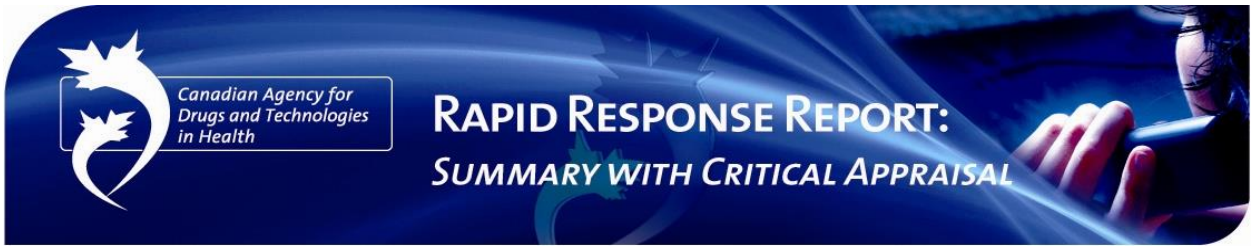

TITLE: Omega-3 Fatty Acids for Proteinuria due to Nephrotic Syndrome: A Review of Clinical Effectiveness and Cost-Effectiveness

DATE: 05 February 2016

CONTEXT AND POLICY ISSUES

Omega-3 (n-3) fatty acids are essential polyunsaturated fatty acids (PUFAs) – fatty acid structures with two or more double bonds. Fatty fish, nuts, and seeds are good dietary sources of n-3s. Dietary sources vary in the composition of essential fatty acids. Fatty fish and fish oils provide a rich source of long-chain (LC) n-3s like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while plant sources are higher in the less therapeutically relevant metabolic precursor alpha-linolenic acid. Various structure-function relationships throughout the body are supported by n-3s. They contribute membrane fluidity through their presence in phospholipid cell membranes and participate in metabolic processes including the provision of cellular energy, optimal neuronal function, and visual acuity. They are also precursors for eicosanoids which act as paracrine hormones and contribute to blood vessel permeability, platelet activity, and modification of inflammatory processes. Thus, they are lauded for their potential cardiovascular, anti-inflammatory, and neurological protective properties.

Suboptimal n-3 status is common in North America.[1] Based on Canadian Health Measures Survey data, a very low percentage (<3%) of Canadians have n-3 index levels (an indicator of n-3 status) associated with low coronary heart disease risk and over 40% have levels associated with high risk while the average Canadian has levels associated with moderate risk.[2] Various formulations of n-3 supplements are available including fish oil, cod liver oil, krill oil, and flax oil. Dietary guidelines suggest consuming the equivalent of two servings of oily fish per week (or at least 500 mg/day of EPA and DHA). Omega-3 supplements are also available in pharmacologic doses for therapeutic purposes, generally considered >3 g/day.

Nephrotic syndrome is a glomerulonephropathy that affects the structure and function of the glomerulus. It is characterized by increased permeability of the glomerular barrier for protein. It is distinct from nephritic syndrome (inflammation of the capillary loops of the glomerulus) and asymptomatic renal disease, through there can be some overlap in clinical presentation. Nephrotic syndrome typically manifests as heavy proteinuria (protein excretion greater than 3.5 g/24 hours) combined with edema and hypoalbuminemia (<3 g/dL).[3] Patients may also have

signs of hyperlipidemia and thrombotic disease, and there is a potential for abnormal bone metabolism.[3] Nephrotic syndrome is of concern as a substantial proportion of patients may eventually progress to end-stage renal disease (ESRD) as is observed in immunoglobulin A nephropathy (IgAN).[4,5] This is suspected to occur due to the formation of circulating immune complexes which deposit in the glomerular mesangium and lead to clinical symptoms; typifying the crossover between nephrotic and nephritic syndromes.[6,7]

Typical components of treatment include immunosuppressive and non-immunosuppressive therapy. Immunosuppressive therapy is uncommon in mild or slowly progressing disease due to potential toxicity. Non-immunosuppressive therapies include angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) which are used to control intraglomerular pressure and slow the progression of kidney disease through antiproteinuric effects, as well as statins to lower cardiovascular disease risk.[5] ACE inhibitors and ARBs may be given in combination, though it is unclear whether this provides any benefit over each treatment alone.[5] Omega-3s are another non-immunosuppressive therapy that has been proposed as an adjuvant therapy due to their purported cardiovascular benefits and anti-inflammatory properties.

The use of high therapeutic doses of n-3 supplements, particularly as fish oil, to treat glomerulonephropathies was first observed over 30 years ago.[8,9] Studies investigating the benefits of n-3 supplements for patients with nephrotic syndrome have shown inconsistent results. Synthesis of evidence on this topic has previously concluded that n-3s have no effect on kidney function and proteinuria.[10] However, some studies have demonstrated that n-3 treatment is more effective in patients with nephrotic syndrome than controls.[11,12]

Clinical practice guidelines by Kidney Disease – Improving Global Outcomes (KDIGO) suggest that high-dose fish oil (3.3 g/day or more) can be trialed as add-on therapy in IgAN patients with risk factors for disease progression as there is potential for benefit and consumption is unlikely to cause harm.[13] However, this guideline noted the inconsistency in the quality and outcomes of the research in this area. Further, the cost-implications of providing this therapy, given the uncertainty surrounding its effectiveness have not been reviewed.

The purpose of this review is to assess the clinical and cost-effectiveness of n-3 fatty acid supplementation for the reduction of proteinuria in patients with nephrotic syndrome.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of omega-3 fatty acid supplementation for reduction of proteinuria in patients with nephrotic syndrome?

2. What is the cost-effectiveness of omega-3 fatty acid supplementation for reduction of proteinuria in patients with nephrotic syndrome?

KEY FINDINGS

Four systematic reviews and two non-randomized studies were identified regarding the clinical effectiveness of omega-3 fatty acid supplementation for reduction of proteinuria in patients with immunoglobulin A nephropathy or idiopathic steroid-resistant nephrotic syndrome. There is insufficient evidence to suggest a benefit of omega-3 treatment for these indications. There is some limited low quality evidence to suggest potential improvements in surrogate kidney

function outcomes, but not relevant clinical endpoints, and no evidence of potential harm. No relevant evidence was identified regarding the cost-effectiveness of omega-3 fatty acids for patients with nephrotic syndrome.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and January 8, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with proteinuria due to mild to moderate nephrotic syndrome (e.g., immunoglobulin A nephropathy, Henoch-Schönlein purpura, idiopathic nephrotic syndrome [minimal change disease])[a]
Intervention	Omega-3, with or without omega-6, fatty acid supplementation (e.g., flax, fish or krill oil extracts) alone or in combination with ace inhibitors and/or angiotensin II receptor blockers as part of outpatient management
Comparator	Placebo; Omega-6 supplementation alone; Ace inhibitors and/or angiotensin receptor blockers alone; Other active comparators
Outcomes	Q1: Clinical benefits (e.g., effect on proteinuria, kidney function, hypertension, lipid profiles, modification of cardiovascular risk factors and long-term cardiovascular outcomes); Harms (e.g., tolerability, gastrointestinal side-effects) Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations

[a]Excluding systemic causes of nephropathy such as systemic lupus erythematosus, diabetes mellitus

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2006. Health Technology Assessment reports, systematic reviews (SR), and meta-analyses were excluded if there was incomplete reporting of methods or if they were superseded by a more recent and/or rigorous review, or an update. Randomized controlled trials (RCTs) and non-randomized studies (NRS) were excluded if they were described within an included SR.

