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Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD013601.
DOI: 10.1002/14651858.CD013601.

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[Intervention Protocol]

Carnitine supplements for people with chronic kidney disease requiring dialysis

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Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 5, 2020.

Citation: Nishioka N, Luo Y, Taniguchi T, Ohnishi T, Kimachi M, Ng RCK, Watanabe N. Carnitine supplements for people with chronic kidney disease requiring dialysis (Protocol). *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No.: CD013601. DOI: 10.1002/14651858.CD013601.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

The objective of this review is to evaluate the effectiveness and safety of carnitine for the treatment of dialysis-related complications.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) stage 5D is an increasingly prevalent problem and is managed using life-long kidney replacement therapy. Dialysis patients often have co-morbidities secondary to the loss of kidney function.

Carnitine is a metabolic cofactor which is essential for fatty acid metabolism. Carnitine exists in two main forms: acylcarnitine and free carnitine. Acylcarnitine, which is converted from free carnitine, transports fatty acids into mitochondria and functions as a scavenger for toxic acyl groups (Schreiber 2006). Carnitine is obtained from dietary intake and is also biosynthesised by the kidney and liver (Guarnieri 2015). Therefore, healthy people rarely lack carnitine. On the other hand, in dialysis patients, carnitine depletion is due to diminished endogenous renal synthesis and from loss through the dialytic membranes. Haemodialysis (HD) removes more free carnitine than acylcarnitine. Therefore, serum free carnitine is decreased in maintenance HD patients but not in CKD patients. Serum acylcarnitine is increased in both CKD and maintenance HD patients because of impaired kidney excretion. The majority of HD patients have low free carnitine levels, and the ratio of acyl to free carnitine in plasma is higher in HD patients (> 0.4) than in healthy controls (0.1 to 0.2) (Evans 2004; Fouque 2006; Hatanaka 2019; Schreiber 2006). It has been reported that the prevalence rates of carnitine deficiency, defined as a serum free carnitine level < 20 µmol/L, and that of carnitine insufficiency, defined as an acyl/free carnitine ratio > 0.4, was 25.3% and 86.7%, respectively (Hatanaka 2019). Carnitine deficiency and insufficiency can cause energy metabolic disorders and symptoms; intradialytic symptoms (e.g. muscle cramps, hypotension, and cardiac arrhythmia) commonly occur during routine HD treatments along with other more chronic complications of kidney failure (e.g. anaemia, cachexia, dyslipidaemia, cardiac dysfunction, muscle weakness, malnutrition, and myopathy) (Evans 2004; Fagher 1985; Kudoh 1983; Matera 2003; Sakurauchi 1998; Schreiber 2005).

In end-stage kidney disease (ESKD) patients, the comorbidities mentioned above influence the quality of life (QoL). The QoL of ESKD patients is lower than that of the general population, and a low QoL is associated with decreased survival in ESKD patients (Chilcot 2012; Kalantar-Zadeh 2001; Kimmel 2001; Lopes 2003; Lowrie 2003; Valderrabano 2001). Fatigue for ESKD patients is associated with poor outcomes related to QoL, cardiovascular disease, and death (Jhamb 2013; Koyama 2010), and has recently been established by patients and health professionals as a critically important outcome to be reported in all clinical studies in HD patients (Evangelidis 2017; Tong 2017).

Description of the intervention

Carnitine is an essential dietary nutrient synthesised from an amino acid and is biologically active only in the "L" isoform that contributes to cellular energy metabolism (Guarnieri 2015; Rebouche 1986). A significant dietary source of L-carnitine is red meat (Koeth 2013). L-carnitine is also available in the form of supplements, and L-carnitine supplementation increases plasma total, free, and acylcarnitine levels. Administration of L-carnitine can be oral or intravenous. The appropriate oral dose in ESKD patients has not been established; however, the maximum oral absorption dose is considered to be 2 g in the healthy population (Harper 1988).

