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Carnitine supplements for people with chronic kidney disease requiring dialysis (Review)

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[Intervention Review]

Carnitine supplements for people with chronic kidney disease requiring dialysis

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ABSTRACT

Background

Carnitine deficiency is common in patients with chronic kidney disease (CKD) who require dialysis. Several clinical studies have suggested that carnitine supplementation is beneficial for dialysis-related symptoms. However, the clinical effectiveness and potential adverse effects of carnitine supplementation in dialysis patients have not been determined.

Objectives

This review aimed to evaluate the effectiveness and safety of carnitine supplementation for the treatment of dialysis-related complications in CKD patients requiring dialysis.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 16 August 2022 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included all randomised controlled trials (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) that compared carnitine supplements with placebo or standard care in people with CKD requiring dialysis.

Data collection and analysis

Two authors independently extracted study data and assessed study quality. We used a random-effects model to perform a quantitative synthesis of the data.

We used the I^2 statistic to measure heterogeneity amongst the studies in each analysis. We indicated summary estimates as a risk ratio (RR) for dichotomous outcomes, mean difference (MD) for continuous outcomes, or standardised mean differences (SMD) if different scales

were used, with 95% confidence intervals (CI). We assessed the certainty of the evidence for each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach.

Main results

We included 52 studies (47 parallel RCTs and five cross-over RCTs) (3398 randomised participants). All studies compared L-carnitine with a placebo, other treatment, or no treatment. Standard care was continued as co-interventions in each group. Most studies were judged to have an unclear or high risk of bias.

L-carnitine may have little or no effect on the quality of life (QoL) SF-36 physical component score (PCS) (4 studies, 134 participants: SMD 0.57, 95% CI -0.15 to 1.28; I^2 = 73%; low certainty of evidence), and the total QoL score (Kidney Disease Quality of Life (KDQOL), VAS (general well-being), or PedsQL) (3 studies, 230 participants: SMD -0.02, 95% CI -0.29 to 0.25; I^2 = 0%; low certainty of evidence). L-carnitine may improve SF-36 mental component score (MCS) (4 studies, 134 participants: SMD 0.70, 95% CI 0.22 to 1.18; I^2 = 42%; low certainty of evidence). L-carnitine may have little or no effect on fatigue score (2 studies, 353 participants: SMD 0.01, 95% CI -0.20 to 0.23; I^2 = 0%; low certainty of evidence), adverse events (12 studies, 1041 participants: RR, 1.14, 95% CI 0.86 to 1.51; I^2 = 0%; low certainty of evidence), muscle cramps (2 studies, 102 participants: RR, 0.44, 95% CI 0.18 to 1.09; I^2 = 23%; low certainty of evidence), and intradialytic hypotension (3 studies, 128 participants: RR, 0.76, 95% CI 0.34 to 1.69; I^2 = 0%; low certainty of evidence). L-carnitine may improve haemoglobin levels (26 studies, 1795 participants: MD 0.46 g/dL, 95% CI 0.18 to 0.74; I^2 = 86%; low certainty of evidence) and haematocrit values (14 studies, 950 participants: MD 1.78%, 95% CI 0.38 to 3.18; I^2 = 84%; low certainty of evidence).

Authors' conclusions

The available evidence does not currently support the use of carnitine supplementation in the treatment of dialysis-related carnitine deficiency. Although carnitine supplementation may slightly improve anaemia-related markers, carnitine supplementation makes little or no difference to adverse events. However, these conclusions are based on limited data and, therefore, should be interpreted with caution.

PLAIN LANGUAGE SUMMARY

Carnitine supplements for people with chronic kidney disease requiring dialysis

What is the issue?

Carnitine deficiency is an important problem in chronic kidney disease (CKD) patients requiring dialysis. Dialysis-related carnitine deficiency can exacerbate intradialytic symptoms (e.g. muscle symptoms including muscle cramps and weakness, and hypotension) and chronic complications of kidney failure (e.g. anaemia). However, it is unknown whether carnitine supplementation can improve the symptoms of dialysis-related carnitine deficiency.

What did we do?

We searched the medical literature for all randomised trials conducted on carnitine supplementation in CKD patients requiring dialysis. Our aim was to determine whether supplementation improves quality of life (QoL) and symptoms due to carnitine deficiency. We also assessed whether carnitine supplementation is safe in terms of adverse events. Evidence certainty was evaluated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

What did we find?

We identified 52 studies with a total of 3398 CKD patients undergoing dialysis. We could not determine the impact of L-carnitine on quality of life (QoL) and symptoms due to dialysis-related carnitine deficiency. L-carnitine may improve anaemia in these patients. Additionally, evidence for the adverse effects of L-carnitine supplementation in this patient population is very limited.

Conclusions

We found that the effects of carnitine supplementation with respect to QoL, fatigue score, muscle cramps, and intradialytic hypotension remain unclear. L-carnitine may improve anaemia-related markers (haemoglobin level and haematocrit values) in CKD patients requiring dialysis. More studies are needed to assess the effectiveness and safety of carnitine supplements in this patient population.

Summary of findings 1. Carnitine supplements versus control (placebo or standard care) for people with chronic kidney disease requiring dialysis

Carnitine supplements versus control (placebo or standard care) for people with CKD requiring dialysis

Patient or population: people with CKD requiring dialysis

Setting: haemodialysis and peritoneal dialysis
Intervention: carnitine supplements

Comparison: placebo or standard care

Outcomes		Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty
		Risk with control	Risk with L-carnitine			
Quality of life	**SF-36 PCS** Follow-up: range 2 to 12 months	The PCS SMD was **0.57 higher** in the L-carnitine group (0.15 lower to 1.28 higher) compared to the control group		-	134 (4)	⨁⨁◯◯ Low[1,2,3]
	SF-36 MCS Follow-up: range 2 to 12 months	The MCS SMD was **0.70 higher** in the L-carnitine group (0.22 higher to 1.18 higher) compared to the control group		-	134 (4)	⨁⨁◯◯ Low[1,3]
	Total scores Follow-up: range 4 to 6 months	The total QoL compared score SMD was **0.02 lower** in the L-carnitine group (0.29 lower to 0.25 higher) compared to the control group		-	230 (3)	⨁⨁◯◯ Low[1,3]
Fatigue score Follow-up: range 3 to 6 months		The fatigue score SMD was **0.01 higher** in the L-carnitine group (0.20 lower to 0.23 higher) compared to the control group		-	353 (2)	⨁⨁◯◯ Low[3,4]
Adverse events Follow-up: range 3 to 12 months		113 per 1,000	**129 per 1,000** (97 to 170)	**RR 1.14** (0.86 to 1.51)	1041 (12)	⨁⨁◯◯ Low[3,5]
Muscle cramps Follow-up: range 2 to 6 months		315 per 1,000	**139 per 1,000** (57 to 343)	**RR 0.44** (0.18 to 1.09)	102 (2)	⨁⨁◯◯ Low[1,3]
Anaemia-related markers	**Hb**	The mean Hb was **0.46 g/dL higher** in the L-carnitine group (0.18 g/dL higher to 0.74 g/dL higher) compared to the control group		-	1795 (26)	⨁⨁◯◯ Low[2,6]

	Follow-up: range 0.5 to 12 months				
	HCT Follow-up: range 3 to 18 months	The mean HCT was **1.78% higher** in the L-carnitine group (0.38% higher to 3.18% higher) compared to the control group	-	950 (14)	⨁⨁◯◯ Low[1,2]
Intradialytic hypotension Follow-up: range 2 to 4 months	179 per 1,000	**136 per 1,000** (61 to 303)	**RR 0.76** (0.34 to 1.69)	128 (3)	⨁⨁◯◯ Low[1,3]

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

CI: confidence interval; **CKD:** chronic kidney disease; **Hb:** haemoglobin; **HCT:** haematocrit; **MCS:** mental component scale; **MD:** mean difference; **PCS:** physical component scale; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMD:** standardised mean difference; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

1. Down-graded one level due to a serious risk of bias: all studies had a high overall risk of bias
2. Down-graded one level due to inconsistency: there was considerable heterogeneity
3. Down-graded because the number of the included participants did not meet the optimal information size of 400
4. Down-graded one level due to a serious risk of bias: 1 of the 2 studies had a high overall risk of bias
5. Down-graded one level due to a serious risk of bias: 8 of the 11 studies had a high overall risk of bias
6. Down-graded one level due to a serious risk of bias: 21 of the 23 studies had a high overall risk of bias

BACKGROUND

Description of the condition

The estimated prevalence of chronic kidney disease (CKD) worldwide is 9.1%, with an estimated 1.2 million deaths due to CKD worldwide in 2017 (GBD Chronic Kidney Disease Collaboration 2022). This growth is continuously outpacing the capacity of kidney replacement therapy (KRT). Therefore, CKD stage 5D is an increasingly prevalent problem and is managed using life-long KRT. 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 loss through the dialytic membranes. Haemodialysis (HD) and peritoneal dialysis (PD) remove more free carnitine than acylcarnitine. Therefore, serum free carnitine is decreased in maintenance dialysis patients but not in CKD patients. Serum acylcarnitine is increased in both CKD and maintenance 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). Similarly, previous studies have reported a high prevalence of carnitine deficiency in patients on PD (Kaneko 2020).

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) (Schreiber 2005; Takashima 2021).

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; Lopes 2003; Lowrie 2003). 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 dialysis 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). 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 (IV). 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. It also has a detoxifying effect by removing acyl groups in the form of acylcarnitine esters (Guarnieri 2015). The kidney maintains serum 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. Moreover, a recent randomised controlled trial (RCT) showed that L-carnitine supplementation reduced the number of intradialytic hypotensive episodes (Ibarra-Sifuentes 2017a). Additionally, L-carnitine supplementation may improve fatigue via anti-inflammatory activity and anti-oxidative stress in HD patients (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 (EPO) 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 of 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 then to trimethylamine-N-oxide (TMAO) in the liver (Wang 2011). TMAO promotes atherogenesis through its interaction with macrophages and lipid metabolism (Koeth 2013; Tang 2013; Tang 2014). It has been reported 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 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 2015a). 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 EPO 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 the completion of the review by Chen 2014, additional 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 2017a found that L-carnitine administration reduced the dose of ESAs required in HD patients. Finally, Ibarra-Sifuentes 2017a 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

This review aimed to evaluate the effectiveness and safety of carnitine supplementation for the treatment of dialysis-related complications in CKD patients requiring dialysis.

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) were included. We included cluster-RCTs and cross-over studies. Cluster-RCTs were analysed using a statistical analysis that properly accounts for the cluster design as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021). 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 PD (CKD stage 5D) were included. No age, sex, or comorbid exclusion criteria were applied.

Exclusion criteria

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

Types of interventions

The intervention was carnitine compared with a placebo, other treatment, or no intervention. Standard care for ESKD was continued in each group. The intervention was 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 included studies assessing a multi-component preparation.

Types of outcome measures

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

Primary outcomes

- QoL: any validated scale used in the studies, such as the Short Form-36 (SF-36) scale
- 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: haemoglobin (Hb) level, haematocrit (HCT) value, EPO dose, EPO resistance index
  - When the dose per body weight was reported (Chazot 2003; Cui 2016, Kletzmayr 1999; Garneata 2005; Song 2013a; Sorge-Haedicke 2001), the total EPO dose was determined using the body weight of the patient when the dose per body weight was reported (Chazot 2003). When body weight data were not provided, body weight values were imputed using data from RCTs of similar patients in the same country (Cui 2016, Kletzmayr 1999; Garneata 2005; Song 2013a; Sorge-Haedicke 2001).
    - Australia (Antlanger 2017)
    - China (Wang 2018)
    - Germany (Wizemann 2008)
    - Romania (Siriopol 2017)
  - When we could not calculate the standard deviation (SD), we imputed SDs from the studies in the same meta-analysis (Cibulka 2005).
- Myocardial function: intradialytic hypotension, left ventricular mass and ejection fraction based on echocardiographic findings*
- Deaths: any cause and cardiovascular*†
- Vascular access failure: only in participants undergoing HD*
- PD infection: only in participants undergoing PD†
- Technique survival (only in participants undergoing PD)†
- Life participation: only in participants undergoing PD†

**Standardised Outcomes in Nephrology (SONG)-HD core outcomes*, †*SONG-PD core outcomes*

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 16 August 2022 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 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 on the Cochrane Kidney and Transplant website under CKT Register of Studies.

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

Data extraction and management

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

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2021) (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)?
- Were 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 risk of bias?

We assessed 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 or fourth assessor was involved, and a consensus was reached.

The overall risk of bias based on the following bias domains was 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 of 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 were expressed as risk ratios (RR) with 95% confidence intervals (CI). When continuous scales of measurement were used to assess the effects of treatment (QoL score, fatigue score, anaemia-related markers (Hb, HCT, EPO dose, EPO resistance index), rate of hypotension during dialysis, cardiac dysfunction (left ventricular mass and ejection fraction based on echocardiographic findings), technique survival, and life participation), mean difference (MD) was used, or standardised mean difference (SMD) if different scales were used. The SMD is the difference in mean effects in the experimental and control groups divided by the pooled SD of participants' outcomes. We assumed 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 were meta-analysed together with studies reporting RR as long as the proportional hazards assumption is reasonable. Otherwise, these studies were analysed as dichotomous data.