Critical Appraisal of Individual Studies

Key methodological aspects specific to each study design were appraised. Systematic reviews were critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR) criteria.[14] The methods used when conducting the literature search, study selection, quality assessment, data extraction, and for summarizing the data were assessed. Primary clinical studies were critically appraised using the Downs and Black checklist.[15] Reporting quality, external validity, internal validity in terms of bias and confounding, and power were assessed. Summary scores were not calculated for the included studies; rather, strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 61 citations were identified in the literature search. Following screening of titles and abstracts, 44 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 17 potentially relevant articles, six publications met the inclusion criteria and were included in this report. This was after exclusion of 11 studies; two RCTs due to inclusion in a selected SR,[9,16] three SRs as they were superseded by more rigorous and/or recent SRs,[17-19] one due to an inappropriate intervention (patients only received n-3 supplementation prior to the treatment phase),[20] three due to an inappropriate comparator (i.e., included omega-3s in both intervention and control groups) or no direct comparisons,[11,12,21] and two as they were post-hoc analyses of included trials with inappropriate outcome measures.[22,23]

The PRISMA flowchart of study selection is presented in Appendix 1.

Summary of Study Characteristics

Four SRs[6,24-26] - three with meta-analysis[6,24,26] - and two NRSs[27,28] were identified regarding the clinical effectiveness of n-3 fatty acid supplementation for the reduction of proteinuria in patients with nephrotic syndrome. No relevant cost-effectiveness evidence was identified. Detailed study characteristics are presented in Appendix 2.

Study Design

One SR was part of a Health Technology Assessment;[25] however, the economic evaluation component did not consider n-3s as an intervention. A total of four SRs[6,24-26] assessing the clinical effectiveness of n-3s for proteinuria due to nephrotic syndrome were considered for this

review. Two SRs included only RCTs.[24,25] One also included quasi-randomized studies[6] and another also included NRSs.[26] There was substantial overlap in the studies included in each SR. Five studies were common to at least two SRs.[22,29-32] Five studies were specific to a single SR.[9,33-36] Some discrepancies can be explained by search dates, study type, and indication. Study overlap is summarized in Table 2.

Table 2. Overlap Among Systematic Review Studies

Primary Clinical Study, Publication Year	Systematic Review Author, Publication Year			
	Chou, 2012[24]	Reid, 2011[6]	Miller, 2009[26]	Colquitt, 2007[25]
Bennett, 1989[29]	■	■	■	
Donadio, 1994[30]	■	■		
Pettersson, 1994[22]	■	■	■	
Chongviriyaphan, 1999[33]				■
Donadio, 1999[34]			■	
Donadio, 2001[35]		■		
Branten, 2002[36]			■	
Alexopoulos, 2004[31]	■	■	■	
North American Immunoglobulin A Nephropathy Study Hogg, 2006[9]		■		
Ferraro, 2009[32] Costanzi, 2006[a37]	■	■		

[a]Conference Abstract

The NRSs included a retrospective cohort study,[27] and a controlled before-and-after study.[28]

Country of Origin

The SRs were conducted by authors in Taiwan,[24] Spain,[26] and a collaboration between authors in Australia, the US, Italy, and Sweden.[6] Both NRSs were conducted in Japan.[27,28]

Patient Population

Three SRs included both adult and pediatric patients with IgAN,[6,24,26] and one included children with idiopathic steroid-resistant nephrotic syndrome.[25] All SRs included studies on patients with varying severity of disease, including severe proteinuria and risk of progression to ESRD. One SR[6] reported that information on disease severity was generally poorly reported. The majority of studies included in the SRs assessed patients in single or multiple clinical centres.

Both NRSs included patients with biopsy-proven IgAN; one included patients of any age,[27] while the other included only adults.[28] One NRS[28] reported that patients with varying prognoses based on glomerular findings were included, the majority in both groups having a relatively poor rating. The retrospective cohort study[27] reported that there was an equal distribution of histological findings across groups. Both NRSs assessed patients in hospital.[27,28]

Interventions

All SRs included studies that tested n-3 fatty acid supplementation[6,24-26] of various doses and

formulations. Two SRs reported that the dose of EPA and/or DHA ranged from 1.4 to 5.1 grams per day.[24,26] Another[6] disclosed that the doses ranged from approximately 3 to 12 grams of total n-3s, with EPA and/or DHA doses ranging from 1.4 grams to 6.7 grams per day. The single RCT[33] included in the final SR[25] used a dose of 4 grams total n-3 (230 mg of EPA + 1.12 grams of DHA). One NRS assessed EPA supplementation (900 to 1900 mg/day) alongside a renin-angiotensin-aldosterone system inhibitor (RAASI),[27] and the other assessed 1.8 grams of isolated EPA supplementation with or without an ARB, ACEi or corticosteroids.[28] It should be noted that DHA was not commercially available in Japan at the time the studies took place.

Duration of therapy varied significantly between primary studies included in the SRs. Ranges for duration of therapy were 6 to 38 months;[24] 6 months to 4 years;[6] 6 weeks to 48 months;[26] and 8 weeks for the SR with a single trial.[25] The NRSs provided therapy for one year.[27,28]

Comparators

The SRs all compared the n-3 groups to placebo or no treatment,[6,24-26] and one also made the comparison to alternative non-immunosuppressive treatments including ACEi, ARBs, beta blockers, calcium channel blockers and diuretics.[6] The NRSs compared the n-3 groups to RAASI plus an adenosine reuptake inhibitor,[27] and no treatment with or without ARB, ACEi or corticosteroids.[28]

Outcomes

All of the SRs assessed outcomes related to kidney function or progression of disease.[6,24-26] Two assessed lipid panels.[24,25] One also assessed all-cause mortality.[6] The NRSs assessed kidney function biomarkers and lipid profiles.[27,28]

Summary of Critical Appraisal

Specific strengths and limitations of the identified evidence are presented in Appendix 3.

Systematic Reviews

One SR[6] provided reference to a pre-published protocol and a priori objectives (including pre-planned subgroup analyses), including an explanation of deviations from the protocol. It was unclear whether all SR processes and analyses were pre-planned for the other three reviews. Duplicate study selection was conducted by two reviews.[6,24] One author was involved in one,[25] and the number of authors involved was unclear in one.[26] In cases where duplicate selection did not occur, there is an increased possibility that eligible studies may have been missed. Duplicate[6,24] or triplicate[26] abstraction was performed most cases. A single author extracted data for the other SR, but it was checked by a second reviewer.[25] All SRs performed a comprehensive database and grey literature search,[6,24,25] though one used only a single database.[26] Two studies did not make restrictions by language,[6,24] date,[6,24] or publication status[6,24] One SR restricted to English language publications and restricted database search dates due to umbrella searching.[25] In one case, search restrictions were unclear.[26] A list of included studies with study characteristics was provided in all cases. Two SRs[6,25] included a list of excluded studies. Formal quality assessments were conducted in most cases using the Cochrane Risk of Bias Tool[6,24] or the UK National Health Service Centre for Reviews and Dissemination criteria.[25] One study only conducted an informal assessment of quality making it difficult to assess the validity of findings.[26] All studies considered study quality in the formulation

of conclusions. All trials that conducted meta-analysis considered statistical heterogeneity and used appropriate methods of combining studies. However, potential risk of clinical and methodological heterogeneity should be noted. Some reviews included studies on patients with a variety of conditions associated with proteinuria, varying doses of n-3s, variable background and combination treatments, and different age groups. Limited subgroup analyses did not fully address the potential heterogeneity introduced by pooling these differences. One study did not conduct any pooling of results as only one eligible study was identified.[25] Two studies planned to use funnel plots to assess publication bias visually, but only one had a sufficient sample size to do so.[24] Two studies did not assess publication bias,[6,26] but one study actively sought out unpublished data[6] and all conducted grey literature searches, reducing the risk of publication bias. Funding sources of included primary studies were discussed in some cases.[6,25] Conflict of interest of the review authors was disclosed in some cases[6,25,26] but not all.[24]

