncompliance
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> ω-3FA: 2 x 1 g softgel capsules of fish oil concentrate (160 mg EPA and 100 mg DHA per capsule) with each meal, or 6 capsules (6 g) per 24 hours, initiated 7 days after graft placement <p>Control group</p>

Bowden 2007 (Continued)

- Placebo: 2 x 1 g softgel capsules of corn or canola oil (94% unsaturated fat, 6% saturated fat) with each meal, or 6 capsules (6 g) per 24 hours, initiated within 7 days of graft placement

Co-interventions

- Vitamin supplements containing 15 mg B₆, 12 mg B₁₂ and 2.5 mg folic acid

Outcomes	<ul style="list-style-type: none"> • Primary graft patency (vascular access thrombosis or venous outflow stenosis > 50% requiring salvage angioplasty) as measured by a fistulagram within 6 months. Clotting and graft failure occurring within 7 days of graft placement were excluded as outcomes • Adverse events
Notes	<ul style="list-style-type: none"> • Funding source: not reported • Inconsistent description of placebo content - described as "corn oil" in 'Experimental Design and Procedures' section and described as "canola oil" in 'Fish Oil and Placebo Composition' section

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "A random number chosen by Microsoft Excel was used to assign which block was chosen to randomise group selection. Permuted block randomizations ensures that treatment group numbers are evenly balanced at the end of each block. After initiation of graft placement, patients were randomly placed, in keeping with the 4-block permuted design, into an n-3 fatty acid (experimental) or a control (corn oil [n-6]) group."</p> <p>Comment: The baseline covariate balance was only shown for the 29 (out of 34 randomised) compliant subjects (Table 1 of the paper) and there were no imbalances of concern.</p>
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This study was conducted according to a triple blind, permuted-block, randomised, placebo-controlled experimental design."
Blinding of outcome assessment (detection bias) Loss of patency	Low risk	Quote: "This study was conducted according to a triple blind, permuted-block, randomised, placebo-controlled experimental design."
Blinding of outcome assessment (detection bias) All adverse outcomes	Low risk	Quote: "This study was conducted according to a triple blind, permuted-block, randomised, placebo-controlled experimental design."
Incomplete outcome data (attrition bias) Loss of patency	Unclear risk	<p>Quote: "... a total of 34 patients met study criteria and were recruited. In all, 2 patients from the placebo group and 3 patients from the n-3 group completed the study but were not included in the analysis because of noncompliance, for a sample size of 29."</p> <p>Comment: This is a 15% drop-out rate and comparable to the average efficacy event rate of 38%. The efficacy effect measure may be sensitive to the method of missing data analysis</p>
Incomplete outcome data (attrition bias) All adverse outcomes	Unclear risk	Quote: "... a total of 34 patients met study criteria and were recruited. In all, 2 patients from the placebo group and 3 patients from the n-3 group completed the study but were not included in the analysis because of noncompliance, for a sample size of 29."

Bowden 2007 (Continued)

		Comment: this is a 15% drop-out rate and higher than most of the average adverse outcome risks. The adverse outcome effect measures may be very sensitive to the method of missing data analysis
Selective reporting (reporting bias)	Unclear risk	<p>Quote: "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption."</p> <p>Comment:</p> <ul style="list-style-type: none"> Not all adverse events may have been reported, as the sentence implies that only adverse events judged by the investigators as being related to the intervention were reported. The HR and 95% CI of the Kaplan-Meier graft survival analysis were not reported
Other bias	Unclear risk	Publication bias: Funding source not reported

Diskin 1990

Methods	<ul style="list-style-type: none"> Study design: parallel RCT - "... a preliminary pilot study as a possible prelude to a larger full-scale investigation." Time frame: not reported Study follow-up period: 6 months (primary outcome)
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre Chronic HD patients undergoing the construction of new PTFE AVG who had already experienced more than 3 episodes of graft thrombosis during the preceding 12 months Number randomised: treatment group (4); control group (3) Mean age $\pm$ SD (years): not reported Sex (M/F): not reported Diabetes: not reported Smokers: not reported Forearm AVG: not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> ω-3FA: 3 g EPA received at each of the 3 weekly dialysis treatments for 6 consecutive months <p>Control group</p> <ul style="list-style-type: none"> Placebo: content of placebo not reported, received at each of the 3 weekly dialysis treatments for 6 consecutive months
Outcomes	<ul style="list-style-type: none"> Angioaccess patency or outflow stenosis as measured by duplex ultrasonography at 6 months Adverse events
Notes	<ul style="list-style-type: none"> Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Study was described as randomised but method was not reported. The baseline covariate balance was shown in Table 1 of the paper, but it was

Diskin 1990 (Continued)

		based on a very small sample of subjects (7) and potential confounding variables were missing. Randomising such a small sample would not provide reliable protection against confounding.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Three patients were randomised to receive placebo and four received 3 g of EPA."
Blinding of outcome assessment (detection bias) Loss of patency	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All adverse outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Loss of patency	Unclear risk	Quote: "One EPA patient died within one week of initiation of the study from an acute myocardial infarction." Comment: This is a 25% drop-out rate and higher than the loss of patency risk in the intervention group (0%). This latter risk is not robust and the efficacy effect measure may be highly sensitive to the method of missing data analysis.
Incomplete outcome data (attrition bias) All adverse outcomes	Unclear risk	Quote: "One EPA patient died within one week of initiation of the study from an acute myocardial infarction." Comment: This is a 25% drop-out rate and comparable or higher than the adverse events risks in the intervention group (major bleeding 25%, minor bleeding 0%, other adverse events 25%). These risks would not be robust and the efficacy effect measure may be highly sensitive to the method of missing data analysis.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes of interest to this review were reported
Other bias	Unclear risk	Publication bias: funding source not reported