Unit of analysis issues

Studies with non-standard designs were analysed in this review using the recommended methods for data extraction and analysis described by The Cochrane Collaboration (Higgins 2021). We only included 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 was thought to be a problem. We attempted 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 were 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 2021).

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing the corresponding author), and any relevant information obtained in

this manner was 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 were carefully performed. Attrition rates, for example, drop-outs, losses to follow-up, and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2021).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We quantified 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 CI for I^2) (Higgins 2021).

Assessment of reporting biases

Funnel plots were used to assess for the potential existence of small study bias (Higgins 2021).

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses to explore the possible sources of heterogeneity.

- Participants: dialysis modality (HD or PD)
- Intervention: average dose (≥ 10 mg/kg/day), duration (≤ 6 months or > 6 months), route of administration (IV or oral), single-agent alone or multi-component

We planned the following subgroup analyses.

- Participants: age (< 18 years versus ≥ 18 years), ethnicity, iron storage parameters (serum ferritin ≤ 200 µg/L versus > 200 µg/L, and transferrin saturation ≤ 20% versus > 20%)
- Treatments (co-prescription): iron, renin-angiotensin-aldosterone system inhibitors.

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

Sensitivity analysis

We performed sensitivity analyses for the primary outcomes to explore the influence of the following factors on effect size:

- Repeated analysis taking account of the risk of bias, as specified
- Repeated analysis excluding studies using the following filters: language of publication and source of funding (industry versus other).

We planned sensitivity analyses for the primary outcomes:

- Repeated analysis excluding unpublished studies
- Repeated analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeated analysis excluding studies using the following filters: diagnostic criteria and country.

However, no large, long, or unpublished studies were included. For the other analyses, there were insufficient data observations to allow the analyses.

Moreover, we performed the following sensitivity analyses for anaemia-related markers (EPO dose).

- The analyses were repeated after excluding studies borrowing body weight or SD values from other studies.

Summary of findings and assessment of the certainty of the evidence

We presented 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 2021a). 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 2021b). We planned 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.

RESULTS

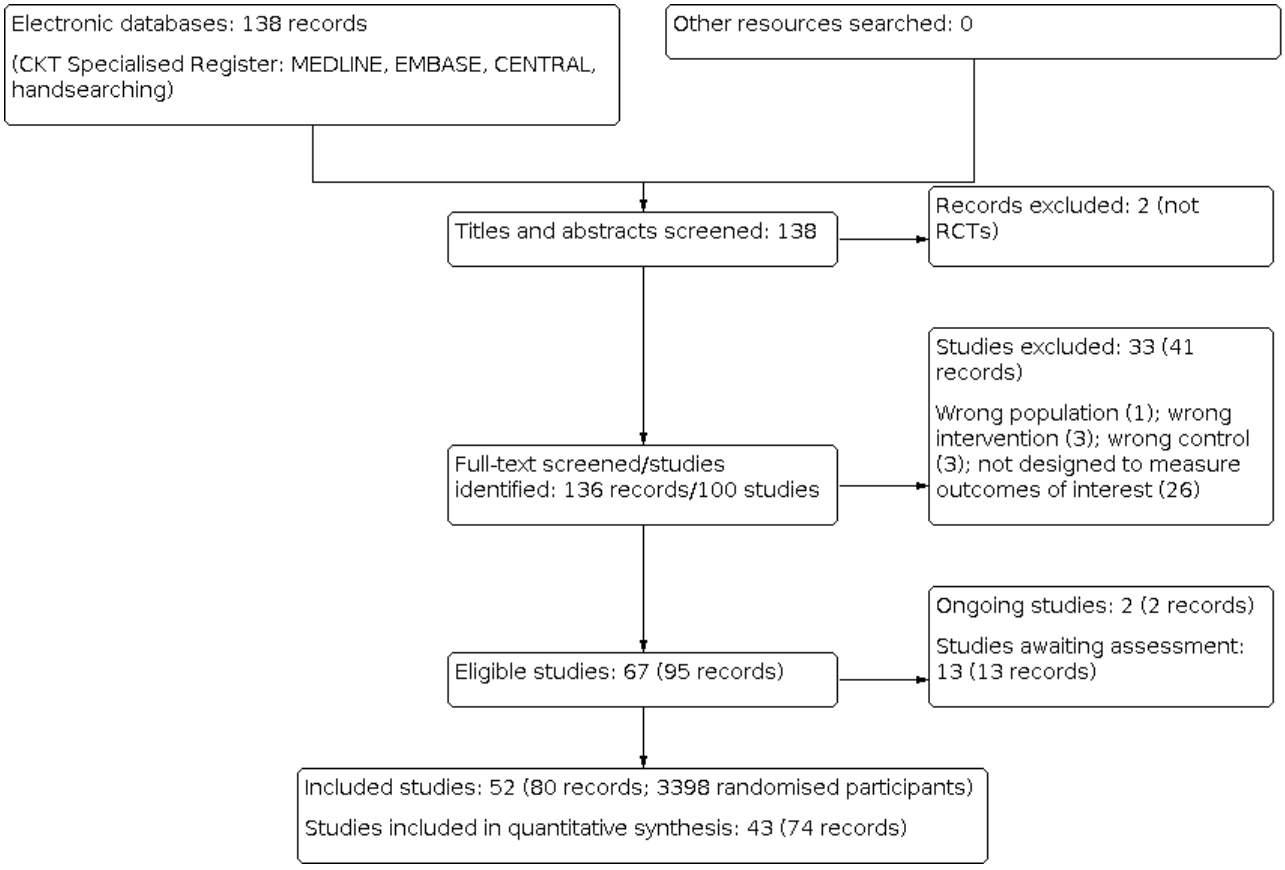
Description of studies

Detailed descriptions of the studies covered in this review are provided in the following tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

After searching the Specialised Register, a total of 143 records were identified. After screening titles and abstracts and full-text review, 52 studies (84 reports) were included, and 35 studies (43 reports) were excluded. Two ongoing studies were identified (IRCT20200225046620N1; IRCT20201027049166N1), and 13 studies were completed prior to publication; however, no results are as yet available (ACCORD 2009; EudraCT2006-005298-23; EudraCT2006-005300-13; IRCT138811212779N2; IRCT20180921041080N1; ISRCTN96315193; Jack 2000; RENACARE 2019; UMIN000011208; UMIN000012222; UMIN000013009; UMIN000031514; Unsal 2006). These 15 studies will be assessed in a future update of this review (Figure 1).

Figure 1. Study flow diagram.



Included studies

A total of 52 studies (80 records, 3398 randomised participants) were included (Figure 1).

Study design

A total of 48 studies were parallel RCTs, and four were cross-over studies (Bellinghieri 1983; Catalano 1999; Semeniuk 2000; Sloan 1998b).

Setting

All studies were single-country-based studies: Argentina (1), Australia (1), Canada (1), Chile (1), China (4), Czech (1), France (2), Germany (2), India (2), Iran (7), Iraq (1), Italy (8), Japan (7), Mexico (1), Romania (1), Saudi-Arabia (1), Sweden (1), Turkey (1), UK (2), USA (7).

Participants

A total of 50 studies only included HD patients, and two studies only included PD patients (Bonomini 2006; Mortazavi 2011a). The mean age ranged from 13 to 72 years. Dialysis duration ranged from 38 days to 28 years.

Interventions

The doses of L-carnitine were as follows.

- IV
  - 40 mg/kg at each dialysis session: one study (Brass 2001b)
  - 30 mg/kg at each dialysis session: one study (Ibarra-Sifuentes 2017)
  - 28.5 mg/kg at each dialysis session: one study (Sorge-Haedicke 2001)
  - 25 mg/kg at each dialysis session: one study (Kletzmayr 1999)
  - 20 mg/kg at each dialysis session: 10 studies (Ahmad 1990; Arduini 2006; Biolo 2008; Brass 2001a; Brass 2001b; Rathod 2006; Semeniuk 2000; Song 2013a; Steiber 2006; Vaux 2004)
  - 15 mg/kg at each dialysis session: three studies (Chazot 2003; Cibulka 2005; Mitwalli 2005)
  - 10 mg/kg at each dialysis session: two studies (Brass 2001b; Mettang 1997)

- 5 mg/kg at each dialysis session: two studies (Bonomini 2006; Kletzmayr 1999)
- 3 mg/kg at each dialysis session: one study (Bonomini 2006)
- 2000 mg at each dialysis session: one study (Zilleruelo 1993)
- 1000 mg at each dialysis session: 15 studies (CARNIDIAL 2012; Caruso 1998; Catalano 1999; Chi 2021; Cui 2016; Fagher 1985; Fu 2010; Harmankaya 2002a; Khodaverdi 2010; Labonia 1995; Maruyama 2017; Pacheco 2008; Saxena 2004; Sugiyama 2021; Yano 2021)
- 1000 mg once/week at dialysis session: one study (Sugiyama 2021)
- 600 mg at each dialysis session: one study (Signorelli 2006)
- 10 mg/kg once/day (Abdul-Hassan Mahdi 2021)
- 10 mg/kg twice/day (Abdul-Hassan Mahdi 2021)

- Oral
  - 6 g/day: one study (Garneata 2005)
  - 1500 mg/day: one study (Trovato 1983)
  - 1000 mg/day: three studies (Ahmadi 2016; Bellinghieri 1983; Naini 2011)
  - 900 mg/day: two studies (Fukami 2013; Kudoh 2013)
  - 750 mg/day: two studies (Mortazavi 2011a; Mortazavi 2012)
  - 500 mg/day: one study (Roozbeh 2007)
  - 50 mg/kg/day: one study (Hamedi-Kalajahi 2021)
  - 20 mg/kg/day: one study (Higuchi 2014)
  - 2000 mg at each dialysis session: one study (Sloan 1998a)
  - 500 mg at each dialysis session: one study (Fukuda 2015)
- Intraperitoneal
  - 2000 mg/day (Bonomini 2013)

The duration of treatment was different between the studies.

- Eighteen months: one study (Trovato 1983)
- Twelve months: five studies (CARNIDIAL 2012; Higuchi 2014; Maruyama 2017; Signorelli 2006; Sugiyama 2021)
- Nine months: two studies (Mortazavi 2011a; Mortazavi 2012)
- Eight months: two studies (Kletzmayr 1999; Song 2013a)
- Seven months: one study (Cui 2016)
- Six months: 18 studies (Abdul-Hassan Mahdi 2021; Ahmad 1990; Arduini 2006; Biolo 2008; Bonomini 2006; Brass 2001a; Brass 2001b; Caruso 1998; Chazot 2003; Cibulka 2005; Fukami 2013; Garneata 2005; Harmankaya 2002a; Labonia 1995; Mitwalli 2005; Sloan 1998a; Sorge-Haedicke 2001; Steiber 2006)
- Four months: four studies (Catalano 1999; Mettang 1997; Naini 2011; Vaux 2004)
- Three months: 12 studies (Ahmadi 2016; Bonomini 2013; Chi 2021; Fu 2010; Fukuda 2015; Ibarra-Sifuentes 2017; Khodaverdi 2010; Kudoh 2013; Pacheco 2008; Semeniuk 2000; Yano 2021; Zilleruelo 1993)
- Two months: three studies (Bellinghieri 1983; Rathod 2006; Roozbeh 2007)
- Ten weeks: one study (Hamedi-Kalajahi 2021)
- Six weeks: one study (Fagher 1985)
- Four weeks: one study (Saxena 2004).

A placebo was used in the control group in 41 studies (Ahmad 1990; Arduini 2006; Bellinghieri 1983; Biolo 2008; Bonomini 2006; Brass 2001a; Brass 2001b; CARNIDIAL 2012; Caruso 1998; Catalano 1999; Cibulka 2005; Cui 2016; Fagher 1985; Fukami 2013; Fukuda 2015; Hamedi-Kalajahi 2021; Harmankaya 2002a; Ibarra-Sifuentes 2017; Khodaverdi 2010; Kletzmayr 1999; Kudoh 2013; Labonia 1995; Mettang 1997; Mitwalli 2005; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Pacheco 2008; Rathod 2006; Roozbeh 2007; Semeniuk 2000; Signorelli 2006; Sloan 1998a; Song 2013a; Sorge-Haedicke 2001; Steiber 2006; Sugiyama 2021; Trovato 1983; Vaux 2004; Zilleruelo 1993).

Outcomes

Further information, including phase 1 data from cross-over studies, could not be obtained.

The following reported outcomes were included in quantitative syntheses for this review.