Primary Clinical Studies

Reporting

All primary studies stated clear hypotheses or objectives.[27,28] All studies discussed main outcomes in the introduction or methods section. All studies described patient characteristics clearly. The two NRSs stated the intervention clearly but lacked detail in terms of brand, source, and form of EPA.[27,28] One also failed to explain the specifics of the comparator treatment (RAASI) in terms of the exact type of drug and doses taken.[27] Distributions of potential confounders were clearly described by one study.[27] The other described some, but not all, relevant confounders.[28] All studies described main study findings clearly. Estimates of random variability were consistently reported by two studies.[27,28] In general, adverse event reporting was poor for all three studies. The retrospective NRS had no losses to follow-up as a result of the study design; however all patients without specific parameters available at all relevant time points were not included in analysis. The other NRS did not describe characteristics of patients lost to follow-up but did provide quantity.[28] All studies reported actual probability values consistently.

External Validity

Patients were representative of the clinical populations from which they were recruited. The patients in the NRSs are likely representative of patients with IgAN in hospitals in Japan; however, due to the absence of random sampling it is unclear whether they are representative of the entire source population. Further, the restriction to patients with comprehensive clinical data available at baseline and one year may limit findings to patients who are under higher surveillance, including those with health seeking behaviors, or those with more severe disease.[27] The staff, places and facilities in all studies are likely representative of hospitals in Japan,[27,28] respectively. One caveat is that much of the therapy likely occurred at home, limiting the ability to monitor external sources of n-3 intake. Patients receiving both treatment and placebo may have been compelled to increase their dose of fish-oil with commercially available supplements, or may have already been consuming them prior to the study. However, without knowledge of additional amounts consumed, or biochemical data to monitor unexpected increases in n-3 index in control groups, the potential influence of this factor on study outcomes is unclear. One study failed to provide detailed information on care providers; so the full context of care is unclear.[28] In all cases it was unclear if the distribution of confounders was the same in the study sample and the source population as these data were not presented.

Internal Validity – Bias

Neither NRS blinded patients or outcome assessors.[27,28] In all cases, a priori nature of analyses was unclear; therefore, data dredging cannot be ruled out. Both NRSs had identical length of follow-up for the treatment and control groups.[27,28] One NRS controlled for this by only recruiting patients with clinical measurements at specific time points so while no adjustment for length of follow-up was required, there are possible differences between these patients and patients with different length of follow-up.[27] One study[28] reported that they assessed compliance at all study visits, but did not report the level of compliance suggesting potential selective reporting bias. The main outcome measures were accurate, valid and reliable for all studies, but not all studies reported hard endpoints such as ESRD or all-cause mortality.

Internal Validity – Confounding

In each study, all patients were recruited from the same source populations. It was unclear whether they were recruited over the same period of time, particularly in the case of the NRS as the recruitment time frames were wide.[27,28] The NRSs did not sufficiently control for potential confounders. One study performed multivariate regression for the main outcome, but secondary outcomes were unadjusted.[27] The other NRS identified parameters associated with the main clinical outcomes but did not adjust for them in analysis. Neither NRS accounted for losses to follow-up in their analysis; however the retrospective cohort study[27] did not have any true losses to follow-up to account for. Neither NRS reported a sample size calculation, but one study commented that the sample size was very small.[27] For one study,[28] conclusions presented in the discussion did not match data presented in the results section. Specifically, they claim that urinary protein levels declined with EPA supplementation despite no significant difference between groups suggested by the data.

Summary of Findings

A detailed summary of findings is presented in Appendix 4.

What is the clinical effectiveness of omega-3 fatty acid supplementation for reduction of proteinuria in patients with nephrotic syndrome?

Kidney Function and Proteinuria

Overall, there is some evidence that n-3 treatment alone or as part of combination therapy in adults and children with IgAN may improve surrogate endpoints associated with better kidney function versus placebo or no treatment, but these findings are inconsistent. There is no evidence of improved kidney function outcomes in children with idiopathic steroid-resistant nephropathy. Further, there is no evidence that n-3s improve the incidence of clinical endpoints such as ESRD or all-cause mortality, or that higher doses of n-3s lead to improved outcomes.

A) Adults or Mixed Populations with Immunoglobulin A Nephropathy

Omega 3 versus Placebo or No Treatment

One SR[24] reported no significant difference in kidney function between patients who received n-3 supplementation versus placebo as represented by glomerular filtration rate (GFR) overall or when stratified by high or low dose intervention. This same SR[24] reported lower urinary protein

excretion in the n-3 group versus placebo overall, but not when stratified by high or low dose in either subgroup. Another SR[6] reported no significant differences in kidney function measures between n-3 supplementation versus placebo, including substantial decreases in serum creatinine (SCr), overall SCr and change in SCr over 2 years; creatinine clearance (CrCl), haematuria, proteinuria, or change in proteinuria, or hard endpoints including incidence of end-stage renal disease (ESRD) or all-cause mortality. However, there was a reduced risk of a greater than 50% increase in SCr in the n-3 group versus placebo.[6] Another SR[26] reported no difference in effect size for n-3 supplementation versus placebo in terms of urine protein excretion or GFR.

High versus Low Dose Omega-3

Based on the results of a single study, one SR[6] reported that there was no difference in the risk of ESRD between high-dose and low-dose n-3 supplementation groups. Further, another SR[24] that reported subgroup analyses of studies providing high (>3 grams) or low dose n-3s concluded that neither dose level resulted in improved GFR or proteinuria.[24]

Omega 3 versus ACEi plus or minus beta blockers, calcium channel blockers or diuretics

Based on the results of one study, compared to symptomatic treatment with ACEi plus or minus other add-on therapies, n-3 therapy alone resulted in reduced SCr but had no significant effect on rate of ESRD, CrCl, proteinuria, or incidence of a greater than 50% increase or decrease in SCr.[6]

Omega 3 + ACEi and/or ARB versus ACEi and/or ARB alone

Based on the results of a single study, one SR[6] reported that there was no difference in CrCl or proteinuria between patients treated with n-3 plus ACEi and/or ARB versus ACEi and/or ARB alone. One NRS[28] reported that there were no significant differences in change from baseline markers of kidney function including urinary protein, creatinine, and total protein however, CrCl rate was significantly improved following treatment with EPA versus placebo.

Omega-3 + ACEi and/or ARB versus ACEi or ARB plus DILAZEP

One NRS[27] conducted multivariate logistic regression analysis on the outcome of reaching a 50% decrease in urinary protein levels at 12 months. Controlling for multiple potential determinants, n-3 therapy was the only factor significantly associated with increased odds of the outcome.

B) *Pediatric Patients with Idiopathic Steroid Resistant Nephrotic Syndrome*

Omega 3 versus Placebo or No Treatment

Based on a single small RCT (n = 5),[33] one SR[25] reported that there was no statistically significant difference in kidney function outcomes including urine protein, CrCl, and SCr after 8 weeks of treatment with n-3 supplementation versus placebo.