FAVoured 2009

Methods	<ul style="list-style-type: none"> Study design: double-blind, 2 x 2 factorial RCT Time frame: August 2008 to February 2015 Study follow-up period: 12 months (primary outcome)
Participants	<ul style="list-style-type: none"> Country: Australia, Malaysia, New Zealand, UK Setting: multicentre (35 sites) Stage 4 or 5 CKD receiving or planning to receive HD within 12 months with planned primary de novo AVF Number randomised: treatment group (284); control group (283) Mean age $\pm$ SD (years): treatment group (54.1 $\pm$ 14.0); control group (55.6 $\pm$ 14.5) Gender (M/F): treatment group (180/104); control group (179/104) Diabetes: treatment group (139/284); control group (125/283) Smokers: treatment group (155/284); control group (135/283)

Omega-3 fatty acids for dialysis vascular access outcomes in patients with chronic kidney disease (Review)

FAVOURED 2009 (Continued)

- Forearm AVF: treatment group (171/284); control group (173/283)
- Exclusion criteria: increased bleeding risk (bleeding disorder, recent or active GI ulcer, platelet count $< 100 \times 10^3/\mu\text{L}$, hepatic insufficiency); taking aspirin within 2 weeks or fish oil within 4 weeks of study commencement; taking NSAIDs, anticoagulants, or antiplatelet agents; contraindications for taking the study agents

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • ω-3FA: 2 g twice daily (4 g total) of fish oil (46% EPA and 38% DHA) capsules, commencing on the day before scheduled AVF surgery and continued for 12 weeks <p>Control group</p> <ul style="list-style-type: none"> • Placebo: olive oil placebo capsules for 12 weeks <p>Co-interventions</p> <ul style="list-style-type: none"> • In June 2011 the exclusion criterion of current use of aspirin was removed (previously in force since August 2008)
Outcomes	<ul style="list-style-type: none"> • AVF access failure at 12 months ("... a composite of any one of AVF thrombosis, AVF abandonment, and cannulation failure.") Thrombosis was defined as the absence of a thrill or bruit by clinical assessment and/or requirement for rescue intervention (medical thrombolysis or surgical thrombectomy). AVF abandonment was defined as no further use of, or attempt to intervene on, the study AVF. Cannulation failure was defined as failure to successfully cannulate the study AVF during 8 or more of 12 consecutive haemodialysis sessions during the cannulation assessment period." • Individual component events of fistula failure outcome • Adverse events
Notes	<ul style="list-style-type: none"> • Funding source: "The FAVOURED trial was funded by grants from National Health and Medical Research Council of Australia Project Grant (APP458652), Amgen Australia Pty Ltd and Mylan EPD (at the time of funding was Abbott Products Operations AG). Study medication was supplied by Mylan EPD (at the time of supply was Abbott Products Operations AG) (fish oil and placebo) and Bayer Healthcare (aspirin and placebo) free of charge." • The efficacy of aspirin co-intervention was a secondary aim of the study ("As a result of the second amendment, the primary objective of FAVOURED was to assess the efficacy of fish oil supplementation on AVF failure at 12 months and the efficacy of aspirin was assessed as a secondary objective.") • Study was terminated early ("Due to early cessation of recruitment, only the first interim analysis was performed, after which the study continued as planned until terminated because of slower than anticipated accrual, funding issues, and lack of ongoing availability of trial medications.")

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "...using an adaptive minimization algorithm with study site and planned location of the AVF (upper vs lower arm) as minimization variables."</p> <p>Participant demographic and clinical characteristics were well balanced between the treatment groups</p>
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a central, web-based system (Flexe-trials)..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, caregivers, treating physicians and surgeons, laboratory staff, and members of the study team were blinded to treatment allocation.

FAVoured 2009 (Continued)

Blinding of outcome assessment (detection bias) Loss of patency	Low risk	Participants, caregivers, treating physicians and surgeons, laboratory staff, and members of the study team were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All adverse outcomes	Low risk	Participants, caregivers, treating physicians and surgeons, laboratory staff, and members of the study team were blinded to treatment allocation.
Incomplete outcome data (attrition bias) Loss of patency	Unclear risk	Fig. 1 quote: "Number of participants whose primary outcome was determined by imputation; fish oil n = 62 (23%), placebo n = 60 (23%)." Comment: A high proportion of missing data, but comparable between groups. The reasons for the drop-outs were not reported. The efficacy effect measure may be sensitive to the method of missing data analysis.
Incomplete outcome data (attrition bias) All adverse outcomes	Unclear risk	Comment: The drop-out rate (23%) is comparable or higher than the Adverse events risks in the intervention group (death 3%, hospitalisation 38% to 39%, any bleeding 4% to 6%, minor bleeding 0%). The adverse outcome effect measures may be sensitive to the method of missing data analysis (Table 3)
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes of interest to this review were reported
Other bias	Unclear risk	Missing primary outcome data was imputed, but the method was not described

FISH 2007

Methods	<ul style="list-style-type: none"> Study design: double-blind, parallel RCT Time frame: November 2003 and December 2010 Study follow-up period: 12 months (primary outcome)
Participants	<ul style="list-style-type: none"> Country: Canada, USA Setting: multicentre (15 sites) Adults ≥ 18 years with ESKD who required a synthetic AVG for chronic HD ("... graft could either be a "first access" ever surgically created or a "subsequent access" after a previously failed access") Number (randomised/analysed): treatment group (101/99); control group (100/97) Mean age, range (years): treatment group (62.2, 28 to 88); control group (63.4, 27 to 87) Sex (M/F): treatment group (47/52); control group (51/46) Diabetes: treatment group (49/99); control group (39/97) Smokers: treatment group (57/99); control group (50/97) Forearm AVG: treatment group (61/99); control group (49/97) Exclusion criteria: reversible kidney failure; active malignancy; pregnancy; malignant hypertension; active major bleed in the prior month; receiving more than 2 antiplatelet agents or anticoagulants (i.e., concomitant use of aspirin and warfarin was not an exclusion); life expectancy less than 6 months; surgical revision of a previous access, such as a jump graft (i.e., the AVG under study needed to be a new graft); AVG that failed prior to and including postoperative day 7; ingestion of any form of fish oil at time of randomisation; allergy to fish or fish products; and enrolment in another interventional study of AVG
Interventions	<ul style="list-style-type: none"> Randomised on the 7th post-operative day of AVG creation <p>Treatment group</p>

