Omega-3 Polyunsaturated Fatty Acid Supplementation to Prevent Arteriovenous Fistula and Graft Failure: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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

Study Design: Systematic review with meta-analysis.

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

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

Intervention: Omega-3 PUFA.

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

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

Limitations: Small number and methodological limitations of included trials.

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

Complete author and article information provided before references.

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Hemodialysis is the most common renal replacement therapy worldwide and ideally is performed using a functioning arteriovenous vascular access. Establishing and maintaining a functional arteriovenous access remains one of the greatest challenges for dialysis care.[1-3] Arteriovenous fistula (AVF) and graft (AVG) dysfunction lead to prolonged use of central venous catheters and repeat hospitalization and procedures, which are associated with higher rates of complications and mortality.[4-6] Patients, caregivers, and health care professionals consider vascular access outcomes a critical priority.[7] Strategies to improve the usability of hemodialysis vascular access are required.

The pathogenesis of arteriovenous access failure is complex and not fully understood.[8] Pathogenic processes that may contribute to patency loss, impaired maturation, and dialysis suitability failure include neointimal hyperplasia formation and impaired vascular remodeling, with insufficient vasodilation and vessel wall thickening in response to the increased pressure, shear stress, and oxygen tension resulting from redirected arterial inflow.[8-10]

Randomized controlled trials have evaluated various local and systemic therapies to improve arteriovenous access maturation and function.[10] Most trials have focused on antiplatelet agents to prevent access thrombosis and maintaining vascular access patency. Although antiplatelet agents may be effective in reducing early arteriovenous access thrombosis,[11-16] they have not been shown to improve long-term patency and dialysis suitability.[16,17] Given the complexity of processes involved in dialysis vascular access failure, an agent with pleiotropic vascular effects may provide a more durable and effective therapeutic strategy for favorably influencing vascular remodeling, neointimal hyperplasia formation, and thrombotic risk in newly formed vascular access. Omega-3

polyunsaturated fatty acids (PUFAs) show promise because they inhibit platelet aggregation[18] and exert anti-inflammatory,[19,20] antiproliferative,[21,22] and vasodilatory effects[23] on vascular structures. These actions may improve maturation and function of a newly created arteriovenous access. Conversely, although previous small studies did not show increased risk for bleeding in dialysis patients taking omega-3 PUFAs,[24,25] the antiplatelet effects of omega-3 PUFAs may continue to pose a concern given the already increased bleeding diathesis in this population.[26-29]

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

Methods

Study Design

This systematic review and meta-analysis was conducted in accordance with Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) guidelines for reporting of systematic reviews of interventions and a prespecified registered protocol.[30,31] Research ethics committee approval was not required for this study.

Search Strategy and Selection Criteria

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

Study Selection and Data Extraction

Two authors (A.K.V. and S.C.P.) independently screened titles and abstracts of all retrieved citations and reviewed the full text of potentially relevant records to identify trials that fulfilled the review eligibility criteria using the Population, Intervention, Comparison, Outcomes (PICO) framework.[32] Baseline characteristics, study design, interventions, and outcome definitions were extracted independently by the same authors.

Outcomes

Standardized definitions for outcomes related to hemodialysis vascular access were used.[33] The primary efficacy outcome was loss of primary vascular access patency (first thrombosis or need for surgical or endovascular intervention to restore patency), and the primary safety outcome was bleeding. Secondary outcomes included the following: need for surgical or radiological intervention(s) to maintain dialysis vascular access patency or assist maturation, dialysis vascular access abandonment (defined as an AVF/AVG that could no longer be used for hemodialysis and the associated access problem was not correctable by a further intervention), early dialysis suitability failure (defined as an access that despite radiologic or surgical interventions could not be used successfully for dialysis by 3 months following access creation), late dialysis suitability failure (defined as an access that despite radiologic or surgical interventions could not be used successfully for dialysis by 6 months following access creation), gastrointestinal adverse effects, all-cause mortality, cardiovascular mortality, hospitalization, and treatment adherence. For each outcome, the number of events and number of people at risk in each treatment arm of included studies were extracted to calculate an individual study relative risk (RR) and 95% confidence interval (CI). To reduce heterogeneity and increase certainty in the review findings, outcome measures from contributing studies were used only in meta-analyses, if consistent with the prespecified outcome definitions reported in the protocol for this systematic review. Additional outcome data consistent with the outcome definitions in the protocol were requested from study investigators in writing (including re-analyses of patient-level data) and included in meta-analyses when provided.

Evidence Quality Assessment

Risks of bias in included studies were adjudicated independently by 2 review authors (A.K.V. and S.C.P.) using Cochrane methodology[34] for random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, attrition, selective reporting of outcomes, and other sources of bias. Discrepancies were resolved by discussion. The certainty of the overall evidence related to each main outcome was assessed by 2 authors (A.K.V. and S.C.P.) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (GRADE 2008)[35,36] to ensure accurate interpretation of effect estimates taking into consideration the certainty of available evidence (ie, a nonsignificant effect estimate may be interpreted as "uncertain" if the certainty of available evidence is very low, and a significant effect estimate, as "probable" if the available evidence is moderate).

Statistical Analysis

Random-effects pairwise meta-analysis was used to estimate treatment effects. Summary effect estimates were expressed as RRs and the associated 95% CIs. Statistical heterogeneity was quantified using the Cochran Q test and the I^2 metric.[37] $I^2 > 75\%$ was considered to indicate substantial heterogeneity.[37] Prespecified subgroup analyses were planned to explore potential sources of