Lipid Profile

The evidence does not suggest that n-3 supplementation with or without combination therapies in adults and children with IgAN or children with idiopathic steroid-resistant nephrotic syndrome leads to improved lipid profiles. One small NRS (n = 38) suggests potential for improved blood pressure; however this observation was not made against a comparator group.[27]

A) Adults or Mixed Population

Omega 3 versus Placebo or No Treatment

One SR[24] reported no significant differences in triglyceride or cholesterol levels between n-3 supplementation and placebo groups.

Omega 3 + ACEi and/or ARB versus ACEi and/or ARB alone

One NRS[28] reported no differences in change from baseline markers of cardiovascular health including mean blood pressure, total cholesterol, high-density lipoprotein (HDL), and triglyceride.

Omega 3 + ACEi and/or ARB versus ACEi and/or ARB plus DILAZEP

One NRS[27] reported that mean blood pressure was significantly reduced in both EPA + ACEi or ARB and ACEi or ARB plus DILAZEP groups. Between-group comparisons were not reported.

B) *Pediatric Patients with Idiopathic Steroid Resistant Nephrotic Syndrome*

Omega 3 versus Placebo or No Treatment

One SR[25] reported that based on results from a single small RCT,[33] there was no statistically significant difference in lipid profile parameters including triglyceride, total cholesterol, HDL and low-density lipoprotein between n-3 supplementation and placebo groups.

Adverse Events

Based on limited adverse event reporting, n-3 supplementation with or without combination therapy is unlikely to cause harm in adults and children with IgAN or children with idiopathic steroid-resistant nephrotic syndrome, despite the observation of minor tolerability issues such as fishy aftertaste and gastrointestinal symptoms.

A) Adults or Mixed Population with Immunoglobulin A Nephropathy

Omega 3 versus Placebo or No Treatment

One SR reported that that most patients treated with n-3 supplementation demonstrated good compliance with no adverse effects but no specific data was presented.[24] Another SR[6] reported minor tolerability concerns due to fishy aftertaste in the n-3 supplementation group, and occasional belching in the n-3 and placebo group.

Omega 3 + ACEi and/or ARB versus ACEi and/or ARB alone

One NRS[28] reported that no patients discontinued EPA treatment due to adverse events.

B) *Pediatric Patients with Idiopathic Steroid Resistant Nephrotic Syndrome*

Omega 3 versus Placebo or No Treatment

One SR[25] based on the results of a single study reported that no adverse effects were noted in the n-3 supplementation or placebo groups.

What is the cost-effectiveness of omega-3 fatty acid supplementation for reduction of proteinuria in patients with nephrotic syndrome?

No relevant evidence was identified regarding the cost-effectiveness of n-3 supplementation for the reduction of proteinuria in patients with nephrotic syndrome; therefore, no summary can be provided.

Limitations

Comparability of Omega-3 Supplements

The quality and potency of n-3 and fish oil supplements may vary substantially. Factors such as variation from the claimed amount of total n-3 fatty acids, natural versus purified fish oil, relative concentrations of EPA and DHA, concentration of contaminants such as PCBs and mercury, delivery method (chewable tablet, liquid, softgel, enteric coating), effect of molecular structure (e.g., triacylglycerols, free acids, ethyl esters, phospholipids) on bioavailability, background nutrients (e.g., other fat soluble vitamins) or meal composition (e.g., high fat versus low fat), and level of oxidation (peroxide levels) have been shown to vary across brands and formulations, independent of dose.[38-40] Therefore, the generalizability of findings of trials that use a specific formulation of n-3 supplements may be limited, even in cases of equivalent dosing.

Compliance

Level of adherence may influence biochemical changes in n-3 status and thus the potential for clinical benefit (assuming a threshold and dose-response relationship). Some studies failed to monitor compliance either through interviews, pill counting or biochemical measurements. Studies reporting low levels of adherence that did not adjust for this factor may influence the observation of null effect. This is of concern given the observations of complaints of fishy taste, burping and other gastrointestinal concerns noted by some study authors,[6,26] which may not lead to discontinuation in the context of a clinical trial but may cause aversion in a real-life setting.

Dose per Body Weight Effect

It has been reported inconsistently that the dose per body weight of n-3 supplements, and thus of DHA and EPA, has an influence on circulating concentrations of n-3s and consequently on the relationship between n-3 treatment and clinical outcomes.[23,41] If a study does not correct for variability in dose per body weight resulting from providing a uniform dose, or dose by patient body weight, there is a risk that some patients may not achieve sufficient blood concentration of long chain n-3 PUFAs to observe a clinical benefit. Further, obesity has been proposed as a

determinant of proteinuria[42] so individuals with higher body weight, who are receiving relatively low doses of n-3s per body weight, may have a greater tendency towards no clinical benefit.

Severity of Disease State and Progression

Patients included in the clinical studies reviewed in this report had varying degrees of disease. For instance, the patients in the trial conducted by the Mayo clinic (included in several SRs) had greater proteinuria and lower CrCl at baseline.[30] It has been proposed that patients recruited during a period of high disease activity may show significant reductions in clinical outcomes as a result of remission, rather than true clinical benefit. These observations may skew observations towards a benefit.[26]

Relevance of Endpoints and Follow-Up Duration

Relevant clinical endpoints (e.g., ESRD, all-cause mortality, cardiovascular mortality) have not been assessed by all clinical studies investigating the clinical effectiveness of n-3 supplements in nephrotic syndrome patients. In addition, due to the slow progressive nature of mild to moderate nephrotic syndrome, it has been observed and proposed that the typical follow-up time reported by the studies included in this review (<1 year to 5 years) may be insufficient to observe changes in hard endpoints.[6,9,24] Many of the outcomes assessed are surrogate outcomes that may provide valuable information about estimated kidney function or cardiovascular risk, but do not necessarily translate into clinical outcomes. Further, studies that only reported on unadjusted SCr versus CrCl or GFR, or urinary protein excretion versus urinary protein to creatinine ratio as outcomes may not provide the most accurate estimate of kidney function. Creatinine clearance measures take into account determinants of kidney function (e.g., age and body weight) and may be a better approximation of this outcome. Also, urinary protein to creatinine ratio is not influenced by void volume and variance in protein excretion to the same extent as urinary protein excretion.[43]

Incomplete Adverse Event Reporting

The risks of consuming high-dose n-3 supplements are low, but some patients in the studies included in this review were receiving other therapies such as ACEi, ARBs and corticosteroids. Relevant adverse effects such as hyperkalemia, increased blood urea nitrogen, hypotension, Cushing's, psychosis, general toxicity, gastrointestinal upset, and hyperglycemia were not discussed. While it is unlikely that any of these outcomes would be attributed to n-3 supplementation, they are important to consider in the context of combination therapy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence contained in the four SRs and two NRSs reviewed in this report suggest that there may be a small improvement in surrogate biomarkers related to kidney function resulting from n-3 supplementation alone or as combination therapy in patients with nephrotic syndrome. Yet, findings have been inconsistent, with many studies showing no benefit for some outcomes of interest and no evidence of improvement in lipid profiles or clinical endpoints such as ESRD, and all-cause or cardiovascular mortality. There is also no evidence of harms, with only minor complaints of fishy aftertaste and minor gastrointestinal upset reported. The quality of studies making up this evidence-base is poor due to small sample sizes, insufficient follow-up time, unclear compliance, and variable dosing.

No relevant evidence was identified regarding the cost-effectiveness of n-3 supplementation for the reduction of proteinuria in patients with nephrotic syndrome. Thus, the potential resource implications of this treatment, with or without other therapeutic agents used in nephrotic syndrome, are unclear.