FISH 2007 (Continued)

- ω -3FA group: 4 x 1 g capsules of MEG-3 fish oil (48% EPA (400 mg/capsule) and 25% DHA (200 mg/capsule)) per day for 12 months

Control group

- Placebo: matching corn oil placebo capsules for 12 months

Outcomes	<ul style="list-style-type: none"> • Loss of native patency as measured by angiography within 12 months ("... defined as the graft having a primary event of thrombosis or requiring radiological or surgical intervention to maintain patency following its creation."). • Graft thrombosis and time-to-event • Graft requiring radiological or surgical intervention to maintain patency and time-to-event • Cumulative graft patency ("... defined as the time from graft creation to unsalvageable graft loss (when the graft was abandoned).") • Adverse events e.g. "The occurrences of minor and major bleeding episodes, changes in lipid status and blood pressure, hospitalizations for cardiovascular events, and death were determined."
Notes	<ul style="list-style-type: none"> • Funding source: the Canadian Institutes for Health Research and the Physicians Services Incorporated Foundation • Study was as an attempt to replicate results of Schmitz 2002: "Indeed, a small, single-centre prospective study of fish oil prophylaxis showed a dramatic (5-fold) improvement in 12-month graft patency and inspired a larger, definitive trial."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "All randomization is determined by a computer generated random number list, using a random permuted block design, and with randomly varied block sizes."</p> <p>"Patient demographics and graft characteristics were well balanced between the 2 treatment groups (TABLE1)... "</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "Patients were randomised (1:1) with concealed allocation to the 2 treatment groups on the seventh postoperative day of their arteriovenous graft creation by a central, independent randomization facility."</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Patients, study coordinators, caregivers, and site pharmacists were blinded to treatment allocation."</p>
Blinding of outcome assessment (detection bias) Loss of patency	Low risk	<p>Quote: "... an independent assessor, unaware of treatment allocation, reviewed the radiology or surgical reports to verify the outcomes."</p>
Blinding of outcome assessment (detection bias) All adverse outcomes	Low risk	<p>Comment: Although not reported, we judge the risk of bias as low due to the objective nature of the outcome measurement.</p>
Incomplete outcome data (attrition bias) Loss of patency	Unclear risk	<p>Drop-out rate was 16.2% (ω-3FA) and 16.5% (placebo). (Fig. 1)</p> <p>Comment: Although survival analysis was done, the primary ITT analysis was based on simple proportions. Since the risk of loss of patency ranges from 48% to 62%, the efficacy effect measure may be sensitive to the method of missing data analysis.</p>

FISH 2007 (Continued)

Incomplete outcome data (attrition bias) All adverse outcomes	Unclear risk	Comment: The drop-out rate (16%) is comparable or higher than the Adverse events risks in the treatment groups (death 8.1% and 8.2%, cardiovascular events 9% and 18%). These risks would not be robust and the adverse outcome effect measures may be sensitive to the method of missing data analysis. (Figure 1)
Selective reporting (reporting bias)	Unclear risk	Quote: "The occurrences of minor and major bleeding episodes, changes in lipid status and blood pressure, hospitalizations for cardiovascular events, and death were determined." Comment: Major and minor bleeding events were not separately reported and hospitalizations were not reported in the results section.
Other bias	Low risk	Study appears free of other biases

Schmitz 2002

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Time frame: December 1996 and January 1998 Study follow-up period: 12 months (primary outcome)
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre Patients close to the initiation of chronic HD who required placement of a new PTFE graft, and patients who were undergoing chronic HD but required placement of a new PTFE graft at a different site Number randomised: treatment group (12); control group (12) Mean age $\pm$ SEM (years): treatment group (52 ± 6); control group (54 ± 3) Sex (M/F): treatment group (5/7); control group (6/6) Diabetes: treatment group (7/12); control group (6/12) Smokers: not reported Forearm AVG: treatment group (9/12); control group (8/12) Exclusion criteria: patients requiring surgical revision (e.g. a "jump graft"); history of GI bleeding, patients already receiving chronic anticoagulation therapy (antiplatelet agents or warfarin); terminal or life-threatening disease; pregnancy; malignant hypertension
Interventions	<ul style="list-style-type: none"> Intervention started within 2 weeks of graft placement <p>Treatment group</p> <ul style="list-style-type: none"> ω-3FA: four x 1 g softgel capsules of fish oil (44% EPA, 24% DHA, 10% to 12% other oils) per day for 12 months <p>Control group</p> <ul style="list-style-type: none"> Placebo: matching 80% ω-6 ethyl esters (corn oil) placebo capsules
Outcomes	<ul style="list-style-type: none"> Graft thrombosis within 12 months, venous pressure monitoring by dialysis delivery system, method of assessment of thrombosis not clearly defined Adverse events e.g. overt bleeding episodes
Notes	<ul style="list-style-type: none"> Funding source: the Missouri Kidney Program, the Baxter HealthCare Extramural Grant Program, and the National Institute of Diabetes and Digestive and Kidney Disease (Grant DK52039).