- QoL: seven studies (Brass 2001 (A+B); CARNIDIAL 2012; Hamedi-Kalajahi 2021; Naini 2011; Rathod 2006; Steiber 2006; Vaux 2004).
- Fatigue score: two studies (Brass 2001 (A+B); Fukuda 2015)
- Adverse events: 12 studies (Ahmad 1990; CARNIDIAL 2012; Chi 2021; Fukami 2013; Fukuda 2015; Higuchi 2014; Kletzmayr 1999; Maruyama 2017; Mettang 1997; Mortazavi 2011a; Mortazavi 2012; Signorelli 2006).
- Muscle symptoms
  - Cramp: two studies (Ahmad 1990; Rathod 2006)
  - Weakness: three studies (Ahmad 1990; Rathod 2006; Yano 2021)
- Anaemia-related markers
  - Hb: 26 studies (Arduini 2006; Biolo 2008; Brass 2001a; Brass 2001b; Chi 2021; Cibulka 2005; Cui 2016; Fu 2010; Fukuda 2015; Garneata 2005; Higuchi 2014; Khodaverdi 2010; Maruyama 2017; Mettang 1997; Mitwalli 2005; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Rathod 2006; Saxena 2004; Song 2013a; Sorge-Haedicke 2001; Steiber 2006; Sugiyama 2021; Vaux 2004; Yano 2021)
  - HCT: 14 studies (Arduini 2006; Brass 2001a; Brass 2001b; Caruso 1998; Chazot 2003; Cui 2016; Harmankaya 2002a; Khodaverdi 2010; Mettang 1997; Mitwalli 2005; Pacheco 2008; Song 2013a; Steiber 2006; Trovato 1983).
  - EPO dose: 13 studies (Caruso 1998; Chazot 2003; Cibulka 2005; Cui 2016; Garneata 2005; Harmankaya 2002a; Kletzmayr 1999; Labonia 1995; Maruyama 2017; Mortazavi 2012; Song 2013a; Sorge-Haedicke 2001; Vaux 2004)
  - EPO resistance index: five studies (CARNIDIAL 2012; Higuchi 2014; Kletzmayr 1999; Maruyama 2017; Steiber 2006).
- Myocardial function
  - Intradialytic hypotension: three studies (Ahmad 1990; Rathod 2006; Vaux 2004).
  - Left ventricular mass: three studies (Higuchi 2014; Kudoh 2013; Sugiyama 2021).
  - Ejection fraction: six studies (Abdul-Hassan Mahdi 2021; Fagher 1985; Higuchi 2014; Kudoh 2013; Maruyama 2017; Sugiyama 2021).
- Death
  - Death (any cause): 13 studies (Ahmadi 2016; CARNIDIAL 2012; Caruso 1998; Chazot 2003; Fukami 2013; Higuchi 2014; Mettang 1997; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Signorelli 2006; Sugiyama 2021; Vaux 2004).

- Death (cardiovascular): 5 studies (Caruso 1998; Fukami 2013; Higuchi 2014; Signorelli 2006; Vaux 2004).
- Vascular access failure: one study (Fukami 2013)
- PD infection: one study (Bonomini 2013)

Excluded studies

See Characteristics of excluded studies.
We excluded 33 studies for the following reasons.

- Wrong population (Gahl 1993)
- Wrong interventions (Al-Madani 2000; Bizzi 1978; Gunal 1999)
- Wrong control (Bonomini 2020; Sakurabayashi 2001; Vacha 1989)
- Not designed to measure the outcomes of interest (Alattiya 2016; Bellinghieri 1990; Bonomini 2007; Candan 2001; Duranay 2006; Fatouros 2010; Guarnieri 1980a; Hakeshzadeh 2010; Iranian 2009; IRCT2013042913160N1; IRCT2014030516848N1; IRCT2015112224645N2; Ito 2019b; Liu 2020; Owen 2007; Sabri 2012; Shakeri 2010; Shojaei 2011; Siami 1991; Sja'bani 2005; Suchitra 2011; Warady 1990; Weschler 1984; Yassari 2020; Yderstraede 1987; Zilleruelo 1989)

Risk of bias in included studies

The assessment of the risk of bias in the included studies is shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (the blank (white) spaces are because the outcomes of interest were not reported)

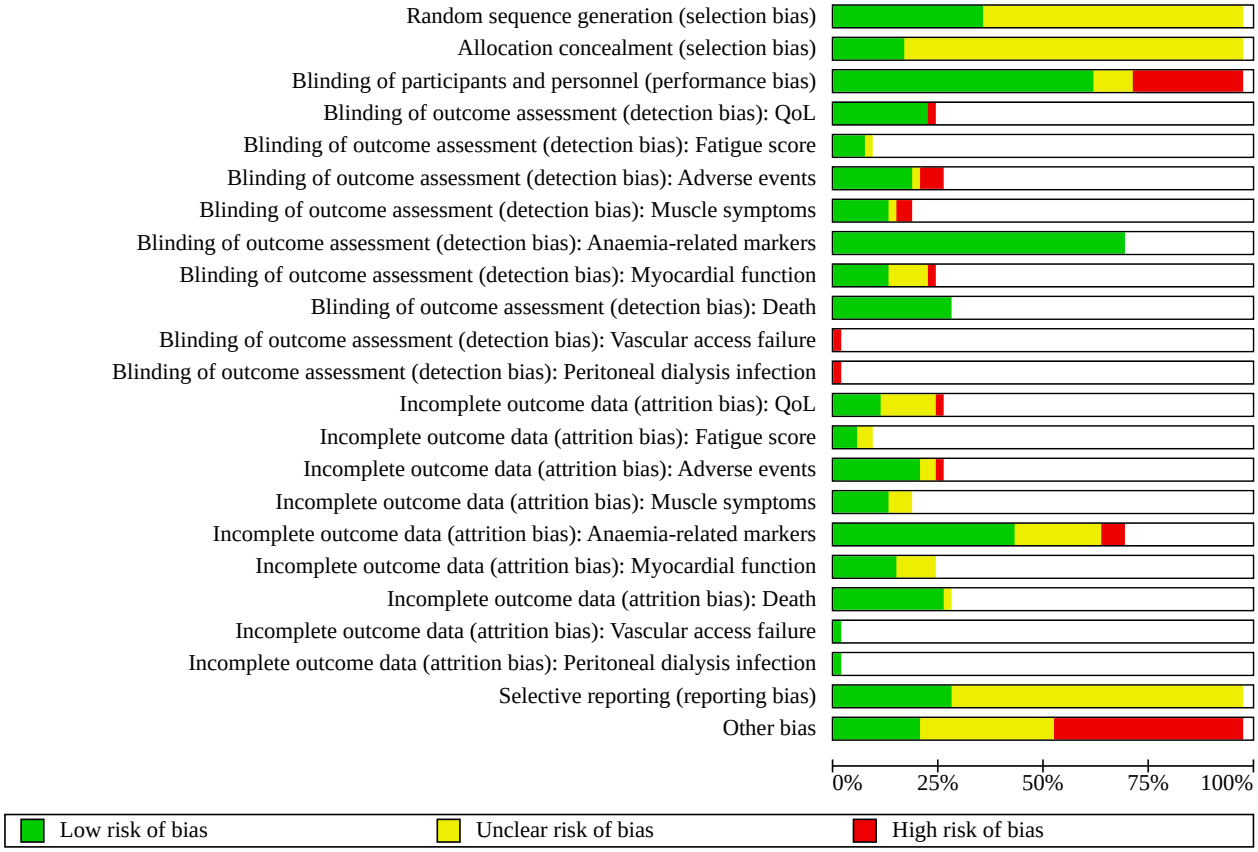


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (the blank (white) spaces are because the outcomes of interest were not reported)

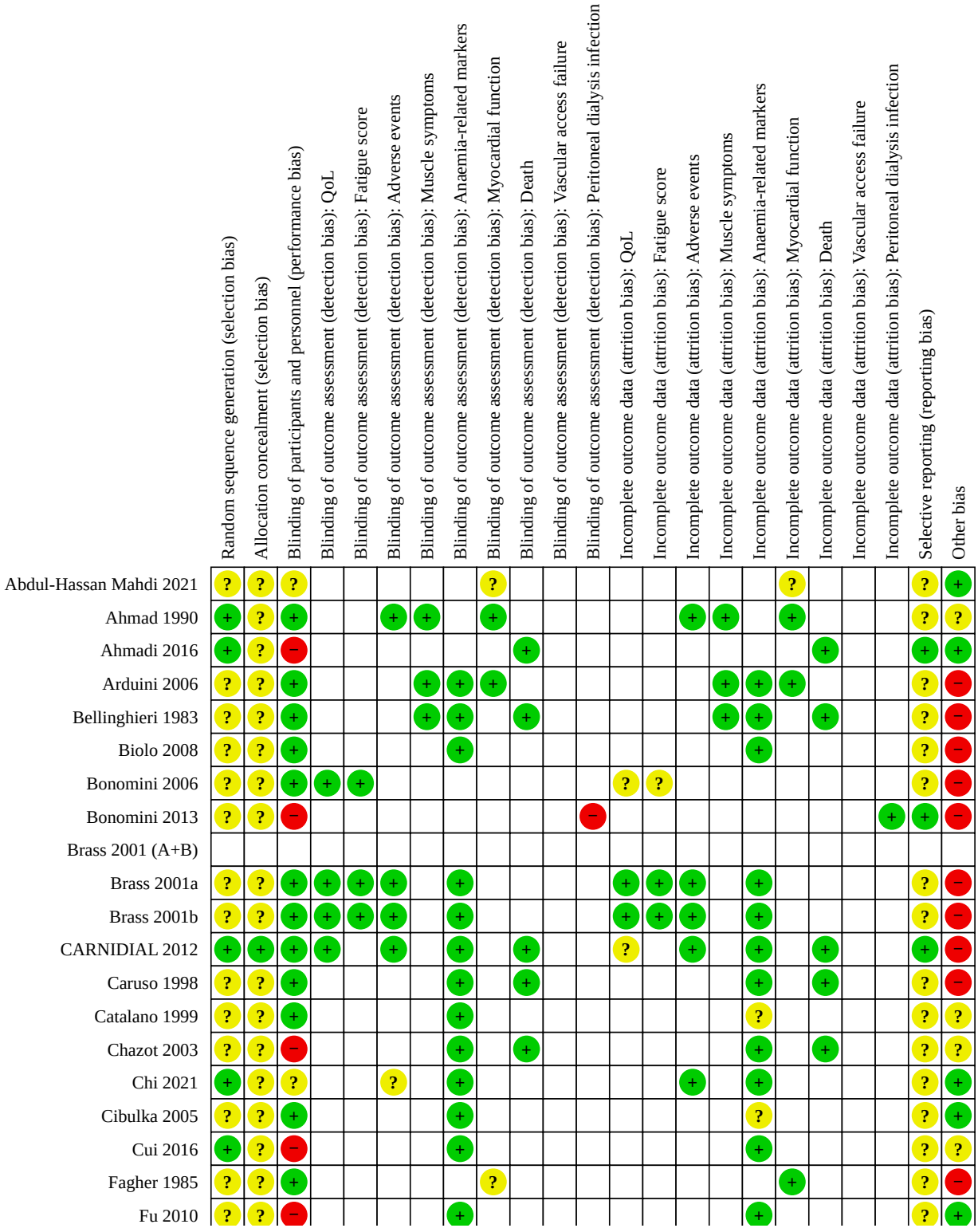
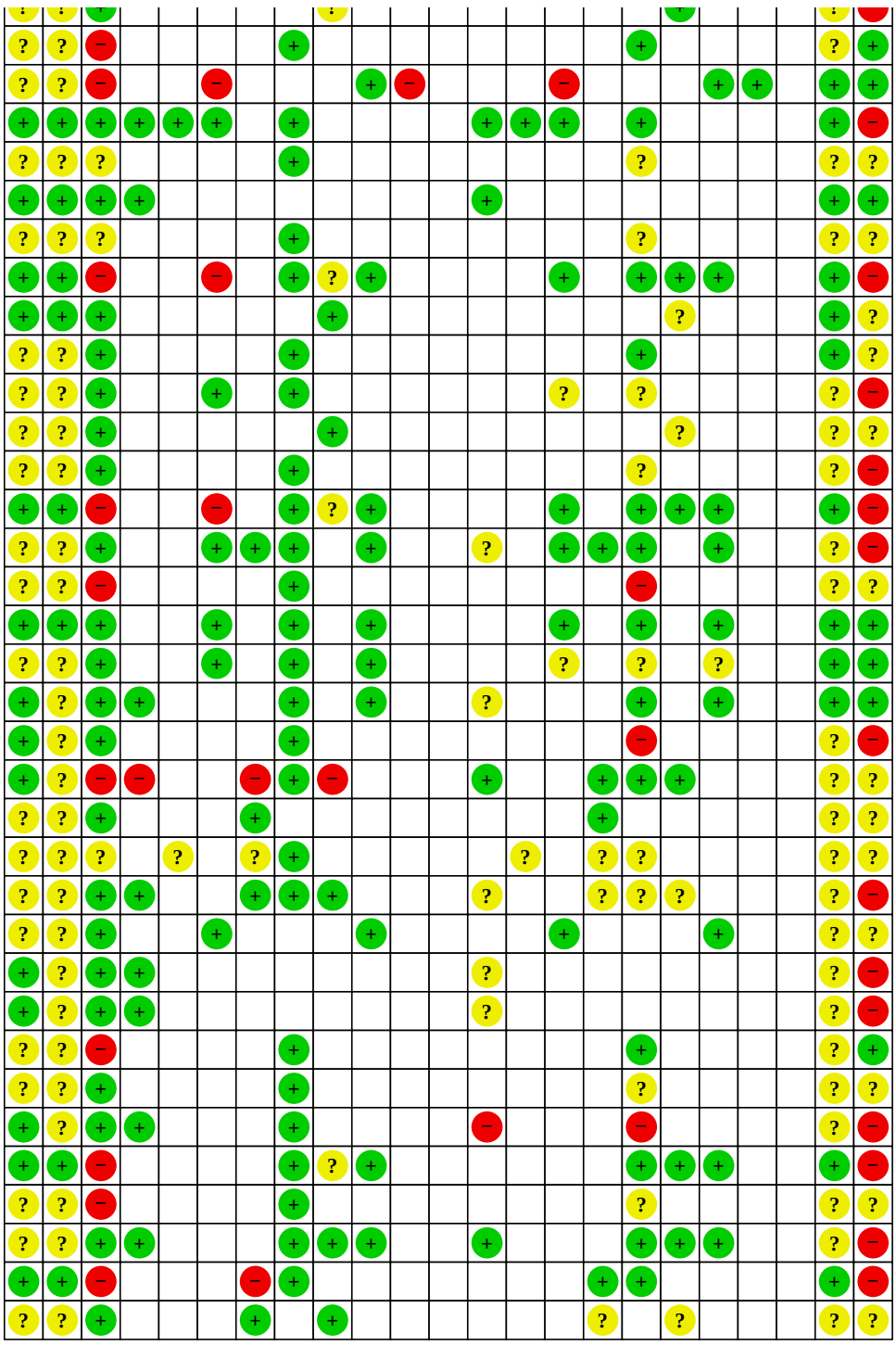


Figure 3. (Continued)



PLEASE NOTE: the blank (white) spaces in Figure 2 and Figure 3 are because the outcomes of interest were not reported.