Evidence-based guidelines released by KDIGO in 2012[13] that consider the majority of the evidence presented in this review, suggest that therapeutic doses of fish oil (3.3 grams or higher per day) can be provided to patients who have stable disease but persistent proteinuria, following 3 to 6 months of treatment with an ACEi and/or ARB. This recommendation is made considering inconsistent study results suggesting a potential benefit of n-3s, and in light of the low risk of adverse effects.

Further research is needed to elucidate subgroup effects such as underlying disease severity, n-3 dosing, and background therapy. Longer follow-up duration, inclusion of relevant clinical endpoints, and increased sample sizes may be needed to clarify persistent uncertainty.

In conclusion, there is currently insufficient evidence to suggest that n-3 supplementation is clinically effective in patients with nephrotic syndrome. The benefit of this intervention as a standalone or adjuvant therapy is unclear.

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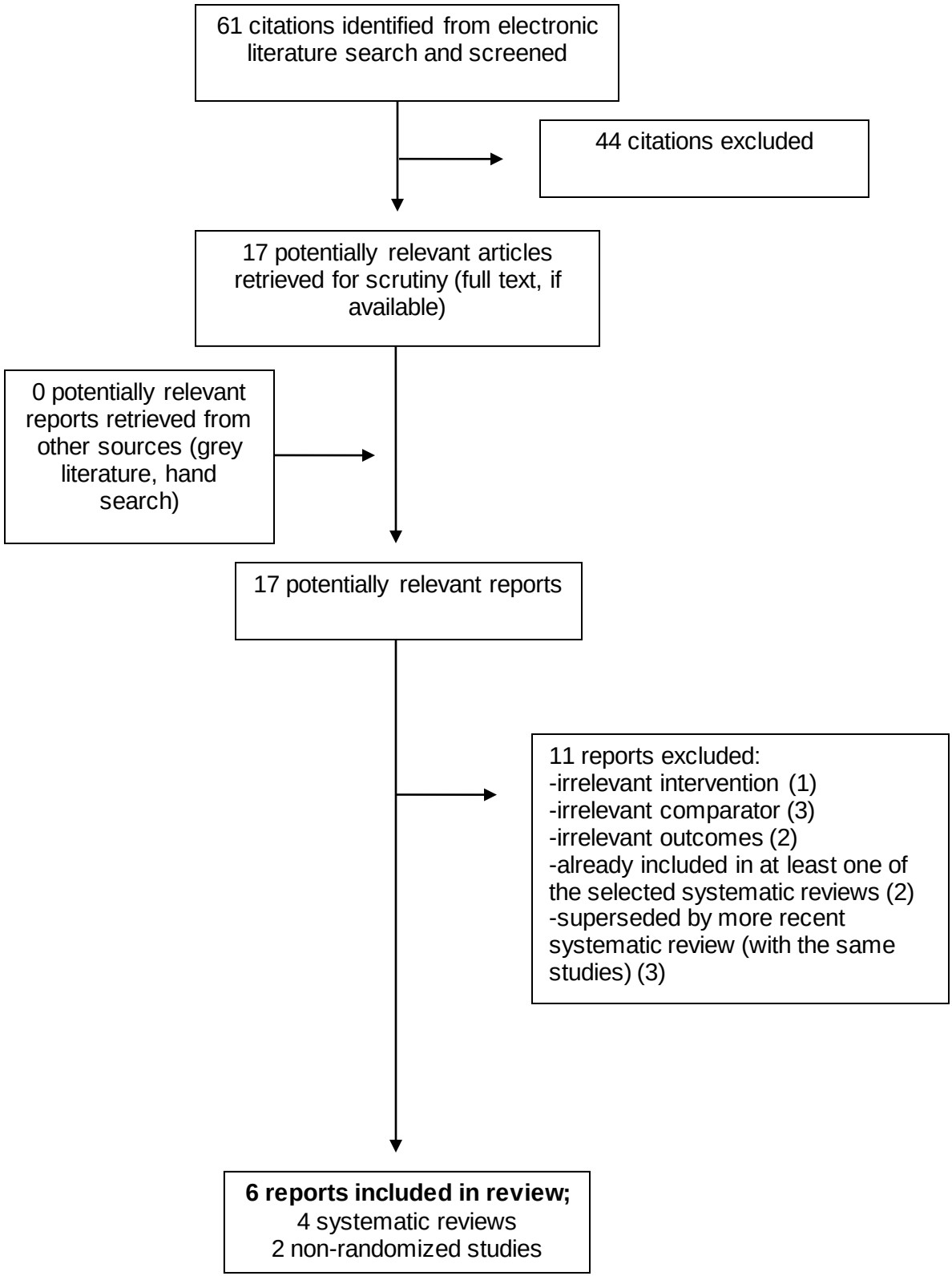
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics, Sample size	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up	Duration of Therapy
Chou, 2012, Taiwan[24]	PubMed, MEDLINE and EMBASE from database inception to August 2011	Randomized controlled trials, n = 5	Patients (of any age) with IgAN, n = 233	n-3 fatty acid treatments	Placebo; No treatment	Kidney function (GFR, proteinuria [urinary protein excretion]),	6 to 38 months
Reid, 2011, Australia, US, Italy, and Sweden[6]	Ovid MEDLINE, EMBASE, CENTRAL, Cochrane Renal Group specialized registry, hand searching of reference lists, contact with experts from database inception until July 2010	Randomized controlled trials, n = 56 studies total on non-immunosuppressive therapy; n = 7 studies for fish oils	Adults and children with biopsy-proven IgAN[a]	Non-immunosuppressive treatment including fish oils	Placebo; No treatment; Alternate non-immunosuppressive treatment[b]	Progression or improvement in kidney disease[c]; All-cause mortality; Adverse events;	6 months to 4 years
Miller, 2009, US, Spain[26]	MEDLINE 1966 to 2008	Randomized (n = 4) and non-randomized (n = 1) clinical studies[d]	Patients of any age with IgAN[e] (unclear method of diagnosis)	n-3 fatty acid supplementation (total dose of EPA and/or DHA ranged from 1.4 to 5.1 grams per day	No treatment, placebo (corn or olive oil)	Kidney function (urine protein excretion; decline in GFR)	6 weeks to 48 months (median 9 months)
Colquitt, 2007, UK[25]	Multiple databases[f] (database inception until February	Systematic reviews of randomized controlled trials and randomized controlled trials (n = 1	Children (n = 5) with idiopathic steroid-resistant nephrotic syndrome (focal segmental	Uni-E® tuna fish oil for 8 weeksg	Placebo (olive oil) for 8 weeks after a six-week washout	Kidney function (urine protein, CrCl, SCr);	8 weeks

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses							
First Author, Publication Year, Country	Search Databases and Dates	Types and numbers of primary studies included	Population Characteristics, Sample size	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up	Duration of Therapy
	2006) Reference lists searched and experts consulted for additional evidence	study regarding fish oil)	glomerulosclerosis, membranoproliferative glomerulonephritis [IgG deposit]) all either malnourished or stunted			Lipid profile (triglycerides, total cholesterol, HDL, LDL)	

CrCl = creatinine clearance; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GFR = glomerular filtration rate; HDL = high-density lipoprotein; IgA = immunoglobulin A; IgAN = immunoglobulin A nephropathy; LDL = low-density lipoprotein; n-3 = omega-3; SCr = serum creatinine; UK = United Kingdom; US = The United States of America

[a]Presence of IgA mesangial deposits evident as mesangial expansion by standard histopathology examination and IgA staining by immunofluorescence[6]

[b]Including antihypertensives, antiplatelet agents/anticoagulants, tonsillectomy, statins, phenytoin, herbal medicines, urokinase, vitamin E, sodium cromoglycate