Risk of bias

Schmitz 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised but the method was not reported.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Abstract quote: "A double-blind, randomised trial was conducted. Twenty-four patients were randomised to receive 4000 mg of fish oil or 4000 mg of control oil. Both preparations were enriched with antioxidants and deodorized with peppermint."
Blinding of outcome assessment (detection bias) Loss of patency	Low risk	Comment: Although not reported, we judge the risk of bias as low due to the objective nature of the outcome measurement
Blinding of outcome assessment (detection bias) All adverse outcomes	Low risk	Comment: Although not reported, we judge the risk of bias as low due to the objective nature of the outcome measurement
Incomplete outcome data (attrition bias) Loss of patency	Unclear risk	Quote: "One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo." Comment: The drop-out rate (8.3%) is comparable to the loss of patency risk in the treatment group (16.7%). This risk would not be robust and the efficacy effect measure may be sensitive to the method of missing data analysis.
Incomplete outcome data (attrition bias) All adverse outcomes	Unclear risk	Comment: The drop-out rate (8.3%) is higher than the Adverse events risks (0%). These risks would not be robust and the adverse outcome effect measures may be highly sensitive to the method of missing data analysis.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes of interest to this review were reported Comment: The reference to overt bleeding in the Results was interpreted to mean both major and minor bleeding.
Other bias	Low risk	Study appears free of other biases

ω-3FA - omega-3 fatty acid; AVF - arteriovenous fistula; AVG - arteriovenous graft; CI - confidence interval; DHA - docosahexaenoic acid; EPA - eicosapentaenoic acid; ESKD - end-stage kidney disease; GI - gastrointestinal; HD - haemodialysis; HR - Hazard ratio; ITT - intention-to-treat; NSAID/s - nonsteroidal anti-inflammatory drug/s; PTFE - polytetrafluoroethylene; SD - standard deviation; SEM - standard error of the mean

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bowden 2009	Wrong outcomes: not relevant to vascular access outcomes
De Fijter 1995	Wrong study design: cross-over study
Donnelly 1992a	Wrong outcomes: not relevant to vascular access outcomes
Gharekhani 2014	Wrong outcomes: not relevant to vascular access outcomes

Study	Reason for exclusion
Hung 2015	Wrong outcomes: not relevant to vascular access outcomes
Saifullah 2007	Wrong outcomes: not relevant to vascular access outcomes
Tumlin 2002a	Wrong outcomes: not relevant to vascular access outcomes

DATA AND ANALYSES

Comparison 1. Omega-3 fatty acids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Loss of patency by 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 AVG	2	41	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.36, 2.28]
2 Loss of patency by 12 months	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 AVF	1	536	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.21]
2.2 AVG	2	220	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.31]
3 Loss of patency: Hazard ratio	1		Hazard Ratio (Random, 95% CI)	Subtotals only
3.1 AVG	1		Hazard Ratio (Random, 95% CI)	0.68 [0.46, 1.01]
4 Serious adverse events: death	5	828	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.03, 0.02]
4.1 AVF	1	567	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.03, 0.02]
4.2 AVG	4	261	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.05, 0.07]
5 Serious adverse events: hospitalisation	4	632	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.06, 0.10]
5.1 AVF	1	567	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.08, 0.08]
5.2 AVG	3	65	Risk Difference (M-H, Random, 95% CI)	0.08 [-0.11, 0.28]
6 Serious adverse events: cardiovascular events	4		Risk Difference (M-H, Random, 95% CI)	Subtotals only
6.1 AVG	4	261	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.11, 0.07]
7 Serious adverse events: major bleeding	4		Risk Difference (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 AVG (excluding FISH 2007)	3	65	Risk Difference (M-H, Random, 95% CI)	0.08 [-0.11, 0.28]
7.2 AVG (including FISH 2007)	4	261	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.05, 0.10]
8 Adverse events: minor bleeding	5		Risk Difference (M-H, Random, 95% CI)	Subtotals only
8.1 AVF	1	567	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.06]
8.2 AVG (excluding FISH 2007)	3	65	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.07, 0.12]
8.3 AVG (including FISH 2007)	4	261	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.04, 0.08]
9 Adverse events: gas-trointestinal events	4	632	Risk Difference (M-H, Random, 95% CI)	0.15 [-0.05, 0.34]
9.1 AVF	1	567	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.03, 0.04]
9.2 AVG	3	65	Risk Difference (M-H, Random, 95% CI)	0.25 [0.07, 0.43]
10 Adverse events: other adverse events	4	632	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
10.1 AVF	1	567	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
10.2 AVG	3	65	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.08, 0.11]
11 Sensitivity analysis: loss of patency by 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Best-case	2	41	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.15, 2.49]
11.2 Middle-case 1	2	41	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.11, 4.05]
11.3 Middle-case 2	2	41	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.35, 2.57]
11.4 Worst-case	2	41	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.26, 4.04]
11.5 Per protocol	2	35	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.15, 3.98]
12 Sensitivity analysis: loss of patency by 12 months	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Best-case	2	220	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.18, 1.17]
12.2 Middle-case 1	2	220	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.14, 1.66]
12.3 Middle-case 2	2	220	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.25, 1.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.4 Worst-case	2	220	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.22, 2.02]
12.5 Per protocol	2	187	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.16, 1.61]
13 Sensitivity analysis: death	4		Risk Difference (M-H, Random, 95% CI)	Subtotals only
13.1 Best-case	4	261	Risk Difference (M-H, Random, 95% CI)	-0.06 [-0.13, 0.01]
13.2 Middle-case 1	4	261	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.05, 0.06]
13.3 Middle-case 2	4	261	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.06, 0.11]
13.4 Worst-case	4	261	Risk Difference (M-H, Random, 95% CI)	0.10 [0.02, 0.17]
13.5 Per protocol	4	239	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.06, 0.07]
14 Sensitivity analysis: hospitalisation	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only
14.1 Best-case	3	65	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.16, 0.09]
14.2 Middle-case 1	3	65	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.08, 0.09]
14.3 Middle-case 2	3	65	Risk Difference (M-H, Random, 95% CI)	0.11 [-0.05, 0.27]
14.4 Worst-case	3	65	Risk Difference (M-H, Random, 95% CI)	0.16 [0.01, 0.30]
14.5 Per protocol	3	58	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.09, 0.10]
15 Sensitivity analysis: cardiovascular events	4		Risk Difference (M-H, Random, 95% CI)	Subtotals only
15.1 Best-case	4	261	Risk Difference (M-H, Random, 95% CI)	-0.09 [-0.27, 0.08]
15.2 Middle-case 1	4	261	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.10, 0.04]
15.3 Middle-case 2	4	261	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.12, 0.13]
15.4 Worst-case	4	261	Risk Difference (M-H, Random, 95% CI)	0.10 [0.02, 0.19]
15.5 Per protocol	4	223	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.12, 0.05]
16 Sensitivity analysis: major bleeding	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only
16.1 Best-case	3	65	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.16, 0.09]
16.2 Middle-case 1	3	65	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.08, 0.09]
16.3 Middle-case 2	3	65	Risk Difference (M-H, Random, 95% CI)	0.11 [-0.05, 0.27]
16.4 Worst-case	3	65	Risk Difference (M-H, Random, 95% CI)	0.16 [0.01, 0.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.5 Per protocol	3	58	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.09, 0.10]
17 Sensitivity analysis: minor bleeding	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only
17.1 Best-case	3	65	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.15, 0.06]
17.2 Middle-case 1	3	65	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.09, 0.09]
17.3 Middle-case 2	3	65	Risk Difference (M-H, Random, 95% CI)	0.09 [-0.06, 0.24]
17.4 Worst-case	3	65	Risk Difference (M-H, Random, 95% CI)	0.14 [0.00, 0.28]
17.5 Per protocol	3	58	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.09, 0.09]
18 Sensitivity analysis: gastrointestinal events	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only
18.1 Best-case	3	65	Risk Difference (M-H, Random, 95% CI)	0.14 [-0.04, 0.31]
18.2 Middle-case 1	3	65	Risk Difference (M-H, Random, 95% CI)	0.18 [0.01, 0.35]
18.3 Middle-case 2	3	65	Risk Difference (M-H, Random, 95% CI)	0.28 [0.09, 0.48]
18.4 Worst-case	3	65	Risk Difference (M-H, Random, 95% CI)	0.33 [0.15, 0.52]
18.5 Per protocol	3	58	Risk Difference (M-H, Random, 95% CI)	0.21 [0.02, 0.40]
19 Sensitivity analysis: other adverse events	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only
19.1 Best-case	3	65	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.20, 0.06]
19.2 Middle-case 1	3	65	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.09, 0.08]
19.3 Middle-case 2	3	65	Risk Difference (M-H, Random, 95% CI)	0.09 [-0.06, 0.24]
19.4 Worst-case	3	65	Risk Difference (M-H, Random, 95% CI)	0.12 [-0.02, 0.26]
19.5 Per protocol	3	58	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.10, 0.09]