Allocation

Random sequence generation

Eighteen studies were judged to be at low risk of bias (Ahmad 1990; Ahmadi 2016; CARNIDIAL 2012; Chi 2021; Cui 2016; Fukuda 2015; Hamedi-Kalajahi 2021; Higuchi 2014; Ibarra-Sifuentes 2017; Maruyama 2017; Mortazavi 2011a; Naini 2011; Pacheco 2008;

Rathod 2006; Sloan 1998a; Steiber 2006; Sugiyama 2021; Yano 2021). The remaining 34 studies gave no description and were categorised as unclear.

Allocation concealment

Nine studies were judged to be at low risk of bias (CARNIDIAL 2012; Fukuda 2015; Hamedi-Kalajahi 2021; Higuchi 2014; Ibarra-Sifuentes 2017; Maruyama 2017; Mortazavi 2011a; Sugiyama 2021; Yano 2021). The remaining 43 studies gave no description and were categorised as unclear.

Blinding

Performance bias

Performance bias (blinding of participants) was judged to be at low risk of bias in 33 studies (Ahmad 1990; Arduini 2006; Bellinghieri 1983; Biolo 2008; Bonomini 2006; Brass 2001a; Brass 2001b; CARNIDIAL 2012; Caruso 1998; Catalano 1999; Cibulka 2005; Fagher 1985; Fukuda 2015; Hamedi-Kalajahi 2021; Ibarra-Sifuentes 2017; Khodaverdi 2010; Kletzmayr 1999; Kudoh 2013; Labonia 1995; Mettang 1997; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Pacheco 2008; Roozbeh 2007; Semeniuk 2000; Signorelli 2006; Sloan 1998a; Sloan 1998b; Sorge-Haedicke 2001; Steiber 2006; Vaux 2004; Zilleruelo 1993). Fourteen studies were not blinding or incomplete blinding studies and were judged to be a high risk of bias (Ahmadi 2016; Bonomini 2013; Chazot 2003; Cui 2016; Fu 2010; Fukami 2013; Higuchi 2014; Maruyama 2017; Mitwalli 2005; Rathod 2006; Song 2013a; Sugiyama 2021; Trovato 1983; Yano 2021). Five studies did not provide sufficient information for assessment.

Detection bias

Quality of life

The blinding of assessment for QoL was graded as low risk for 11 studies as the personnel and participants were blinded (Bonomini 2013; Brass 2001 (A+B); CARNIDIAL 2012; Fukuda 2015; Hamedi-Kalajahi 2021; Naini 2011; Semeniuk 2000; Sloan 1998a; Sloan 1998b; Steiber 2006; Vaux 2004). One study was graded as high risk of bias as the personnel were not blinded (Rathod 2006).

Fatigue score

The blinding of assessment for fatigue score was graded as low risk for three studies as the personnel and participants were blinded (Bonomini 2006; Brass 2001 (A+B); Fukuda 2015). One study did not provide sufficient information for assessment (Saxena 2004).

Adverse events

The blinding of assessment for adverse events was graded as low risk for 10 studies as the personnel and participants were blinded (Ahmad 1990; Brass 2001a; Brass 2001b; CARNIDIAL 2012; Fukuda 2015; Kletzmayr 1999; Mettang 1997; Mortazavi 2011a; Mortazavi 2012; Signorelli 2006). Three studies were graded as having a high risk of bias as the personnel and participants were not blinded (Fukami 2013; Higuchi 2014; Maruyama 2017), and one study did not provide sufficient information for assessment (Chi 2021).

Muscle symptoms

The blinding of assessment for muscle symptoms was graded as low risk for seven studies as the personnel and participants were blinded (Ahmad 1990; Arduini 2006; Bellinghieri 1983; Mettang 1997; Roozbeh 2007; Semeniuk 2000; Zilleruelo 1993). Two studies were graded as having a high risk of bias as the personnel were not blinded (Rathod 2006; Yano 2021), and one study did not provide sufficient information for assessment (Saxena 2004).

Anaemia-related markers

Blinding of assessment for anaemia-related markers was graded as low risk for 37 studies; 21 studies reported blinding of personnel (Arduini 2006; Bellinghieri 1983; Brass 2001a; Brass 2001b; Biolo 2008; CARNIDIAL 2012; Caruso 1998; Cibulka 2005; Fukuda 2015; Khodaverdi 2010; Kletzmayr 1999; Labonia 1995; Mettang 1997; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Pacheco 2008; Semeniuk 2000; Sorge-Haedicke 2001; Steiber 2006; Vaux 2004), and 16 studies were deemed low risk as the measurement of anaemia-related markers was not likely to be influenced despite the lack of blinding (Catalano 1999; Chazot 2003; Cui 2016; Chi 2021; Fu 2010; Garneata 2005; Harmankaya 2002a; Higuchi 2014; Maruyama 2017; Mitwalli 2005; Rathod 2006; Saxena 2004; Song 2013a; Sugiyama 2021; Trovato 1983; Yano 2021).

Myocardial function

The blinding of assessment for the myocardial function was graded as low risk for six studies, as the personnel and participants were blinded (Ahmad 1990; Arduini 2006; Ibarra-Sifuentes 2017; Kudoh 2013; Semeniuk 2000; Vaux 2004). One study was graded as having a high risk of bias, as the outcome assessor was not blinded (Rathod 2006), and five studies did not provide sufficient information for the outcome assessment (Abdul-Hassan Mahdi 2021; Fagher 1985; Higuchi 2014; Maruyama 2017; Sugiyama 2021).

Death

Blinding of assessment for death was graded as low risk for 15 studies (Ahmadi 2016; Bellinghieri 1983; CARNIDIAL 2012; Caruso 1998; Chazot 2003; Fukami 2013; Higuchi 2014; Maruyama 2017; Mettang 1997; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Signorelli 2006; Sugiyama 2021; Vaux 2004).

Vascular access failure

The blinding of assessment for vascular access failure was graded as high risk for one study as the outcome assessor was non-blinded (Fukami 2013).

Peritoneal dialysis infection

The blinding of assessment for PD infection was graded as high risk for one study as the outcome assessor was non-blinded (Bonomini 2013).

Incomplete outcome data

Quality of life

Five studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Brass 2001 (A+B); Fukuda 2015; Hamedi-Kalajahi 2021; Rathod 2006; Vaux 2004). One study was judged to be at high risk for attrition bias as there was an imbalance in numbers for missing data across the intervention and the control group (Steiber 2006). Seven studies with incomplete outcome data were judged unclear (Bonomini 2006; CARNIDIAL 2012; Mettang 1997; Naini 2011; Semeniuk 2000; Sloan 1998a; Sloan 1998b).

Fatigue score

Two studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Brass 2001 (A+B); Fukuda 2015). Two studies with incomplete outcome data were judged unclear (Bonomini 2006; Saxena 2004).

Adverse events

Eleven studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Ahmad 1990; Brass 2001a; Brass 2001b; CARNIDIAL 2012; Chi 2021; Fukuda 2015; Higuchi 2014; Maruyama 2017; Mettang 1997; Mortazavi 2011a; Signorelli 2006). One study was judged to be at high risk for attrition bias as there was an imbalance in numbers for missing data across the intervention and control groups (Fukami 2013). Two studies with incomplete outcome data were judged unclear (Kletzmayr 1999; Mortazavi 2012).

Muscle symptoms

Seven studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Ahmad 1990; Arduini 2006; Bellinghieri 1983; Mettang 1997; Rathod 2006; Roozbeh 2007; Yano 2021). Three studies with incomplete outcome data were judged unclear (Saxena 2004; Semeniuk 2000; Zilleruelo 1993).

Anaemia-related markers

Twenty-four studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Arduini 2006; Bellinghieri 1983; Biolo 2008; Brass 2001a; Brass 2001b; CARNIDIAL 2012; Caruso 1998; Chazot 2003; Chi 2021; Cui 2016; Fu 2010; Fukuda 2015; Fu 2010; Higuchi 2014; Khodaverdi 2010; Maruyama 2017; Mettang 1997; Mortazavi 2011a; Naini 2011; Rathod 2006; Song 2013a; Sugiyama 2021; Vaux 2004; Yano 2021). Three studies were judged to be at high risk for attrition bias as there was an imbalance in numbers for missing data across the intervention and control groups (Mitwalli 2005; Pacheco 2008; Steiber 2006). Eleven studies with incomplete outcome data were judged unclear (Catalano 1999; Cibulka 2005; Garneata 2005; Harmankaya 2002a; Kletzmayr 1999; Labonia 1995; Mortazavi 2012; Saxena 2004; Semeniuk 2000; Sorge-Haedicke 2001; Trovato 1983).

Myocardial function

Eight studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Ahmad 1990; Arduini 2006; Fagher 1985; Higuchi 2014; Maruyama 2017; Rathod 2006; Sugiyama 2021; Vaux 2004). Five studies with incomplete outcome data were judged unclear (Abdul-Hassan Mahdi 2021; Ibarra-Sifuentes 2017; Kudoh 2013; Semeniuk 2000; Zilleruelo 1993).

Death

Fourteen studies were judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Ahmadi 2016; Bellinghieri 1983; CARNIDIAL 2012; Caruso 1998; Chazot 2003; Fukami 2013; Higuchi 2014; Maruyama 2017; Mettang 1997; Mortazavi 2011a; Naini 2011; Signorelli 2006; Sugiyama 2021; Vaux 2004). One study with incomplete outcome data was judged unclear (Mortazavi 2012).

Vascular access failure

One study was judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Fukami 2013).

Peritoneal dialysis infection

One study was judged to be at low risk for attrition bias because almost all the participants were followed up and missing outcome data balanced across the intervention and control groups (Bonomini 2013).

Selective reporting

All prespecified outcomes were reported in 15 studies and were judged to be at low risk of bias (Ahmadi 2016; Bonomini 2013; CARNIDIAL 2012; Fukami 2013; Fukuda 2015; Hamedi-Kalajahi 2021; Higuchi 2014; Ibarra-Sifuentes 2017; Khodaverdi 2010; Maruyama 2017; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Sugiyama 2021; Yano 2021). The remaining 37 studies were classified as unclear for reporting bias because their study protocol was not available.

Other potential sources of bias

We judged 11 studies to be at low risk of bias due to funding (Abdul-Hassan Mahdi 2021; Ahmadi 2016; Chi 2021; Cibulka 2005; Fu 2010; Fukami 2013; Hamedi-Kalajahi 2021; Mortazavi 2011a; Mortazavi 2012; Naini 2011; Song 2013a). Twenty-four studies were judged to be at high risk of bias because they were partly funded by a pharmaceutical company (Arduini 2006; Bellinghieri 1983; Biolo 2008; Bonomini 2006; Bonomini 2013; Brass 2001a; Brass 2001b; CARNIDIAL 2012; Caruso 1998; Fagher 1985; Fukuda 2015; Higuchi 2014; Kletzmayr 1999; Labonia 1995; Maruyama 2017; Mettang 1997; Pacheco 2008; Semeniuk 2000; Sloan 1998a; Sloan 1998b; Steiber 2006; Sugiyama 2021; Vaux 2004; Yano 2021). The risk of bias was judged to be unclear in the remaining 17 studies.

Evaluation of publication bias

We constructed a funnel plot to investigate potential publication bias. For anaemia-related markers (Hb, HCT, and EPO dose) and death (any cause), we found reasonable symmetry indicating a low risk of publication bias (Figure 4; Figure 5; Figure 6; Figure 7).

Figure 4.