[c]ESRD requiring renal replacement therapy; doubling of SCr concentration; >50% increase in SCr; >50% decrease in CrCl; remission of haematuria; remission of proteinuria; absolute change in SCr; absolute change in CrCl; changes in daily proteinuria;

[d]SR included additional studies focused on patients with diabetes or lupus nephritis that were not considered for this review

[e]Excluding patients who had undergone organ transplant or with end-stage kidney failure

[f]Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews and Effectiveness, Cochrane Library, Health Technology Assessment Database, NHS Economic Evaluation Database, EconLit, Medline, PubMed (6 months), EMBASE, Science Citation Index, BIOSIS, Inside Information Plus, National Library of Medicine, Gateway Database, Conference Proceedings Index, PapersFirst, National Research Register, Current Controlled Trials and Clinical Trials.gov

[g]SR assessed alternative therapies such as Cyclophosphamide, Ciclosporin, Azathioprine, Methylprednisolone, Dexamethasone, Enalapril

Table A2: Characteristics of Included Non-Randomized Studies					
First Author, Publication Year, Country	**Study Design**	**Patient Characteristics, Sample Size**	**Intervention(s), Sample Size**	**Comparator(s), Sample Size**	**Clinical Outcomes and Length of Follow-Up**
Moriyama, 2012, Japan[27]	Retrospective cohort study	Patients (of any age) with primary IgAN as confirmed by renal biopsy[a]	EPA[b] supplementation (900 to 1800 mg/day) with renin-angiotensin-aldosterone system inhibitors, n = 18	renin-angiotensin-aldosterone system inhibitors plus dilazep dihydrochloride (adenosine reuptake inhibitor) (300 mg/day), n = 20	Proteinuria and lipid profile at one year
Uchiyama-Tanaka, 2009, Japan[28]	Controlled before-and-after study	Adult patients with biopsy proven IgAN[c]	EPA (with or without ARB, ACEi, or corticosteroids), n = 18 (2 drop outs)	No treatment (with or without ARB, ACEi, or corticosteroids), n = 5 (7 drop outs)	Kidney function and lipid profile at one year: Including SCr, urinary protein excretion, total cholesterol, HDL, serum total protein

ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; EPA = eicosapentaenoic acid; HDL = high density lipoprotein cholesterol; IgAN = immunoglobulin A nephropathy; UK = United Kingdom; SCr = serum creatinine

[a]Including idiopathic membranous nephropathy, focal segmental glomerulosclerosis, mesangiocapillary glomerulonephritis, IgA nephropathy and unclassified chronic glomerulonephritis; excluding patients with diabetes mellitus or patients being treated with corticosteroids, immunosuppressive agents or warfarin

[b]DHA is not available commercially in Japan

[c]Excluding patients with systemic diseases including diabetes, collagen disorders, abnormal hyper-gammaglobulinemia, and chronic liver disease

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[14]

Strengths	Limitations
Chou[24]	
• Duplicate study selection and extraction conducted • Comprehensive search of multiple databases and grey literature • No restrictions by language or date • Unpublished research considered in analysis • List of included studies and study characteristics provided • Quality was assessed using the Cochrane Risk of Bias tool • Quality considered in formulation of conclusions • Statistical heterogeneity between trials was assessed using the I^2 statistic • Potential for publication bias assessed visually using a funnel plot	• Availability of published protocol unclear • A priori objectives not reported • No list of excluded studies provided • Conflict of interest and funding sources for primary studies unclear • Conflict of interest and funding sources for review authors unclear
Reid[6]	
• Reference to previously published survey protocol and explanation of deviations from protocol • Subgroup analyses planned a priori • Duplicate study selection and extraction conducted • List of included and excluded studies as well as study characteristics provided • Comprehensive search of multiple databases and grey literature • No restrictions by date, language or study type • Cochrane risk of bias tool used in duplicate to assess study quality • Quality considered in formulation of conclusions • Statistical heterogeneity between trials assessed using the I^2 statistic • Appropriate method of combining studies • Likelihood of publication bias minimized by actively seeking unpublished data • Funding sources for included studies discussed • Authors declared no conflict of interest	• No formal assessment of publication bias
Miller[26]	
• Triplicate abstraction • Grey literature search (Cochrane database, reference list and review articles) • List of included studies provided along with study characteristics • Quality considered in formulation of conclusions • Appropriate method of combining studies • Statistical heterogeneity assessed for pooled analyses • Authors reported no conflict of interest	• Availability of a published protocol unclear • A priori objectives not reported • Number of people involved in study selection unclear • Single database searched • Exclusions based on publication type or language unclear • List of excluded studies not provided • No formal quality assessment • Publication bias not assessed

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[14]

Strengths	Limitations
	• Funding sources for included studies unclear
Colquitt[25]	
• Comprehensive search of multiple databases and grey literature; some elements of umbrella searching • Unpublished data considered • List of included studies and study characteristics provided • List of excluded studies provided • Quality assessment conducted using National Health Service Centre for Reviews and Dissemination criteria by a single reviewer (checked by a second) • The quantity of trials regarding fish oils identified (n = 1) prevented pooling of results • Publication bias assessment (visual funnel plot) was planned, but not conducted for fish oils • Conflict of interest of primary study authors reported • Funding sources disclosed	• Availability of a published protocol unclear • A priori objectives not reported • Only one author involved in study selection and abstraction (noted that a second author checked results) • Variable date restrictions imposed on database search • Search restricted to English language publications • Author affiliations unclear

Table A4: Strengths and Limitations of Non-Randomized Studies using Downs and Black[15]

Strengths	Limitations
Moriyama, 2012, Japan[27]	
Reporting • Study objectives clearly stated • Main outcomes clearly described in Introduction and Methods sections • Characteristics of included patients clearly described • Distributions of potential confounders clearly described • Main findings clearly described • Study provides estimates of random variability for the main outcomes *External Validity* • Staff, places and facilities representative of the treatment the majority of patients would receive at a hospital in Japan from 1990 to 2009 *Internal Validity – Bias* • Appropriate statistical tests used to assess main outcomes • Main outcome measures accurate and reliable *Internal Validity – Confounding* • All cohort patients selected from the same hospital	*Reporting* • Reporting on interventions of interest lacked detail (i.e., unclear what the brand/source of EPA was, or what the specific renin-angiotensin-aldosterone system inhibitor treatment was in all cases) • Adverse events not reported • Retrospective analysis; therefore, no losses to follow-up, however, only patients with before and after parameters for all outcomes of interest were included • Actual probability values only provided if <0.5 otherwise reported as not significant *External Validity* • Subjects only representative of patients diagnosed with primary IgAN with full outcome data available at baseline and 1 year • No differences between source population and selected patients were assessed *Internal Validity – Bias* • No blinding of study subjects or outcome assessors • No protocol referenced and a priori nature of analyses unclear • Only patients with outcome measures at baseline and one year after were included; thus, those with alternative follow-up were