How the intervention might work

Carnitine plays a critical role in the transport of free long-chain fatty acids into the mitochondrial matrix for beta-oxidation for the production of energy in the muscles, and has a detoxifying effect by removing acyl groups in the form of acylcarnitine esters (Brass 1988; Guarnieri 2015; Rebouche 1986). The kidney maintains plasma free carnitine levels in the homeostatic range via tubular reabsorption (Rebouche 2004). The combined loss of renal biosynthesis and of carnitine via dialysis leads to "dialysis-related carnitine deficiency" that may produce a number of clinical symptoms (Hedayati 2006). It is noteworthy that carnitine deficiency is associated with intradialytic symptoms such as muscle cramps and hypotension. L-carnitine supplementation may improve skeletal and cardiac muscle energy metabolism, and a recent randomised study showed that L-carnitine supplementation reduced the number of intradialytic hypotensive episodes (Ibarra-Sifuentes 2017). Additionally, L-carnitine supplementation may improve fatigue via anti-inflammatory activity and anti-oxidative stress in HD patients (Bellinghieri 1983; Laviano 2006). Other studies have reported that L-carnitine stabilises the erythrocyte membrane structure in mature erythrocytes, prolongs erythrocyte survival, stimulates erythropoiesis, and improves response to erythropoietin through its anti-inflammatory effect (Calo 2008; Kitamura 2005; Nikolaos 2000). L-carnitine, therefore, has been evaluated as an adjuvant to erythropoiesis-stimulating agents (ESAs) for treating anaemia. Carnitine supplementation may alleviate a number of symptoms from dialysis-related carnitine deficiency, thus contributing to improved QoL of ESKD patients. However, L-carnitine is metabolised to trimethylamine in the gut by the gut microflora and thence to trimethylamine-N-oxide (TMAO) in the liver (Wang 2011). TMAO is a molecule which promotes atherogenesis through its interaction with macrophages and lipid metabolism (Koeth 2013; Tang 2013; Tang 2014). It has been shown that high TMAO concentrations predict an increased risk of cardiovascular disease and an increased incidence of major adverse cardiac events in CKD patients (Kim 2016).

Why it is important to do this review

Dialysis imposes a considerable psychosocial burden on patients that results in impaired functionality. This is exacerbated by comorbidities that influence the QoL. Therefore, treatment for the complications and poor functioning observed in ESKD patients is imperative. An increasing number of studies have suggested that L-carnitine supplementation is beneficial for dialysis-related symptoms. Carnitine supplementation has been used effectively to improve the fatigue domain of the Kidney Disease Questionnaire (Brass 2001) and to reduce the muscle symptoms on their original scale (Bellinghieri 2005). However, its benefits remain controversial, and one study reported that the carnitine-containing multi-nutritional supplementation improved the fatigue score but not the visual analogue scale (VAS) score (Fukuda 2015). Some authors report that the improvement in the erythrocytes' fragility and increased life span reduced the ESA usage (Hurot 2002; Matsumoto 2001; Matsumura 1996), while others showed no significant improvement in haemoglobin (Hb) and erythropoietin dose (Mercadal 2012; Sabry 2010).

A recent systematic review indicated that L-carnitine significantly decreases the serum LDL-cholesterol and C-reactive protein (Chen 2014) levels; however, its impact on patient-reported outcomes, such as QoL and fatigue, remains unclear. Indeed, since completion of the review by Chen 2014, additional randomised controlled trials (RCTs) have reported on the effect of L-carnitine. Higuchi 2016 showed that oral L-carnitine improved cardiac function in HD patients with left ventricular hypertrophy. Maruyama 2017 found that L-carnitine administration reduced the dose of ESAs required in HD patients. Finally, Ibarra-Sifuentes 2017 noted that L-carnitine supplementation reduced the number of intradialytic hypotensive episodes. Thus, a systematic assessment is necessary to resolve the various controversies regarding the outcomes of carnitine supplementation in ESKD patients.

OBJECTIVES

The objective of this review is to evaluate the effectiveness and safety of carnitine for the treatment of dialysis-related complications.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) will be included. We will include cluster-randomised studies and cross-over studies. Cluster-RCTs will be analysed using a statistical analysis that properly accounts for the cluster design as recommended in the Cochrane Handbook for Systematic Reviews of Interventions, and cross-over studies will be analysed using the data from the first period only.

Types of participants

Inclusion criteria

Adults and children of any age with CKD requiring HD or peritoneal dialysis (PD) (CKD stage 5D) will be included. No age, sex, or comorbid inclusions will be applied.