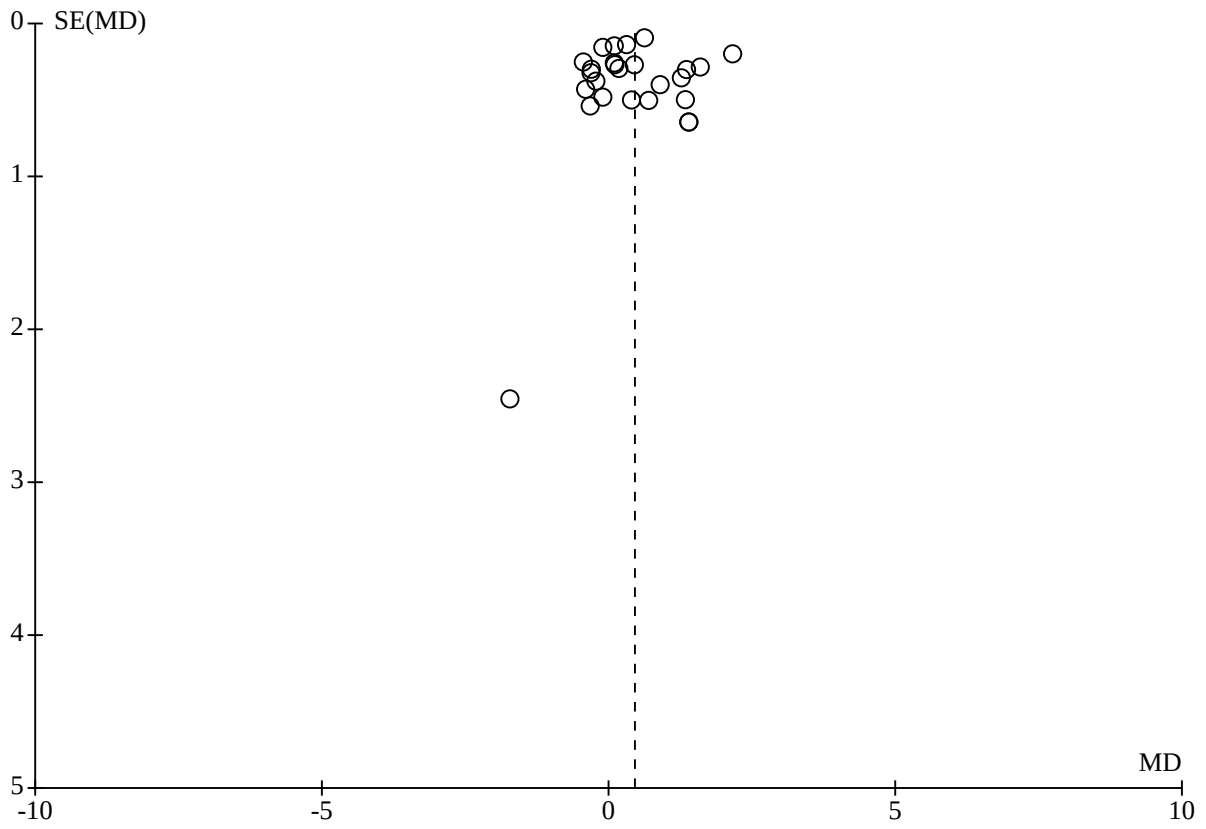


Figure 5.

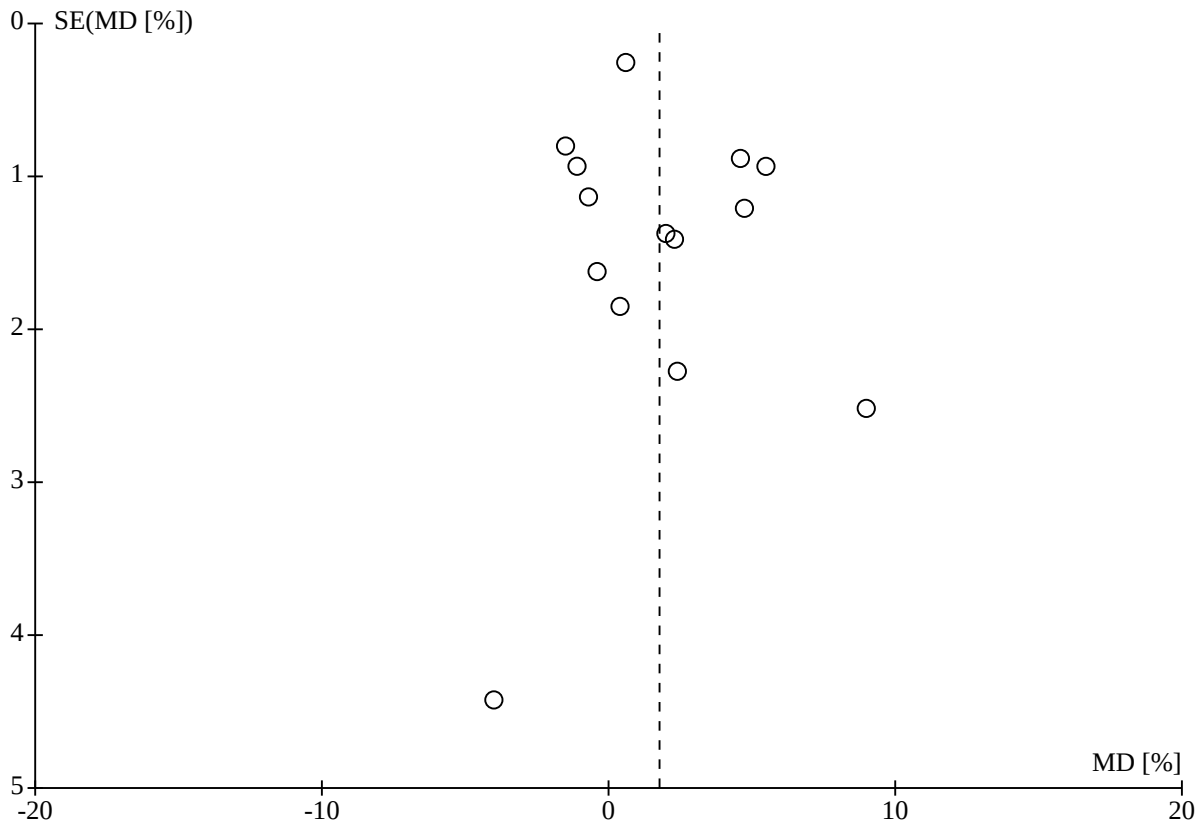


Figure 6.

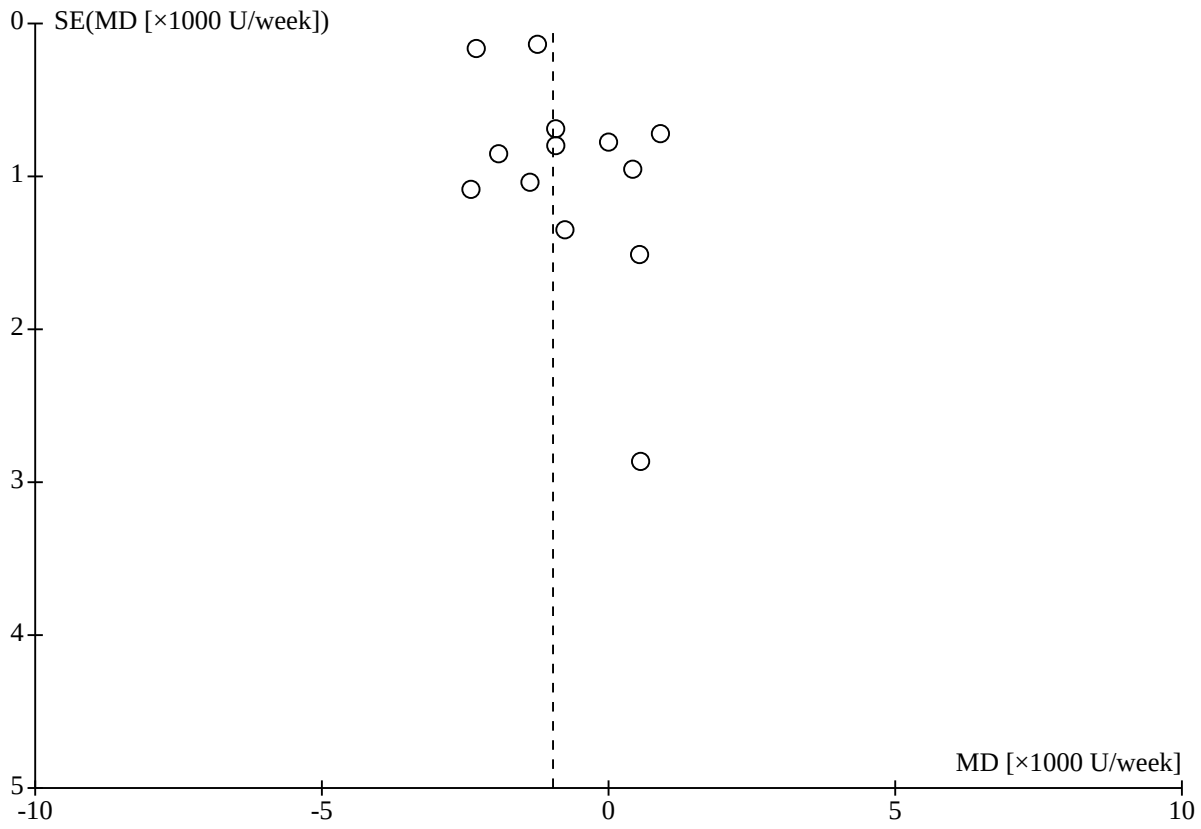
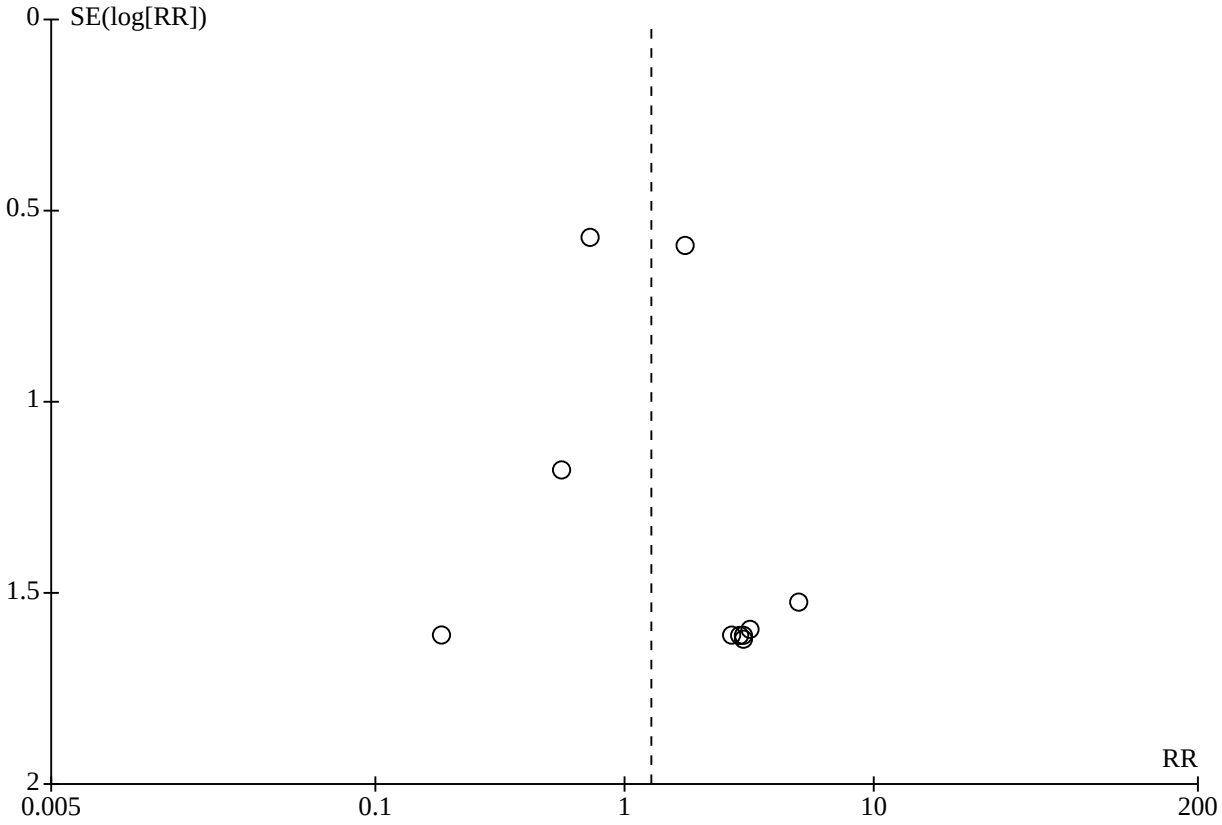


Figure 7.



Effects of interventions

See: **Summary of findings 1** Carnitine supplements versus control (placebo or standard care) for people with chronic kidney disease requiring dialysis

See Summary of findings 1 for L-carnitine supplementation versus control (placebo or standard care) for CKD patients requiring dialysis.