Table A4: Strengths and Limitations of Non-Randomized Studies using Downs and Black[15]	
Strengths	**Limitations**
	ineligible and no correction was made for different lengths of follow-up • Compliance with interventions unclear *Internal Validity – Confounding* • Unclear whether dates of patient enrolment were equally distributed over the 19 year recruitment time period • No randomization of study subjects • Effect of potential confounders analyzed using multivariate logistic regression but only for the main outcome, unclear whether adjustment for confounders may have affected the results for secondary outcomes • Losses to follow-up not taken into account *Power* • No sample size or power calculation disclosed; however, authors state "First, the study design is a retrospective observational study and the sample size was very small."[27] *Other* • A component of the comparator – dilazep dihydrochloride – is not approved for use in Canada
Uchiyama-Tanaka, 2009, Japan[28]	
Study Quality • Study objectives clearly described • Main outcomes clearly described in Methods section • Interventions of interest clearly described • Main findings clearly described • Estimates of random variability presented alongside main outcomes • Actual probability values reported for main outcomes *External Validity* • Facilities where treatment took place representative of in-hospital treatment of IgAN *Internal Validity – Bias* • Length of follow-up the same for treatment and control groups • Statistical tests appropriate for main outcomes *Internal Validity – Confounding* • All patients for comparison groups selected from the same hospital population	*Study Quality* • Limited patient characteristics presented • Specific characteristics of the intervention unclear (i.e., source, brand) • Distribution of some confounders described, others unclear • Very limited detail in adverse event reporting • Characteristics of patients lost to follow-up not described (2 in treatment, 7 in control group – mentioned travel time as a factor and no withdrawals due to adverse events)[28] • Conclusions presented in Discussion do not match data presented in Results section (i.e., claim urine protein excretion improved with EPA supplementation despite no significant difference between groups) *External Validity* • Subjects included patients being treated for IgAN with various prognoses within hospital; whether this is representative of the source population is unclear as there was no random sampling • Unclear whether proportion of patients who agreed is representative of the source population • Due to limited disclosure of information on care

Table A4: Strengths and Limitations of Non-Randomized Studies using Downs and Black[15]	
Strengths	**Limitations**
	providers, whether context of care is representative is unclear *Internal Validity – Bias* • No blinding of study subjects or outcome assessors • A priori nature of analyses unclear • While compliance was assessed, level of compliance was not reported *Internal Validity – Confounding* • Patients in the intervention and control groups recruited over different time periods (patients recruited first) • No randomization of study subjects • Inadequate adjustment for confounding in the analyses (no intention to treat, regression analysis to assess potential determinants of outcomes not conducted) • Parameters related to the clinical outcomes of doubling of baseline SCr and ESRD were identified but not adjusted for in analysis • Losses to follow-up not taken into account *Power* • Sample size calculation and/or level of power not reported

EPA = eicosapentaenoic acid; ESRD = end stage renal disease; IgAN = immunoglobulin A nephropathy; SCr = serum creatinine

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Outcome Measure, Number of studies	Intervention (Fish oil/n-3 supplementation)	Comparator (specified)	Pooled estimate (95% CI)[a]	Author's Conclusions
Chou[24]				
Kidney Function (Standardized Mean Difference, 95% CI)				
	n-3 supplementation	**Placebo or no treatment**		
Kidney function (GFR)[b] MD (95% CI), n = 5	NR	NR	MD = 0.13 (-0.16 to 0.42)	No significant difference in kidney function observed between treatment and control overall or when stratified by high or low dose intervention
Subgroup Analysis High dose (>3 g/day), n = 2	NR	NR	MD = -0.03 (-0.43 to 0.36)	
Low dose (≤3 g/day), n = 3	NR	NR	MD = 0.32 (-0.09 to 0.73)	
Urinary protein excretion, n = 6	NR	NR	**MD = -0.44 (-0.70 to -0.17)**	Urinary protein excretion was significantly lower in the treatment group compared to placebo
Subgroup Analysis High dose (>3 g/day), n = 2	NR	NR	MD = -0.43 (-0.89 to 0.04)	
Low dose (≤3 g/day), n = 4	NR	NR	MD = -0.38 (-0.82 to 0.06)	
Lipid Profile[c] (Described Narratively)				
Lipid Profile	NR	NR	NR	No significant differences in triglycerides or cholesterol levels between groups
Adverse Effects (Described Narratively)				
Adverse Effects	NR	NR	NR	"Most patients treated with n-3 fatty acids demonstrated good compliance with no adverse effects"[24]
Reid[9]				
Fish Oil versus Placebo or No Treatment				
Kidney Function and All-Cause Mortality (RR or MD, 95% CI)				
	n-3 supplementation	**Placebo or no treatment**		
ESRD, n = 2	6/72	6/71	RR = 1.01 (0.34 to 2.97)	No significant differences in ESRD, >50% decrease in SCr, all-cause mortality, SCr and change in SCr over 2 years, or CrCl, despite a reduced risk of >50% increase in SCr
>50% increase in SCr, n = 1	3/55	14/51	**RR = 0.20 (0.06 to 0.65)**	
>50% decrease in SCr, n = 1	8/31	4/29	RR = 1.87 (0.63 to 5.55)	
All cause mortality, n = 1	1/55	1/51	RR = 0.93 (0.06 to 4.44)	
SCr, n =1	Mean (SD) = 139 (39)	121(40)	MD = 18.0 (-9.41 to 45.41)	
Change in SCr over 2 years, n = 2	NR	NR	MD = 13.25 (-74.88 to 101.38)	
CrCl, n = 2	NR	NR	MD = -15.57 (-34.94 to 3.79)	
Proteinuria, n = 1	Mean (SD) = 1.7 (0.9)	1.8 (1.2)	MD = -0.10 (-0.83 to	No significant

Table A5: Summary of Findings of Included Systematic Reviews and Meta-Analyses				
Outcome Measure, Number of studies	**Intervention (Fish oil/n-3 supplementation)**	**Comparator** (specified)	**Pooled estimate (95% CI)[a]**	**Author's Conclusions**
			0.63)	changes observed in proteinuria, or haematuria
Change in proteinuria, n = 2	NR	NR	MD = -0.20 (-0.96 to 0.57)	
Change in haematuria, n = 2	NR	NR	MD = 2.58 (-3.30 to 8.46)	
Adverse Effects				
Adverse Effects	• Fishy aftertaste (n = NR) • No discontinuation due to adverse effects • Occasional belching (n not specified)	• Occasional belching (n not specified)	N/A	Minor tolerability and gastrointestinal side-effects observed; unclear effect on compliance
Fish Oil versus Symptomatic Treatment[p] (RR or MD, 95% CI)				
Kidney Function (RR or MD, 95% CI)				
	n-3 supplementation	**Symptomatic treatment[b]**		
ESRD, n =1	1/14	6/14	RR = 0.17 (0.02 to 1.21)	Compared to symptomatic treatment, fish oil resulted in reduced SCr but had no significant effect on ESRD, greater than 50% increase or decrease in SCr, CrCl, or proteinuria
>50% increase in SCr, n =1	1/14	6/14	RR = 0.17 (0.02 to 1.21)	
>50% decrease in SCr, n = 1	1/14	7/14	RR = 0.14 (0.02 to 1.01)	
SCr, n =1	Mean (SD) = 203.32 (194.48)	521.56 (344.76)	**MD = -318.24 (-525.58 to -110.90)**	
CrCl, n =1	Mean (SD) = 41(13)	34(30)	MD = 7.00 (-1013, 24.13)	
Proteinuria, n =1	Mean (SD) = 0.8 (0.4)	0.9 (0.6)	MD = -0.10 (-0.48 to 0.28)	
High Dose Fish Oil versus Low Dose Fish Oil (RR, 95% CI)				
	High dose n-3 supplementation	**Low dose n-3 supplementation**		
ESRD, n =1	8/36	10/37	RR = 0.82 (0.37 to 1.85)	No significant difference between high dose and low dose fish oil for ESRD
Fish Oil + ACEi + ARB versus ACEi + ARB (MD, 95% CI)				
	n-3 supplementation + ACEi and/or ARB	**ACEi and/or ARB**		
CrCl, n =1	Mean (SD) = 93.9 (35.4)	67.7 (35)	**MD = 26.20 (1.01 to 51.39)**	Fish oil as add on therapy to ACEi and ARB leads to an increase in CrCl and reduction in proteinuria
Proteinuria, n =1	Mean (SD) = 0.367 (0.52)	1.35 (1.304)	**MD = -0.99 (-1.70 to -0.28)**	
Miller[26]				
Kidney Function (Effect Size, 95% CI)				
	n-3 supplementation	**Placebo or no treatment**		
Difference in urine protein excretion, n =5	NR	NR	Cohen's D (95% CI) = -0.05 (-0.31 to 0.21)	No differences observed in effect size for difference in