Analysis 1.1. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 1 Loss of patency by 6 months.

Study or subgroup	ω -3FA n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: $\tau^2=0.09$; $\chi^2=1.16$, $df=1$ ($P=0.28$); $I^2=14\%$ Test for overall effect: $Z=0.2$ ($P=0.84$)					
Less risk with ω -3FA 0.01 0.1 1 10 100 Less risk with placebo					

Analysis 1.2. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 2 Loss of patency by 12 months.

Study or subgroup	ω -3FA n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 AVF					
FAVOURED 2009	128/270	125/266		100%	1.01[0.84,1.21]
Subtotal (95% CI)	270	266		100%	1.01[0.84,1.21]
Total events: 128 (ω -3FA), 125 (Placebo) Heterogeneity: Not applicable Test for overall effect: $Z=0.1$ ($P=0.92$)					
1.2.2 AVG					
Schmitz 2002	3/12	9/12		32.51%	0.33[0.12,0.94]
FISH 2007	48/99	60/97		67.49%	0.78[0.61,1.01]
Subtotal (95% CI)	111	109		100%	0.59[0.27,1.31]
Total events: 51 (ω -3FA), 69 (Placebo) Heterogeneity: $\tau^2=0.23$; $\chi^2=2.53$, $df=1$ ($P=0.11$); $I^2=60.43\%$ Test for overall effect: $Z=1.29$ ($P=0.2$)					
Less risk with ω -3FA 0.1 0.2 0.5 1 2 5 10 Less risk with placebo					

Analysis 1.3. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 3 Loss of patency: Hazard ratio.

Study or subgroup	ω -3FA N	Placebo N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
1.3.1 AVG						
FISH 2007	0	0	-0.4 (0.199)		100%	0.68[0.46,1.01]
Subtotal (95% CI)					100%	0.68[0.46,1.01]
Heterogeneity: Not applicable Test for overall effect: $Z=1.93$ ($P=0.05$)						
Less risk with ω -3FA 0.1 0.2 0.5 1 2 5 10 Less risk with placebo						

Analysis 1.4. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 4 Serious adverse events: death.

Study or subgroup	ω -3FA n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.4.1 AVF					
FAVOURED 2009	8/284	9/283		81.66%	-0[-0.03,0.02]
Subtotal (95% CI)	284	283		81.66%	-0[-0.03,0.02]
Total events: 8 (ω -3FA), 9 (Placebo)					
Less risk with ω -3FA -1 -0.5 0 0.5 1 Less risk with placebo

Analysis 1.5. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 5 Serious adverse events: hospitalisation.

Analysis 1.6. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 6 Serious adverse events: cardiovascular events.

Analysis 1.7. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 7 Serious adverse events: major bleeding.

Analysis 1.8. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 8 Adverse events: minor bleeding.