Quality of Life

Eleven studies reported this outcome (Bonomini 2006; Brass 2001 (A+B); CARNIDIAL 2012; Fukuda 2015; Hamedi-Kalajahi 2021; Naini 2011; Rathod 2006; Semeniuk 2000; Sloan 1998a; Steiber 2006; Vaux 2004). Six studies used the SF-36 QoL questionnaire. The SF-36 is a generic QoL measure that consists of eight domains (physical functioning, role-physical, bodily pain, general health, social functioning, vitality, role-emotional, and mental health) that are summarised in the physical component score (PCS) and mental component score (MCS). Four studies (CARNIDIAL 2012; Naini 2011; Rathod 2006; Steiber 2006) reported treatment effects on PCS and MCS scores in sufficient detail to be included in the meta-analysis. SMD was used as PCS and MCS were both reported on a 0 to 100 scale or norm-based scoring. Two studies (Fukuda 2015; Sloan 1998a) could not be incorporated into the meta-analysis as they did not report the SF-36 PCS and MCS. Sloan 1998a reported significant differences between groups in the general health and physical function domains, with improvements seen in the L-carnitine group. Fukuda 2015 reported no significant differences in each domain of the SF-36. The KDQOL questionnaire was used in three studies (Bonomini 2006; Brass 2001 (A+B); Semeniuk 2000). Of these, two studies (Bonomini 2006; Semeniuk 2000) reported no significant differences in scores; one study provided only the P values (Bonomini 2006), while Semeniuk 2000 did not report the data from the first period prior to cross-over. Thus, we could not incorporate these two studies into the meta-analysis. Vaux 2004 used VAS, and Hamedi-Kalajahi 2021 (a study in children) used PedsQL (Pediatric Quality of Life).

This outcome was quantitatively synthesised for each of the three indicators. We integrated SF-36 separately because the total score was not reported.

- L-carnitine may have little or no effect on the PCS (Analysis 1.1 (4 studies, 134 participants): SMD 0.57, 95% CI -0.15 to 1.28; I^2 = 73%; low certainty of evidence) but may improve the MCS (Analysis 1.2 (4 studies, 134 participants): SMD 0.70, 95% CI 0.22 to 1.18; I^2 = 42%; low certainty of evidence).
- L-carnitine may make little or no difference to the total QoL score (Kidney Disease Quality of Life (KDQOL), VAS (general well-being), or PedsQL) (Analysis 1.3 (3 studies, 230 participants): SMD -0.02, 95% CI -0.29 to 0.25; I^2 = 0%; low certainty of evidence).

Quality of life subgroup analyses

Physical component score

- Average L-carnitine dose: PCS improved in the ≥ 10 mg/kg/day group (Analysis 2.1.1 (1 study, 51 participants): SMD 1.13, 95% CI 0.53 to 1.73), but not in the < 10 mg/kg/day group (Analysis 2.1.2 (3 studies, 83 participants): SMD 0.34, 95% CI -0.45 to 1.13; I^2 = 66%) (Test for subgroup differences: Chi^2 = 2.43, df = 1 (P = 0.12), I^2 = 58.8%).
- Duration of treatment: PCS improved in the ≤ 6 months group (Analysis 2.2.1 (3 studies, 98 participants): SMD 0.89, 95% CI 0.39 to 1.38; I^2 = 24%), but not in the > 6 months group (Analysis 2.2.2 (1 study, 36 participants): SMD -0.31, 95% CI -0.99 to 0.38) (Test for subgroup differences: Chi^2 = 7.72, df = 1 (P = 0.005), I^2 = 87.0%).
- Route of administration: PCS improved in the oral administration group (Analysis 2.3.2 (1 study, 51 participants): SMD 1.13, 95% CI 0.53 to 1.73), but not in the IV administration group (Analysis 2.3.1 (3 studies, 83 participants): SMD 0.34, 95% CI -0.45 to 1.13; I^2 = 66%) (Test for subgroup differences: Chi^2 = 2.43, df = 1 (P = 0.12), I^2 = 58.8%).

Mental component score

- Average L-carnitine dose: MCS improved in the ≥ 10 mg/kg/day group (Analysis 2.4.1 (1 study, 51 participants): SMD 1.05, 95% CI 0.47 to 1.64), but was unclear in the < 10 mg/kg/day group (Analysis 2.4.2 (3 studies, 83 participants): SMD 0.53, 95% CI -0.03 to 1.10; I^2 = 34%) (Test for subgroup differences: Chi^2 = 1.58, df = 1 (P = 0.21), I^2 = 36.8%)
- Duration of treatment: MCS improved in the ≤ 6 months group (Analysis 2.5.1 (3 studies, 98 participants): SMD 0.84, 95% CI 0.25 to 1.42; I^2 = 44%), but not in the > 6 months group (Analysis 2.5.2 (1 study, 36 participants): SMD 0.32, 95% CI -0.36 to 1.01) (Test for subgroup differences: Chi^2 = 1.26, df = 1 (P = 0.26), I^2 = 20.6%)
- Route of administration: MCS improved in the oral administration group (Analysis 2.6.1 (1 study, 51 participants): SMD 1.05, 95% CI 0.47 to 1.64), but was unclear in the IV administration group (Analysis 2.5.2 (3 studies, 83 participants): SMD 0.53, 95% CI -0.03 to 1.10) (Test for subgroup differences: Chi^2 = 1.58, df = 1 (P = 0.21), I^2 = 36.8%)

Total quality of life score

There was no difference in the results based on the average dose, the route of administration (IV or oral), or participant age (≥ 18 years or < 18 years). Insufficient data for subgroup analysis by the other pre-planned items prevented these analyses.

Quality of life sensitivity analyses

We conducted sensitivity analyses excluding 1) studies based on the source of funding (industry) and 2) studies with a high risk of overall bias.

- One study with non-government organisation/not-for-profit funding showed an improvement in PSC with L-carnitine (Analysis 3.1 (1 study, 51 participants): MD 18.00, 95% CI 9.22 to 26.78).
- One study with non-government organisation/not-for-profit funding showed an improvement in MSC with L-carnitine (Analysis 3.2 (1 study, 51 participants): MD 20.60, 95% CI 9.90 to 31.30).
- One study at low risk of overall bias showed no significant differences between the two groups (Analysis 3.3 (1 study, 24 participants): MD 0.66, 95% CI -5.36 to 6.67).

No large, long, or unpublished studies were included in the analysis. For other pre-planned analyses, the data were insufficient for analyses.

Fatigue score

L-carnitine may have little or no effect on fatigue score (Analysis 1.4 (2 studies, 353 participants): SMD 0.01, 95% CI -0.20 to 0.23; I^2 = 0%; low certainty evidence).

Saxena 2004 reported that L-carnitine improved fatigue but did not provide the score value. Bonomini 2006 reported no significant difference in scores but only provided P values. Thus, these studies were excluded from the meta-analysis.

Fatigue score subgroup analyses

There were no differences in the results based on the route of administration (IV or oral) or whether the study used a single agent or had multiple components. No other pre-planned subgroup analyses could be undertaken.

Fatigue score sensitivity analysis

We conducted a sensitivity analysis excluding studies with a high risk of overall bias.

There were no significant differences in fatigue score (Analysis 3.4), similar to the findings of Analysis 1.4.

No large, long, or unpublished studies were included in the analysis. No other pre-planned subgroup analyses could be undertaken.

Adverse events

L-carnitine may make little or no difference to the risk of adverse events (Analysis 1.5 (12 studies, 1041 participants): RR, 1.14, 95% CI 0.86 to 1.51; I^2 = 0%; low certainty evidence).

Brass 2001a reported the total number of adverse events but did not report the number of patients experiencing any adverse events.

The adverse effects were not specific, including gastrointestinal symptoms (nausea, peculiar smell), hyperglycaemia, thirst, and hypertension, and there was no consistency in reporting adverse events.

Adverse events subgroup analyses

No differences were observed in results based on dialysis modality or method of intervention, average dose (< 10 mg/kg/day or ≥ 10 mg/kg/day), duration (≤ 6 months or > 6 months), route of administration (IV or oral), or single agent or multi-component.

No other pre-planned subgroup analyses could be undertaken

Adverse events sensitivity analysis

We conducted sensitivity analyses excluding 1) studies based on the source of funding (industry), 2) studies with a high risk of overall bias, and 3) studies published in languages other than English.

No significant differences in the incidence of adverse events for these sensitivity analyses (Analysis 3.5; Analysis 3.6; Analysis 3.7) and were similar to the results of Analysis 1.5.

No large, long, or unpublished studies were included in the analysis. For other pre-planned analyses, the data were insufficient for analyses.

Muscle symptoms

Cramps

L-carnitine may have little or no effect on muscle cramps (Analysis 1.6.1 (2 studies, 102 participants): RR, 0.44, 95% CI 0.18 to 1.09; I^2 = 23%; low certainty evidence).

Four studies (Bellinghieri 1983; Mettang 1997; Semeniuk 2000; Zilleruelo 1993) did not report the number of patients with cramps and reported this outcome in different formats. Thus, these studies were excluded from the meta-analysis. One study reported no differences in VAS scores (Mettang 1997), and two studies did not provide the number of patients or the score values (Bellinghieri 1983; Zilleruelo 1993). Semeniuk 2000 did not report data from the first period prior to cross-over.

No other pre-planned subgroup analyses could be undertaken

Weakness

L-carnitine may have little or no effect on muscle weakness (Analysis 1.6.2 (2 studies, 102 participants): RR, 0.77, 95% CI 0.47 to 1.25; I^2 = 0%; low certainty evidence). Six studies reported this outcome in different formats and were excluded from the meta-analysis (Arduini 2006; Mettang 1997; Roozbeh 2007; Saxena 2004; Yano 2021; Zilleruelo 1993). Two studies reported no significant differences in VAS scores (Arduini 2006; Mettang 1997), and two studies did not provide the number of patients or the score values (Roozbeh 2007; Saxena 2004). Yano 2021 reported that the 10-minute walk test and the chair stand test improved in L-carnitine-treated patients. Zilleruelo 1993 described a significant improvement in the muscle symptoms score in the L-carnitine group but did not report the data.

No other pre-planned subgroup analyses could be undertaken.

Anaemia-related markers

Haemoglobin

L-carnitine may improve Hb levels compared to control (Analysis 1.7 (26 studies, 1795 participants): MD 0.46 g/dL, 95% CI 0.18 to 0.74; I^2 = 86%; low certainty evidence). Two cross-over studies (Catalano 1999; Semeniuk 2000) reported no significant differences in Hb levels; however, they did not report the data from the first period prior to cross-over. Thus, these studies were excluded from the meta-analysis.

Haemoglobin subgroup analyses

- Dialysis modality: Hb levels increased in HD patients (Analysis 2.17.1 (25 studies, 1740 participants): MD 0.48 g/dL, 95% CI 0.20 to 0.77; I^2 = 86%) but not in PD patients (Analysis 2.17.2 (1 study, 55 participants): MD -0.32 g/dL, 95% CI -1.38 to 0.74) (Test for subgroup differences: Chi^2 = 2.07, df = 1 (P = 0.15), I^2 = 51.8%).
- Average L-carnitine dose: Hb levels increased in the < 10 mg/kg/day group (Analysis 2.18.2 (18 studies, 1199 participants): MD 0.50 g/dL, 95% CI 0.16 to 0.83; I^2 = 86%), but not in the ≥ 10 mg/kg/day group (Analysis 2.18.1 (8 studies, 596 participants): MD 0.39 g/dL, 95% CI -0.14 to 0.92; I^2 = 85%) (Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 = 0%)
- Duration of treatment: Hb levels increased in the ≤ 6 months group (Analysis 2.19.1 (20 studies, 1119 participants): MD 0.55 g/dL, 95% CI 0.19 to 0.91; I^2 = 87%), but not in the > 6 months group (Analysis 2.19.2 (6 studies, 676 participants): MD 0.21 g/dL, 95% CI -0.11 to 0.54; I^2 = 64%) (Test for subgroup differences: Chi^2 = 1.82, df = 1 (P = 0.18), I^2 = 45.1%).
- Route of administration: there was no difference in the results based on the route of administration (IV or oral) (Analysis 2.20) (Test for subgroup differences: Chi^2 = 0.34, df = 1 (P = 0.56), I^2 = 0%).
- Single or multi-component agent: Hb levels increased with single agents (Analysis 2.21.1 (25 studies, 1622 participants): MD 0.49 g/dL, 95% CI 0.20 to 0.78; I^2 = 85%) but not with multi-component agents (Analysis 2.21.2 (1 study, 173 participants): MD -0.10, 95% CI -0.41 to 0.21) (Test for subgroup differences: Chi^2 = 7.57, df = 1 (P = 0.006), I^2 = 86.8%).

No other pre-planned subgroup analyses could be undertaken.

Haematocrit

L-carnitine may improve HCT values compared to control (Analysis 1.8 (14 studies, 950 participants): MD 1.78%, 95%, CI 0.38 to 3.18; I^2 = 84%; low certainty evidence).

Haematocrit subgroup analyses

- Average L-carnitine dose: HCT increased in the < 10 mg/kg/day group (Analysis 2.22.2 (11 studies, 741 participants): MD 2.07%, 95% CI 0.52 to 3.62; I^2 = 82%), but not in the ≥ 10 mg/kg/day group (Analysis 2.22.1 (3 studies, 209 participants): MD 1.18%, 95% CI -2.59 to 4.96; I^2 = 87%) (Test for subgroup differences: Chi^2 = 0.18, df = 1 (P = 0.67), I^2 = 0%).
- There was no difference in the results based on intervention duration (Analysis 2.23) or route of administration (Analysis 2.24).