Table A5: Summary of Findings of Included Systematic Reviews and Meta-Analyses				
Outcome Measure, Number of studies	**Intervention (Fish oil/n-3 supplementation)**	**Comparator** (specified)	**Pooled estimate (95% CI)[a]**	**Author's Conclusions**
Difference in GFR, n =5	NR	NR	Cohen's D (95% CI) = 0.16 (-0.10 to 0.42)	urine protein excretion or GFR between n-3 group or placebo
Colquitt[25e]				
	n-3 supplementation	**placebo**	**P-value[f]**	
Kidney Function Outcomes (Baseline versus Endline, mean [SD])				
Urine protein (g/day), mean (SD)	Baseline = 2.68 (3.7); 8 weeks = 1.12 (1.6)	Baseline = 2.71 (3.12); 8 weeks = 3.26 (4.83)	NS	No statistically significant differences in kidney function outcomes between fish oil or placebo groups after 8 weeks of treatment
CrCl (ml/minute/1.73m^2)	Baseline = 76.9 (45.8); 8 weeks = 71.22 (41.1)	Baseline = 77.34 (50.6); 8 weeks = 77.21 (46.68)	NS	
SCr (mg/dL)	Baseline = 1.4 (0.9); 8 weeks = 1.7 (1.5)	Baseline = 1.6 (1.5); 8 weeks = 1.6 (1.5)	NS	
Lipid Profile (Baseline versus Endline, mean [SD])				
Triglycerides (mg/dL)	Baseline = 242 (155.4); 8 weeks = 156 (77)	Baseline = 250 (76.1); 8 weeks = 192 (62.3)	NS	No statistically significant differences in lipid profile between fish oil and placebo groups
Cholesterol (mg/dL)	Baseline = 552 (289.6); 8 weeks = 616 (412.5)	Baseline = 473 (178.1); 8 weeks = 541 (177.4)	NS	
HDL (mg/dL)	Baseline = 30.5 (10.3); 8 weeks = 38.7 (10.3)	Baseline = 31.4 (8.7); 8 weeks = 34.2 (7.5)	NS	
LDL (mg/dL)	Baseline = 473.5 (266.9); 8 weeks = 546.3 (404.9)	Baseline = 392 (174.8); 8 weeks = 468.2 (171.2)	NS	
Adverse effects (n)				
Adverse effects	0	0	NR	No adverse effects reported in treatment or placebo groups

ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blocker; CI = confidence interval; CrCl = creatinine clearance; ESRD = end stage renal disease; g = grams; GFR = glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; n-3 = omega-3; N/A = not applicable; NR = not reported; NS = not significant; RR = relative risk; SCr = serum creatinine; SD = standard deviation

[a]Bolded outcomes indicate statistically significant results

[b]Either CCr, eGFR or Cr-EDTA; pooled results reflect mean differences and 95% CIs in GFR

[c] To convert HDL or LDL cholesterol from mg/dL to mmol/L divide by 38.67; to convert triglycerides from mg/dL to mmol/L divide by 88.57.[44]

[d]Symptomatic treatment is ACEi plus or minus beta-blocker, calcium channel blocker, or diuretics; All results only informed by a single RCT

[e]All results based on a single RCT, no pooled results presented; change from baseline not reported

[f]Specific p-values not reported

Table A6: Summary of Findings of Included Non-Randomized Studies

Moriyama[27a]

Factors Associated with Achieving 50% Decrease in Urinary Protein Levels (at 12 Months)[b]

Outcome Measure	OR (95% CI)	P-value[c]	Author's Conclusions
Mean blood pressure (per 10 mmHg decrease)	1.012 (0.41 to 2.52)	0.9781	Controlling for multiple potential determinants, EPA therapy was the only factor in the multivariate logistic regression model to be associated with significantly higher odds of achieving 50% decrease in urinary protein levels at 12 months. Mean blood pressure was significantly reduced in both the EPA and DILAZEP groups, and urinary protein was reduced in the EPA group after 1 year of treatment[d]
Urinary protein excretion (per 0.5g/g Cr decrease)	0.837 (0.47 to 1.33)	0.4619	
urinary-red blood cells (per 25/high power field decrease)	0.732 (0.35 to 1.41)	0.3430	
eGFR (per 10 ml/min increase)	0.763 (0.46 to 1.18)	0.2312	
With EPA therapy (vs. without EPA)	5.073 (1.18 to 26.7)	**0.0285**	
Mesangial hypercellularity	5.17 (0.78 to 48.1)	0.0896	
Endocapillary cellularity	0.29 (0.04 to 1.47)	0.1411	
Segmental glomerulosclerosis	2.19 (0.30 to 23.7)	0.4517	
Tubular atrophy/Interstitial fibrosis	0.68 (0.19 to 2.12)	0.5133	

Uchiyama-Tanaka[28]

Outcome Measure	n-3 group (n = 18)	Placebo Group (n = 5)	p-value	Author's Conclusions
Change in markers of Kidney Function after one year (Mean ± SE)				
Urinary protein to creatinine ratio (mg/g Cr)	-352 ± 132	-156 ± 285	NS	No significant differences in change from baseline for kidney function measures
Cr (mg/dL)	-0.039 ± 0.023	0.020 ± 0.020	NS	
Total protein (mg/dL)	0.02 ± 0.04	0.10 ± 0.11	NS	
CCr (mL/min)	11.06 ± 2.73	-5.40 ± 2.85	**0.0073**	Significant improvement in CCr following treatment with EPA versus placebo
Change in markers of Cardiovascular Function after one year (Mean ± SE)[e]				
Mean blood pressure (mmHg)	-4 ± 2	-11 ± 10	NS	No significant different in change from baseline lipid panel measures or mean blood pressure
Total cholesterol (mg/dL)	-10 ± 7	17 ± 14	NS	
HDL (mg/dL)	1.7 ± 0.9	-0.2 ± 0.9	NS	
Triglycerides (mg/dL)	-2.7 ± 1.7	-0.6 ± 1.7	NS	
Adverse Events				
Withdrawal due to adverse events	NR	NR	NR	"no patient discontinued EPA treatment due to adverse effects"

Cr = creatinine; CCr = creatinine clearance rate; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; HDL = high density lipoprotein; NR = not reported; NS = not significant; SE = standard error

[a]Note that while serial changes in mean blood pressure, urinary protein, and other clinical parameters (glomerular filtration rate, total cholesterol, triglycerides and urinary red blood cells) were recorded for the EPA and DILAZEP groups, no direct comparisons between groups were reported, only within group changes; therefore, these results are not reported in detail

[b]Overall regression coefficient and model significance not presented

[c]Bolded outcomes indicate statistically significant results

[d]p-values only reported for the difference between baseline and post-treatment within groups, not between groups

[e] To convert HDL or LDL cholesterol from mg/dL to mmol/L divide by 38.67; to convert triglycerides from mg/dL to mmol/L divide by 88.57.[44]