Exclusion criteria

Studies of patients with acute kidney injury, CKD not requiring dialysis, including conservative care and kidney transplant recipients, will be excluded.

Types of interventions

The intervention will be carnitine compared with placebo, other treatment, or no intervention. It will be made between any form of carnitine administered at a minimum average of 100 mg/day or 2.5 mg/kg/day for at least two weeks by any route of administration. We will include studies assessing a multi-component preparation and perform subgroup analysis (single agent or multidrug).

Types of outcome measures

The outcomes selected include the relevant SONG core outcome sets as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017).

Primary outcomes

- QoL (any validated scale used by the studies, such as SF-36)
- Fatigue score*
- Adverse events (cardiovascular events*†, high blood pressure, seizures, gastrointestinal events, any self-reported adverse events).

Secondary outcomes

- Muscle symptoms (cramps, weakness)
- Anaemia-related markers (Hb, haematocrit (HCT), erythropoietin dose, erythropoietin resistance index)
- Myocardial function (intradialytic hypotension, left ventricular mass and ejection fraction based on echocardiographic findings)*
- Death (all-cause and cardiovascular)*†
- Vascular access failure (only in participants undergoing HD)*
- Peritoneal dialysis (PD) infection (only in participants undergoing PD)†
- Technique survival (only in participants undergoing PD)†
- Life participation (only in participants undergoing PD)†

The SONG-HD core outcomes, † The SONG-PD core outcomes

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following 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 Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search 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 strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable. However, studies and reviews that might include relevant data or information on studies will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfy the inclusion criteria. Any differences in opinion will be resolved by discussion and where necessary, by consultation with a third author.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together, and the publication with the most complete data will be used in the analyses. For cross-over studies, we will preferentially extract data from the first period only. Where relevant outcomes are only published in earlier versions, these data will be used. Any discrepancy between published versions will be highlighted. Differences in opinion on data collection will be resolved by discussion and where this fails by arbitration by a third author.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

We will assess the risk of bias for each outcome in the selected studies using the checklist for quality assessment. Where necessary in the case of differences, a third assessor or fourth assessor will be involved and a consensus will be reached.

The overall risk of bias based on the following bias domains will be defined:

Random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessors (performance bias), or incomplete outcome data (attrition bias).

- Low risk of bias: all the above domains are at low risk of bias
- High risk of bias: one or more the above domains are at high or unclear risk of bias.

Measures of treatment effect

For dichotomous outcomes (death, adverse events, muscle symptoms (cramps, weakness), hypotension during dialysis, vascular access failure, and PD infection) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (QoL score, fatigue score, anaemia-related markers (Hb, HCT, erythropoietin dose, erythropoietin resistance index), rate of hypotension during dialysis, cardiac dysfunction (left ventricular mass and ejection fraction based on echocardiographic findings), technique survival, and life participation), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used. The SMD is the difference in mean effects in the experimental and control groups divided by the pooled standard deviation (SD) of participants' outcomes. We will assume that 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect. Studies reporting time to an event of outcomes as hazard ratios and CIs will be meta-analysed together with studies reporting RRs as long as the proportional hazards assumption is reasonable. Otherwise, these studies will be analysed as dichotomous data.

Unit of analysis issues

Studies with non-standard designs will be analysed in this review using the recommended methods for data extraction and analysis described by The Cochrane Collaboration (Higgins 2011). We will only include data for endpoints reported during the first period of study in studies in which the order of receiving treatments was randomised when considering cross-over studies because carry-over will be thought to be a problem. We will attempt to combine all relevant experimental intervention groups of the study into a single group, and to combine all relevant control intervention groups into a single control group to enable a single pair-wise comparison when considering studies with multiple treatment groups. Cluster-RCTs will be analysed using a statistical analysis that properly accounts for the cluster design. Some examples of these are based on a "multi-level model," a "variance components analysis," or may use "generalized estimating equations" (Higgins 2011).

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing corresponding author), and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat, as-treated, and per-protocol population will be carefully performed. Attrition rates, for example, drop-outs, losses to follow-up, and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2011).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values will be as follows:

- 0% to 40%: might not be important;

- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data will be pooled using the random-effects model, but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analysis to explore possible sources of heterogeneity.