No other pre-planned subgroup analyses could be undertaken.

Erythropoietin dose

L-carnitine may reduce the required EPO dose compared to control (Analysis 1.9 (13 studies, 967 participants): MD -0.97 × 1000 U/week, 95% CI -1.59 to -0.34; I^2 = 77%; low certainty evidence).

Semeniuk 2000 reported no significant differences in Hb but did not report the data from the first period and was excluded from the meta-analysis.

Erythropoietin dose subgroup analyses

- Average L-carnitine dose: EPO dose was reduced in the < 10 mg/kg/day group (Analysis 2.25.2 (8 studies, 720 participants): MD -1.09 ×1000 U/week, 95% CI -1.84 to -0.35; I^2 = 84%), but not in the ≥ 10 mg/kg/day group (Analysis 2.25.1 (5 studies, 247 participants): MD -0.69 × 1000 U/week, 95% CI -1.67 to 0.28; I^2 = 8%) (Test for subgroup differences: Chi^2 = 0.41, df = 1 (P = 0.52), I^2 = 0%).
- Route of administration: EPO dose was reduced in the IV group (Analysis 2.27.1 (11 studies, 891 participants): MD -1.03 × 1000

U/week, 95% CI -1.70 to -0.35; I^2 = 80%), but not in the oral group (Analysis 2.27.2 (2 studies, 76 participants): MD -0.60 × 1000 U/week, 95% CI -1.99 to -0.78; I^2 = 0%) (Test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.59), I^2 = 0%).

- There was no difference in the results based on the intervention duration (Analysis 2.26).

No other pre-planned subgroup analyses could be undertaken.

Erythropoietin dose sensitivity analysis

Sensitivity analysis was conducted after excluding studies that borrowed body weight or SD values from other studies. This sensitivity analysis (Analysis 3.8) showed similar findings to Analysis 1.9.

Erythropoietin resistance index

L-carnitine may make little or no difference to the EPO resistance index (Analysis 1.10 (5 studies, 343 participants): MD -1.56, 95% CI -3.59 to 0.46; I^2 = 60%; low certainty evidence).

Erythropoietin resistance index subgroup analyses

- Average L-carnitine dose: EPO resistance index was reduced in the ≥ 10 mg/kg/day group (Analysis 2.28.1 (2 studies, 208 participants): MD -2.17, 95% CI -3.13 to -1.11; I^2 = 0%), but not in the < 10 mg/kg/day group (Analysis 2.28.2 (2 studies, 107 participants): MD 1.21, 95% CI -7.63 to 10.05; I^2 = 88%) (Test for subgroup differences: Chi^2 = 0.55, df = 1 (P = 0.46), I^2 = 0%).
- Route of administration: EPO resistance index was reduced in the oral group (Analysis 2.29.2 (1 study, 148 participants): MD -2.00, 95% CI -3.10 to -0.90), but not in the IV group (Analysis 2.29.1 (4 studies, 195 participants): MD -0.71, 95% CI -4.25 to 2.83; I^2 = 70%) (Test for subgroup differences: Chi^2 = 0.47, df = 1 (P = 0.50), I^2 = 0%).

No other pre-planned subgroup analyses could be undertaken.

Myocardial function

Intradialytic hypotension

L-carnitine may make little or no difference to intradialytic hypotension (Analysis 1.11 (3 studies, 128 participants): RR, 0.76, 95% CI 0.34 to 1.69; I^2 = 0%; low certainty evidence).

Five studies (Arduini 2006; Ibarra-Sifuentes 2017; Kudoh 2013; Semeniuk 2000; Zilleruelo 1993) reported an improvement in the intradialytic hypotension but did not report the number of patients. Zilleruelo 1993 described intradialytic hypotension but did not report the results. Semeniuk 2000 did not report data from the first period prior to cross-over.

Subgroup analysis

There were no differences in the results based on the average dose of L-carnitine (Analysis 2.30). No other pre-planned subgroup analyses could be undertaken.

Left ventricular mass

L-carnitine may prevent left ventricular mass hypertrophy compared to control (Analysis 1.12 (3 studies, 217 participants): MD -7.18 g/m^2, 95% CI -14.24 to -0.13; I^2 = 0%; low certainty evidence).

Left ventricular subgroup analyses

- Average L-carnitine dose: left ventricular mass was reduced in the ≥ 10 mg/kg/day group (Analysis 2.32.1 (2 studies, 166 participants): MD -7.72 g/m^2, 95% CI -15.1 to -0.34; I^2 = 0%), but not in the < 10 mg/kg/day group (Analysis 2.32.2 (1 study, 51 participants): MD -1.40 g/m^2, 95% CI -25.53 to 22.73; I^2 = 0%) (Test for subgroup differences: Chi^2 = 0.24, df = 1 (P = 0.62), I^2 = 0%).
- Duration of treatment: left ventricular mass was reduced in the > 6 months group (Analysis 2.33.2 (2 studies, 199 participants): MD -7.38 g/m^2, 95% CI -14.76 to -0.01; I^2 = 0%), but not in the ≤ 6 months group (Analysis 2.33.1 (1 study, 18 participants): MD -5.00 g/dL, 95% CI -29.27 to 19.27) (Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.85), I^2 = 0%).
- Route of administration: left ventricular mass was reduced in the oral group (Analysis 2.34.2 (2 studies, 166 participants): MD -7.72 g/m^2, 95% CI -15.1 to -0.34; I^2 = 0%), but not in the IV group (Analysis 2.34.1 (1 study, 51 participants): MD -1.40 g/m^2, 95% CI -25.53 to 22.73; I^2 = 0%) (Test for subgroup differences: Chi^2 = 0.24, df = 1 (P = 0.62), I^2 = 0%).

No other pre-planned subgroup analyses could be undertaken.

Ejection fraction

L-carnitine may improve the ejection fraction compared to control (Analysis 1.13 (6 studies, 410 participants): MD 2.26%, 95% CI -0.26 to 4.79; I^2 = 64%; low certainty evidence).

Ejection fraction subgroup analyses

- Average L-carnitine dose: ejection fraction increased in the ≥ 10 mg/kg/day group (Analysis 2.35.1 (3 studies, 271 participants): MD 4.68%, 95% CI 3.17 to 6.19; I^2 = 0%), but not in the < 10 mg/kg/day group (Analysis 2.35.2 (3 studies, 139 participants): MD -0.45%, 95% CI -2.95 to 2.04; I^2 = 0%) (Test for subgroup differences: Chi^2 = 11.91, df = 1 (P = 0.0006), I^2 = 91.6%).
- Route of administration: ejection fraction increased in the oral group (Analysis 2.37.2 (2 studies, 166 participants): MD 5.15%, 95% CI 3.28 to 7.02; I^2 = 0%), but not in the IV group (Analysis 2.37.1 (4 studies, 244 participants): MD 1.03%, 95% CI -1.76 to 3.81; I^2 = 53%) (Test for subgroup differences: Chi^2 = 5.80, df = 1 (P = 0.02), I^2 = 82.8%).
- There was no difference in the results based on the duration of the intervention (Analysis 2.36).

No other pre-planned subgroup analyses could be undertaken.

Death

Death (any cause)

L-carnitine may make little or no difference to the risk of death (any cause) compared to control (Analysis 1.14 (13 studies, 857 participants): RR 1.28, 95% CI 0.68 to 2.43; I^2 = 0%; low certainty evidence).

Death (any cause) subgroup analysis

There were no differences in results based on dialysis modality (Analysis 2.38), average L-carnitine dose (Analysis 2.39), duration of the intervention (Analysis 2.40), or route of administration (Analysis 2.41). No other pre-planned subgroup analyses could be undertaken.

Death (cardiovascular)

L-carnitine may make little or no difference to the risk of cardiovascular death compared to control (Analysis 1.15 (5 studies, 444 participants): RR, 0.97, 95% CI 0.30 to 3.19; $I^2 = 0\%$; low certainty evidence).

Cardiovascular death subgroup analysis

There were no differences in results based on average L-carnitine dose (Analysis 2.42), duration or intervention (Analysis 2.43), or route of administration (Analysis 2.44). No other pre-planned subgroup analyses could be undertaken.

Vascular access failure

L-carnitine may make little or no difference to the risk of vascular access failure compared to control (Analysis 1.16 (1 study, 102 participants): RR, 1.33, 95% CI 0.13 to 13.34; low certainty evidence).

Pre-planned subgroup analyses could not be undertaken.

Peritoneal dialysis infection

L-carnitine may make little or no difference to the risk of PD infection compared to control (Analysis 1.17 (1 study, 35 participants): RR, 1.33, 95% CI 0.13 to 13.34; low certainty evidence).

Pre-planned subgroup analyses could not be undertaken.

Technique survival

This outcome was not reported by any of the included studies.

Life participation

This outcome was not reported by any of the included studies.

DISCUSSION

Summary of main results

This review included 52 studies (3398 randomised participants) that compared carnitine supplements to placebo or standard care in CKD patients requiring dialysis.

L-carnitine may make little or no difference to SF-36 PCS and total QoL score but may improve SF-36 MCS; however, the studies were limited by high selection and attrition bias. L-carnitine may have little or no effect on fatigue score, muscle cramps, and muscle weakness (low certainty evidence). L-carnitine may increase Hb and HCT, may reduce the required dose of EPO, and may make little or no difference to the EPO resistance index (low certainty evidence). L-carnitine may prevent left ventricular mass hypertrophy and improve ejection fraction but may make little or no difference to intradialytic hypotension (low certainty evidence). L-carnitine may make little or no difference to death (any cause or cardiovascular), adverse events, vascular access failure, and PD infection.

Overall completeness and applicability of evidence

We performed a comprehensive systematic search of the Cochrane Kidney and Transplantation Specialised Register. The analyses included studies with participants receiving HD and PD. Our approach yielded evidence for three primary outcomes and six secondary outcomes. However, as our prespecified outcomes of interest were often not reported, we were only able to present limited evidence for a few outcomes in each comparison. This meta-analysis included 52 studies; however, the number of studies reporting our outcomes of interest ranged from one to 26 studies. Five cross-over studies did not provide data for the first phase (i.e. before cross-over); therefore, we could not incorporate these studies into our meta-analyses.

Moreover, for some outcomes, we could not perform predetermined subgroup or sensitivity analyses due to the limited availability of data. We also recognise that the applicability of our review evidence is limited, as the majority of the included studies were conducted more than 10 years ago. Clinical practice for the treatment of patients undergoing dialysis has changed over the years, and these differences in practice may reduce the external validity of our findings.

Quality of the evidence

We graded the certainty of evidence by using the GRADE approach (GRADE 2008). As shown in the Summary of findings 1, we assessed the overall certainty of the evidence as low certainty in this review. We rated the certainty of QoL, fatigue score, adverse events, muscle cramps, and intradialytic hypotension as low because of serious issues with risks of bias and serious imprecision. The certainty of the evidence for anaemia-related markers (Hb, HCT) was also rated low because of serious issues with risks of bias and considerable heterogeneity between the included studies. We were unable to perform pre-planned subgroup analyses on iron storage parameters and could not clearly identify the sources of heterogeneity of the results of anaemia markers.

Nine included studies were only available as conference abstracts. We were unable to obtain additional information on these studies from the authors. The analysis of the included studies was difficult due to the lack of important methodological details. Thus, there might be potential biases influenced by data availability or publication status.

Potential biases in the review process

For this review, we conducted a comprehensive search of the Cochrane Kidney and Transplant Specialised Register, which reduced the possibility of exclusion of potentially eligible studies. However, some studies, such as unpublished data and studies with negative or no effects, may not have been identified. Eligible studies published since the date of the last search may have been missed.

The key limitation of this review is the data provided by available studies. Selective outcome reporting limited the number of included studies and participants. Different tools for assessing QoL prevented the meta-analysis of some data. We also considered the integration of results by inconsistent reporting of adverse events as one of the limitations in the interpretation of this systematic review. Moreover, some subgroup analyses were planned to explore potential sources of heterogeneity in our review; however, the lack of data pertaining to patient ethnicity, iron storage parameters (serum ferritin and transferrin saturation), and co-prescription (iron, renin-angiotensin-aldosterone system inhibitors) prevented us from performing these analyses. These analyses should be repeated when such data are available.

Agreements and disagreements with other studies or reviews

The findings of this review suggest that carnitine supplements may have little or no effect on improving QoL (except for SF-36 MCS), muscle cramps, and intradialytic hypotension in CKD patients requiring dialysis. This finding is consistent with the results of two previous systematic reviews (Chen 2014; Yang 2014). However, there were some differences between the results of our systematic review and these reviews. Our systematic review assessed the effects of L-carnitine on myocardial function (left ventricular mass and ejection fraction) and death, which had not been evaluated in the previous meta-analyses. Previous studies had failed to show any favourable effect of L-carnitine on anaemia-related markers (Hb and the required EPO dose). Our meta-analysis shows L-carnitine may improve anaemia-related markers (Hb, HCT, and the required EPO dose), albeit with low certainty evidence. One reason for these differences may be the variations in the studies included in this review. In particular, we included 13 studies published since 2012, which were not included in the studies by Chen 2014 and Yang 2014. Additionally, some non-RCTs were included in the previous meta-analyses, and these studies may have influenced the overall estimate of the effects on anaemia-related markers.