Analysis 1.9. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 9 Adverse events: gastrointestinal events.

Analysis 1.10. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 10 Adverse events: other adverse events.

Analysis 1.11. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 11 Sensitivity analysis: loss of patency by 6 months.

Analysis 1.12. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 12 Sensitivity analysis: loss of patency by 12 months.

Analysis 1.13. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 13 Sensitivity analysis: death.

Analysis 1.14. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 14 Sensitivity analysis: hospitalisation.

Analysis 1.15. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 15 Sensitivity analysis: cardiovascular events.

Analysis 1.16. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 16 Sensitivity analysis: major bleeding.

Analysis 1.17. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 17 Sensitivity analysis: minor bleeding.

**Analysis 1.18. Comparison 1 Omega-3 fatty acids versus placebo,
Outcome 18 Sensitivity analysis: gastrointestinal events.**

Analysis 1.19. Comparison 1 Omega-3 fatty acids versus placebo, Outcome 19 Sensitivity analysis: other adverse events.

ADDITIONAL TABLES

Table 1. Intention-to-treat (ITT) case scenarios

ITT Scenario	Losses to follow-up assumed to have events ¹ of interest	
	ω -3FA Group	Control Group
Best-case	no	yes

Table 1. Intention-to-treat (ITT) case scenarios *(Continued)*

Middle-case 1	no	no
Middle-case 2	yes	yes
Worst-case	yes	no

¹In this review, all outcome events were bad events e.g. loss of patency, serious adverse events, non-serious adverse events

Table 2. Intention-to-treat (ITT) case scenarios used in the analyses

Study	Default ITT scenario used	Analyses
Bowden 2007	Middle-case 1	All
Diskin 1990	Middle-case 2 ¹	All except Analysis 1.4 and Analysis 1.6
	Only one scenario needed ²	Analysis 1.4 (death); Analysis 1.6 (cardiovascular event)
FAVOURED 2009	Middle-case 1	All except Analysis 1.2
	Authors' modified ITT analysis ³	Analysis 1.2 (loss of patency)
FISH 2007	Middle-case 1	All
Schmitz 2002	Middle-case 2	All

¹Middle-case 2 scenario used because the middle-case 1 scenario was identical with the best-case scenario.

²No ITT scenario analysis was required as there was complete follow-up and ascertainment for these two outcomes.

³Authors performed a modified ITT analysis on 536 out of 567 randomised participants, that involved imputing values for the primary outcome of AVF failure for 122 "missing data" see [FAVOURED 2009](#) Fig 1 and Table 2.

Table 3. Reporting and extraction of AE data

Type of serious adverse events/adverse events	Study ID	Manner of reporting in paper	How outcome data values were inferred for extraction and analysis
Death	Diskin 1990	Fully reported	Direct
	FAVOURED 2009	<ul style="list-style-type: none"> "One EPA patient died within 1 week of initiation of the study from an acute myocardial infarction." (Diskin 1990) See Table 3 of FAVOURED 2009 See Figure 1 of FISH 2007 	
	FISH 2007		
	Bowden 2007	Indirect	ITT analysis assumed no deaths occurred
		<ul style="list-style-type: none"> "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption." 	
	Schmitz 2002	Indirect	ITT analysis assumed this participant to have died

Table 3. Reporting and extraction of AE data (Continued)

"One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo."

Hospitalisation	Diskin 1990	Fully reported	Direct
	FAVOURED 2009	<ul style="list-style-type: none"> "One patient receiving EPA developed a gastrointestinal bleed requiring hospitalization." (Diskin 1990) See Table 3 of FAVOURED 2009. 	
	Bowden 2007	Indirect <ul style="list-style-type: none"> "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption." 	ITT analysis assumed no hospitalisation occurred
	Schmitz 2002	Indirect <ul style="list-style-type: none"> "One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo." 	ITT analysis assumed this participant to have been hospitalised
Cardiovascular events	FISH 2007	Measured but partially reported <ul style="list-style-type: none"> "The occurrences of minor and major bleeding episodes, changes in lipid status and blood pressure, hospitalizations for cardiovascular events, and death were determined. All endpoints reported were prespecified." "There was no difference in bleeding (9 events in the fish oil group vs 8 in the placebo group; $P > .99$) or other significant clinical adverse events between the 2 treatment groups." 	Study excluded from meta-analysis
	Diskin 1990	Fully reported	Direct
	FISH 2007	<ul style="list-style-type: none"> "One EPA patient died within 1 week of initiation of the study from an acute myocardial infarction." (Diskin 1990) See Table 2 of FISH 2007. 	
	Bowden 2007	Indirect <ul style="list-style-type: none"> "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption." 	ITT analysis assumed no cardiovascular events occurred
	Schmitz 2002	Indirect <ul style="list-style-type: none"> "One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo." 	ITT analysis assumed this participant to have experienced a cardiovascular event
	FAVOURED 2009	Measured but not reported <ul style="list-style-type: none"> "Secondary outcomes included components of the primary outcome, and safety outcomes." "Adverse drug events, including bleeding events (16 [6%] vs 10 [4%]; $P = .23$) and gastrointestinal adverse effects (15 [5%] vs 14 [5%]; $P = .86$), were similar for the fish oil and placebo groups. Death 	Study excluded from meta-analysis. Although it might be reasonable to assume there were no events there was too much missing data (> 20% in each arm) for any ITT scenario analysis

Table 3. Reporting and extraction of AE data (Continued)

occurred in 8 participants allocated to fish oil and 9 allocated to placebo (Table 3)."