- Participants: age (< 18 years versus ≥ 18 years or older), dialysis modality (HD or PD), dialysis duration(≤ 3 months or > 3 months), ethnicity of patients, iron store parameters (serum ferritin ≤ 200 µg/L versus > 200 µg/L and transferrin saturation ≤ 20% versus > 20%)
- Intervention: average of dose (10 mg/kg/day or more), duration (≤ 6 months or > 6 months), route of administration (intravenous or oral), single agent alone or multi-component
- Treatments (co-prescribing): iron, renin-angiotensin-aldosterone system inhibitors.

Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias (Schunemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- QoL
- Fatigue score
- Adverse events
- Muscle cramps
- Anaemia-related markers (Hb, HCT)
- Intradialytic hypotension.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Kidney and Transplant Group for the template protocol. The authors are grateful to the following peer reviewers for their time and comments: Prof Dr Francesco Locatelli (Department of Nephrology, Alessandro Manzoni Hospital, a.s.s.t. Lecco, Lecco, Italy), Winnie Chan (University Hospitals Birmingham NHS Foundation Trust, UK), Laetitia Koppe MD, PhD (Department of Nephrology, Hospices Civils de Lyon, France).

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APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Renal Replacement Therapy] this term only 2. MeSH descriptor: [Renal Dialysis] this term only

(Continued)

	3. MeSH descriptor: [Hemodiafiltration] this term only 4. MeSH descriptor: [Hemodialysis, Home] explode all trees 5. MeSH descriptor: [Hemofiltration] explode all trees 6. (hemodialysis or haemodialysis):ti,ab,kw (Word variations have been searched) 7. (hemofiltration or haemofiltration):ti,ab,kw (Word variations have been searched) 8. (hemodiafiltration or haemodiafiltration):ti,ab,kw (Word variations have been searched) 9. MeSH descriptor: [Peritoneal Dialysis] explode all trees 10.(peritoneal dialysis):ti,ab,kw (Word variations have been searched) 11.(CAPD or CCPD or APD):ti,ab,kw (Word variations have been searched) 12.{or #1-#11} 13.MeSH descriptor: [Carnitine] explode all trees 14.(carnitine):ti,ab,kw (Word variations have been searched) 15.(levocarnitine):ti,ab,kw (Word variations have been searched) 16.("vitamin bt".tw):ti,ab,kw (Word variations have been searched) 17.{or #13-#16} 18.{and #12, #17}
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.exp Peritoneal Dialysis/ 11.peritoneal dialysis.tw. 12.(CAPD or CCPD or APD).tw. 13.or/1-12 14.exp CARNITINE/ 15.carnitine.tw. 16.bicarnesine.tw. 17.levocarnitine.tw. 18."vitamin bt".tw. 19.or/14-18 20.and/13,19
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.Peritoneal Dialysis/ 13.Continuous Ambulatory Peritoneal Dialysis/ 14.peritoneal dialysis.tw.

(Continued)

15.(PD or CAPD or CCPD or APD).tw.
16.peritoneal dialysis fluid/
17.peritoneal dialysis catheter/
18.or/1-17
19.exp carnitine/
20.carnitine.tw.
21.bicarnesine.tw.
22.levocarnitine.tw.
23."vitamin bt".tw.
24.or/19-23
25.and/18,24

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	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: 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.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* 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).
	High risk of bias: 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.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: 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.
	High risk of bias: 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.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment	*Low risk of bias:* 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.

(Continued)

Detection bias due to knowledge of the allocated interventions by outcome assessors.	*High risk of bias:* 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.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* 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 observed 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 standardised 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. sub-scales) 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 5, 2020

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DECLARATIONS OF INTEREST

NN, YL, TT, TO, MK: none

RCKN has stock interest in Liberty Dialysis Hawaii, Inc. However, his stock interest is in a company that doesn't have a real or potential vested interest in the findings of our review.

NW has research funds from the Japanese Ministry of Health Labor and Welfare and the Japanese Ministry of Education, Science, and Technology. He has also received royalties from Sogensha, Medical Review and Akatsuki for writings. The results in the review are completely independent of the intention of these grants.