Major bleeding	Diskin 1990	Fully reported	Direct
	Schmitz 2002	<ul style="list-style-type: none"> "One patient receiving EPA developed a gastrointestinal bleed requiring hospitalization." (Diskin 1990) "No overt bleeding episodes were observed in either group." (Schmitz 2002) 	
	Bowden 2007	Indirect <ul style="list-style-type: none"> "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption." 	ITT analysis assumed no major bleeding occurred
	FISH 2007	Measured but partially reported <ul style="list-style-type: none"> "There was no difference in bleeding (9 events in the fish oil group vs 8 in the placebo group; P>.99)..." 	<p>Study excluded from default meta-analysis, as bleeding events were aggregated and not separately reported as major or minor</p> <p>Sensitivity analysis done included the study by assuming all were major bleeding events</p>
	FAVOURED 2009	Measured but not reported	Study excluded from meta-analysis. Although it might be reasonable to assume there were no events (see Table 3 of FAVOURED 2009) there was too much missing data (> 20% in each arm) for any ITT scenario analysis.
Minor bleeding	FAVOURED 2009	Fully reported <ul style="list-style-type: none"> See Table 3 of FAVOURED 2009. 	Direct. We assumed that all the bleeding events were minor as they were not listed under the serious adverse events category
	Bowden 2007	Indirect <ul style="list-style-type: none"> "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption." 	Our ITT analysis assumed no minor bleeding occurred
	Diskin 1990	Measured but not reported <ul style="list-style-type: none"> "One EPA patient died within 1 week of initiation of the study from an acute myocardial infarction. One patient receiving EPA developed a gastrointestinal bleed requiring hospitalization. One patient receiving placebo developed gas gangrene secondary to <i>Clostridium perfringens</i> which required debridement and antibiotics." 	As there were only seven participants, ITT analysis assumed complete reporting of all adverse events i.e. no minor bleeding events except for the one imputed for the scenario

Table 3. Reporting and extraction of AE data (Continued)

	Schmitz 2002	Indirect <ul style="list-style-type: none"> "One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo." 	ITT analysis assumed this individual to have experienced a minor bleed
	FISH 2007	Measured but partially reported <ul style="list-style-type: none"> "There was no difference in bleeding (9 events in the fish oil group vs 8 in the placebo group; $P>.99$)..." 	Study excluded from default meta-analysis, as bleeding events were aggregated and not separately reported as major or minor Sensitivity analysis done included the study by assuming all were minor bleeding events
Gastrointestinal events	Bowden 2007	Fully reported	Direct
	FAVOUR 2009	<ul style="list-style-type: none"> "A total of 5 patients in the treatment group (n-3) and 2 in the control group (n-6) reported gastrointestinal distress that included bloating, gas, and a "fish" after-taste." (Bowden 2007) See Table 3 of FAVOUR 2009. 	
	Diskin 1990	Measured but not reported	As there were only seven participants, ITT analysis assumed complete reporting of all adverse events i.e. no gastrointestinal events except for the one imputed for the scenario analysis.
	Schmitz 2002	Indirect <ul style="list-style-type: none"> "One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo." 	ITT analysis assumed this participant to have experienced a gastrointestinal event
	FISH 2007	Measured but partially reported <ul style="list-style-type: none"> "There was no difference in bleeding... or other significant clinical adverse events between the 2 treatment groups." 	Study excluded from meta-analysis
Other adverse events	Diskin 1990	Fully reported	Direct
	FAVOUR 2009	<ul style="list-style-type: none"> "One patient receiving placebo developed gas gangrene secondary to Clostridium perfringens which required debridement and antibiotics." (Diskin 1990) See Table 3 of FAVOUR 2009. 	
	Bowden 2007	Indirect <ul style="list-style-type: none"> "During the course of this study, no adverse events occurred that were related to n-3 or n-6 fatty acid consumption." 	ITT analysis assumed no other adverse events occurred
	Schmitz 2002	Indirect	ITT analysis assumed this participant to have experienced some other adverse events.

Table 3. Reporting and extraction of AE data (Continued)

- "One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo."

FISH 2007	Measured but partially reported	Study excluded from meta-analysis
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ITT - intention-to-treat

Table 4. Study drop-outs and analysis totals (Bowden 2007)

Group	No. randomised	Drop-outs from authors' analysis (see Bowden 2007 Table 1)	No. analysed in our ITT scenarios	Reasons for analysis drop-out
ω-3FA	17	3 (14 participants analysed)	17	"In all, 2 patients from the placebo group and 3 patients from the n-3 group completed the study but were not included in the analysis because of noncompliance..."
Placebo	17	2 (15 participants analysed)	17	

ITT- intention-to-treat

Table 5. Study drop-outs and analysis totals (Diskin 1990)

Group	No. randomised	Loss to follow-up	No. analysed in our ITT scenarios	Reasons for loss to follow-up
ω-3FA	4	1	4	"One EPA patient died within 1 week of initiation of the study from an acute myocardial infarction."
Placebo	3	0	3	

ITT - intention-to-treat

Table 6. Study drop-outs and analysis totals (FAVOURED 2009)

Group	No. randomised	Drop-outs from authors' analysis (see FAVOURED 2009 Table 2 and 3)	No. analysed in our ITT scenarios	Reasons for analysis drop-outs
ω-3FA	284	Efficacy outcomes: 14 (270 participants analysed) Safety outcomes: 0 (284 participants analysed)	Efficacy outcome: 270 Safety outcomes: 284	See FAVOURED 2009 Fig 1 .
Placebo	283	Efficacy outcomes: 17 (266 participants analysed) Safety outcomes: 0 (283 participants analysed)	Efficacy outcome: 266 Safety outcomes: 283	

ITT - intention-to-treat

Table 7. Study drop-outs and analysis totals (FISH 2007)

Group	No. randomised	Drop-outs from authors' analysis (see FISH 2007 Figure 1)	No. analysed in our ITT scenarios	Reasons for analysis drop-outs
ω-3FA	101	2 (99 participants analysed)	99	See FISH 2007 Fig 1 .
Placebo	100	3 (97 participants analysed)	97	

ITT - intention-to-treat

Table 8. Study drop-outs and analysis totals (Schmitz 2002)

Group	No. randomised	Loss to follow-up	No. analysed in our ITT scenarios	Reasons for loss to follow-up
ω-3FA	12	1	12	"One patient in the fish oil-treated group was lost to follow-up monitoring at 7 mo."
Placebo	12	0	12	

ITT - intention-to-treat

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. (fistula* or AVF* or graft or grafts or shunt or shunts):ti,ab,kw 2. "blood vessel prosthesis":kw 3. ("vascular access" or "venous access"):ti,ab,kw 4. ("dialysis access" or "hemodialysis access"):ti,ab,kw 5. {or #1-#3} 6. hemodialysis:ti,ab,kw 7. hemodiafiltration:ti,ab,kw 8. hemofiltration:ti,ab,kw 9. dialysis:ti,ab,kw 10. ("kidney failure" or "kidney disease" or "renal failure" or "renal disease"):ti,ab,kw 11. (ESKD or ESKF or ESRD or ESRF):ti,ab,kw 12. {or #6-#11} 13. {and #5, #12} 14. {or #4, #13} 15. (fish next (oil or oils)):ti,ab,kw 16. (("omega three" or "omega 3") near/2 (fatty next acid*)):ti,ab,kw 17. (docosahexaenoic next acid*):ti,ab,kw 18. (eicosapentaenoic next acid*):ti,ab,kw 19. {or #15-#18} 20. {and #14, #19}

(Continued)

MEDLINE

1. Renal Replacement Therapy/
2. Renal Dialysis/
3. Hemodiafiltration/
4. Hemodialysis, home/
5. exp Hemofiltration/
6. dialysis.tw.
7. (hemodialysis or haemodialysis).tw.
8. (hemofiltration or haemofiltration).tw.
9. (hemodiafiltration or haemodiafiltration).tw.
- 10.or/1-9
- 11.Arteriovenous Shunt, Surgical/
- 12.Arteriovenous Fistula/
- 13.Blood Vessel Prosthesis/
- 14.Vascular Patency/
- 15.(fistula\$ or avf\$ or avg\$ or graft\$ or shunt\$).tw.
- 16.vascular access.tw.
- 17.(dialysis access or h?emodialysis access).tw.
- 18.or/11-17
- 19.exp Fish Oils/
- 20.((omega three or omega 3) adj2 fatty acid*).tw.
- 21.docosahexaenoic acid*.tw.
- 22.eicosapentaenoic acid*.tw.
- 23.fish oil*.tw.
- 24.or/19-23
- 25.and/10,18,24

EMBASE

1. exp renal replacement therapy/
2. extended daily dialysis/
3. hemodialysis/
4. home dialysis/
5. hemofiltration/
6. hemodiafiltration/
7. dialysis.tw.
8. (hemodialysis or haemodialysis).tw.
9. (hemofiltration or haemofiltration).tw.
- 10.(hemodiafiltration or haemodiafiltration).tw.
- 11.renal replacement therapy-dependent renal disease/
- 12.or/1-11
- 13.artieriovenous fistula/
- 14.artieriovenous shunt/
- 15.blood vessel prosthesis/
- 16.(fistula\$ or avf\$ or avg\$ or grafts or shunt\$).tw.
- 17.vascular access.tw.
- 18.(dialysis access or h?emodialysis access).tw.
- 19.or/13-17
- 20.fish oil/
- 21.omega 3 fatty acid/ or docosahexaenoic acid/ or icosapentaenoic acid/
- 22.((omega three or omega 3) adj2 fatty acid*).tw.
- 23.docosahexaenoic acid*.tw.
- 24.eicosapentaenoic acid*.tw.
- 25.fish oil*.tw.

(Continued)

26.or/20-25
27.and/12,20,25

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available.</p>
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Incomplete outcome data	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with ob-</p>

(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.

served event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear: Insufficient information to permit judgement

Selective reporting

Reporting bias due to selective outcome reporting

Low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: Insufficient information to permit judgement

Other bias

Bias due to problems not covered elsewhere in the table

Low risk of bias: The study appears to be free of other sources of bias.

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 10, 2014

Review first published: Issue 11, 2018

Date	Event	Description
24 October 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: MYW, KWT
2. Study selection: MYW, KWT
3. Extract data from studies: MYW, KWT, YNZ, ESYC

4. Enter data into RevMan: MYW, KWT, YNZ, ESYC
5. Carry out the analysis: MYW, KWT, YNZ, ESYC
6. Interpret the analysis: MYW, KWT, SFJ, ESYC, TJ
7. Draft the final review: MYW, KWT, ESYC, YNZ
8. Disagreement resolution: MYW, KWT, FJS, TJ
9. Update the review: MYW, KWT, ESYC

DECLARATIONS OF INTEREST

- Mei-Yi Wu: none known
- Ka-Wai Tam: none known
- Fahad Javaid Siddiqui: none known
- Edwin Shih-Yen Chan: none known
- Yanan Zhu: none known
- Tazeen Jafar: none known

SOURCES OF SUPPORT

Internal sources

- Singapore Clinical Research Institute, Singapore.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Tightened the inclusion criteria by excluding quasi-randomised studies
- Reorganized components of the primary and secondary outcomes
- Increased the types of sensitivity analyses
- Added Yanan Zhu as a co-author

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis [adverse effects] [mortality]; *Vascular Access Devices; Arteriovenous Shunt, Surgical [*methods]; Fatty Acids, Omega-3 [*administration & dosage] [adverse effects]; Graft Occlusion, Vascular [complications] [epidemiology] [*prevention & control]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*therapy]; Thrombosis [*prevention & control]; Time Factors

MeSH check words

Humans