AUTHORS' CONCLUSIONS

Implications for practice

The current review found that carnitine supplementation may have little or no effect on the symptoms of dialysis-related carnitine deficiency (QoL, fatigue, muscle cramps, and intradialytic hypotension), with low certainty evidence. There is low certainty evidence suggesting that carnitine supplementation may improve anaemia-related markers (Hb and HCT). Moreover, carnitine supplementation does not appear to have any adverse effects. Nonetheless, this review could not definitively establish the effectiveness or safety of carnitine supplementation because of the limited evidence.

Implications for research

Additional well-designed RCTs are required to make a more comprehensive assessment of carnitine supplements before they can be recommended for clinical practice. Most of the current studies were small, with a high risk of bias (especially selection and reporting bias), and high-quality, large-scale RCTs are necessary. Additionally, since most studies involved only HD and adult patients, more studies in PD and paediatric patients are needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdul-Hassan Mahdi 2021

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: August 2019 to March 2020 • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Iraq • Setting: teaching hospital (1 site) • Inclusion criteria: CKD on regular HD • Randomised number (intervention 1/intervention 2/control): 35/35/35 • Dialysis modality: HD • Age range: 22 to 65 years • Sex (M/F): intervention group 1 (20/15); intervention group 2 (21/14); control group (22/13) • Dialysis duration: not reported • Exclusion criteria: unclear
Interventions	Intervention group 1

Abdul-Hassan Mahdi 2021 *(Continued)*

	• L-carnitine (IV): 10 mg/kg once/day for 6 months Intervention group 2 • L-carnitine (IV): 10 mg/kg twice/day for 6 months Control group • Standard care
Outcomes	Outcomes relevant to this review • Myocardial function: ejection fraction
Notes	Other information • Funding source: not reported • All patients had 2 sessions of HD/week, and each dialysis session lasted 3 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Low risk	The study appears to be free of other sources of bias

Ahmad 1990

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months
Participants	Baseline characteristics

Ahmad 1990 *(Continued)*

- Country: USA
- Setting: multicentre (4 sites)
- Inclusion criteria: stable maintenance HD patients; > 18 years, dialysis duration > 9 months; prognosis to survive for the duration of the study; no imminent prospect of kidney transplant
- Randomised number (intervention/control): 47/50
- Dialysis modality: HD
- Mean age ± SD (years): intervention group (47.5 ± 15.4); control group (48.0 ± 15.9)
- Sex (M/F): intervention group (24/14); control group (27/17)
- Dialysis duration (mean ± SD) years: intervention group (3.47 ± 2.35); control group (3.35 ± 1.9)
- Exclusion criteria: medical instability; previous unreliable behaviour patterns; diabetes; endocrinopathies known to interfere with lipid metabolism; known genetic defects in lipid metabolism; previous or current carnitine therapy; class IV angina; liver failure; malignant hypertension; lipid-lowering drug therapy; high likelihood of imminent living donor transplantation; malignancies other than basal cell carcinomas of the skin

Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 6 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Muscle symptoms • Intradialytic hypotension
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized separately at each study center into treatment or control groups using a modified 4 × 4 Latin square. Patients were stratified by sex."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind placebo-controlled" study

Ahmad 1990 *(Continued)*

Incomplete outcome data (attrition bias) Adverse events	Low risk	Quote: "These dropouts occurred for the following reasons: transplantation (2 carnitine, 2 placebo); noncompliance (2 carnitine); patient's request (5 carnitine, 4 placebo). Six of the patients requesting dropout did so during the baseline period (3 from each group)." Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Muscle symptoms	Low risk	Quote: "These dropouts occurred for the following reasons: transplantation (2 carnitine, 2 placebo); noncompliance (2 carnitine); patient's request (5 carnitine, 4 placebo). Six of the patients requesting dropout did so during the baseline period (3 from each group)." Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Myocardial function	Low risk	Quote: "These dropouts occurred for the following reasons: transplantation (2 carnitine, 2 placebo); noncompliance (2 carnitine); patient's request (5 carnitine, 4 placebo). Six of the patients requesting dropout did so during the baseline period (3 from each group)." Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Ahmadi 2016

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: September 2013 to June 2014 • Study follow-up: 12 weeks
Participants	Baseline characteristics • Country: Iran • Setting: multicentre (3 sites) • Inclusion criteria: > 20 years; HD for at least 1 year • Randomised number (intervention/control): 25/25 • Dialysis modality: HD • Mean age ± SD (years): intervention group (64.4 ± 12.9); control group (62.1 ± 10.2) • Sex (M/F): not reported • Mean dialysis duration ± SD (years): intervention group (3.47 ± 2.35); control group (3.35 ± 1.9) • Exclusion criteria: infectious, liver, thyroid, or cancer disease; receiving L-carnitine at least 8 weeks prior to the start of the study; on corticosteroids
Interventions	Intervention group • L-carnitine (oral): 1000 mg/day for 12 weeks Control group • Standard care

Ahmadi 2016 *(Continued)*

Outcomes	Outcomes relevant to this review • Muscle weakness • Death (any cause)
Notes	Funding source: Shahid Sadoughi University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were divided by random allocation using random numbers table into 2 the carnitine group and the control group."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Death	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Death	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Quote. "This study was supported by the Shahid Sadoughi University of Medical Sciences"

Arduini 2006

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: UK • Setting: not reported • Inclusion criteria: stable HD patients with secondary carnitine deficiency • Randomised number (intervention/control): 14/15 • Dialysis modality: HD • Mean age ± SD (years): not reported • Sex (M/F): not reported • Mean dialysis duration ± SD (years): not reported

Arduini 2006 *(Continued)*

	• Exclusion criteria: Hb < 8 g/dL in past 2 months; change in rHuEPO dose in previous 4 weeks; serum ferritin < 200mg/L; URR < 65%; PTH > 60 pmol/L; BP > 160/105 mm Hg; bodyweight > 100 kg; presence of an infection, malignancy, or extrarenal cause of anaemia
Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, HCT • Intradialytic hypotension
Notes	Funding source: not clearly reported, but the first author is the Director of the Research and Development Department of Iperboreal Pharma Srl

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Muscle symptoms	Low risk	Missing outcome data balanced in numbers across intervention groups Quote: "Two placebo patients withdrew (one underwent transplantation, one due to abdominal pain), and one LC patient receiving a blood transfusion was excluded from the analysis."
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups Quote: "Two placebo patients withdrew (one underwent transplantation, one due to abdominal pain), and one LC patient receiving a blood transfusion was excluded from the analysis."
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across intervention groups

Arduini 2006 *(Continued)*

Myocardial function		Quote: "Two placebo patients withdrew (one underwent transplantation, one due to abdominal pain), and one LC patient receiving a blood transfusion was excluded from the analysis."
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: not clearly reported, but the first author is the Director of the Research and Development Department of Iperboreal Pharma Srl

Bellinghieri 1983

Study characteristics	
Methods	Study characteristics • Study design: cross-over RCT • Study duration: not reported • Study follow-up: 8 weeks
Participants	Baseline characteristics • Country: UK • Setting: not reported • Inclusion criteria: HD patients • Randomised number (intervention/control): 7/7 • Dialysis modality: HD • Mean age ± SD (years): 49.0 ± 15.0 • Sex (M/F): intervention group (4/3); control group (5/2) • Mean dialysis duration ± SD (months): 23 ± 15 • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (oral): 1000 mg/day for 8 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Muscle symptoms
Notes	Funding source: not clearly reported, but L-carnitine was supplied by Sigma-Tau, SpA, Pomezia, Rome, Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Bellinghieri 1983 *(Continued)*

Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind" study
Incomplete outcome data (attrition bias) Muscle symptoms	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Death	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: not clearly reported, but L-carnitine was supplied by Sigma-Tau, SpA, Pomezia, Rome, Italy

Biolo 2008

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 2 weeks
Participants	Baseline characteristics • Country: Italy • Setting: university hospital and private hospital (2 sites) • Inclusion criteria: 18 and 75 years; ESKD; regular HD 3 times/week for at least 6 months; equilibrated Kt/V above 1.2; absence of DM on the basis of fasting blood glucose or oral glucose tolerance test where appropriate; stable clinical condition during the 4 weeks immediately prior to baseline as demonstrated by medical history, physical examination and laboratory testing; Hb > 9.5 g/dL • Randomised number (intervention/control): 9/10 • Dialysis modality: HD • Mean age ± SD (years): intervention group (63 ± 3); control group (57 ± 4)

Biolo 2008 *(Continued)*

	• Sex (M/F): intervention group (2/7); control group (1/9) • Mean dialysis duration ± SD (months): intervention group (75 ± 33); control group (104 ± 32) • Exclusion criteria: immunosuppressant, glucocorticoid, androgen or thyroid hormone therapy in the 6 months immediately prior to entering the protocol; significant comorbidities - abnormal liver function test, alcohol abuse, infections, moderate-severe CHF (NYHA class III and IV), central nervous system diseases, cancer, and immunologic diseases
Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb
Notes	Funding source: Medications were prepared by Sigma-Tau i.f.r. S.p.A. Rome, Italy; This study was supported by grants from Ministero Universita` Ricerca Scientifica e Tecnologica PRIN 2001 and 2003 and Sigma Tau SpA (Pomezia, Italy)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: Medications were prepared by Sigma-Tau i.f.r. S.p.A. Rome, Italy; This study was supported by grants from Ministero Universita` Ricerca Scientifica e Tecnologica PRIN 2001 and 2003 and Sigma Tau SpA (Pomezia, Italy).

Bonomini 2006

Study characteristics

Bonomini 2006 *(Continued)*

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: Italy • Setting: dialysis centres (52 sites) • Inclusion criteria: HD patients with left ventricular hypertrophy • Number randomised (intervention 1/intervention 2/control): 106/117/107 • Dialysis modality: HD • Mean age ± SD (years): not reported • Sex (M/F): not reported • Dialysis duration: not reported • Exclusion criteria: unclear
Interventions	Intervention group 1 • L-carnitine (IV): 3 mg/kg at each dialysis session for 24 weeks Intervention group 2 • L-carnitine (IV): 6 mg/kg at each dialysis session for 24 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Fatigue score: fatigue domain of KDQ • Other domains of the KDQ including frustration, depression, relationship, and total score
Notes	Other information • Abstract-only publication • Funding source: Grant/Research Support: Sigma-Tau S.p.A.; Other: One of the authors is an employee of Sigma-Tau S.p.A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study

Bonomini 2006 *(Continued)*

Blinding of outcome assessment (detection bias) Fatigue score	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Quote: "Thirty-one patients dropped out, mainly due to kidney transplantation (N=13) or informed consent withdrawal (N=10)." Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Fatigue score	Unclear risk	Quote: "Thirty-one patients dropped out, mainly due to kidney transplantation (N=13) or informed consent withdrawal (N=10)." Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Funding source: Grant/Research Support: Sigma-Tau S.p.A.; Other: Sigma-Tau S.p.A.; R. Camerini is an employee of Sigma-Tau S.p.A.

Bonomini 2013

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 120 days
Participants	Baseline characteristics • Country: Italy • Setting: dialysis centres (8 sites) • Inclusion criteria: stable patients with ESKD; ≥ 18 years; CAPD therapy for at least 3 months • Randomised number (intervention/control): 21/14 • Dialysis modality: PD • Mean age ± SD (years): intervention group (56 ± 13); control group (62 ± 12) • Sex (M/F): intervention group (8/11); control group (5/9) • Mean dialysis duration ± SD (years): intervention group (24 ± 17); control group (29 ± 32) • Exclusion criteria: received L-carnitine or its derivatives in the previous month or experienced a peritonitis episode in the last 3 months; type 2 diabetes, Hb < 8.5 g/day; severe diseases or acute infectious conditions; treatment with drugs affecting insulin sensitivity; history of epilepsy or central nervous system disease; pregnancy or lactation; life expectancy < 12 months
Interventions	Intervention group • L-carnitine (IP): 2000 mg/day for 120 days Control group • Standard glucose-based solution Co-intervention • PD solutions containing glucose (1.5 or 2.5%, w/v)

Bonomini 2013 *(Continued)*

Outcomes	Outcomes relevant to this review • PD infection
Notes	Other information • Funding source: The study was supported in part by CoreQuest and Baxter Healthcare. Sponsors had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication • One of the authors is an employee of Baxter Healthcare. Another of the authors is an employee of CoreQuest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The random allocation of patients was made in blocks composed of 2 intervention and 2 control participants sequentially allocated to each center"; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Only states the study was randomised, does not ensure how allocation concealment was done
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Peritoneal dialysis infection	High risk	The outcome is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Peritoneal dialysis infection	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	Funding source: The study was supported in part by CoreQuest and Baxter Healthcare. Sponsors had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication One of the authors is an employee of Baxter Healthcare. Another one of the authors is an employee of CoreQuest

Brass 2001 (A+B)

Study characteristics

Methods	Study A characteristics • Study design: parallel RCT (2-arm) • Study duration: not reported • Study follow-up: 24 weeks

Brass 2001 (A+B) *(Continued)*

	Study B characteristics • Study design: parallel RCT (4-arm) • Study duration: not reported • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: USA • Setting: dialysis centres (12 sites) • Inclusion criteria: ESKD, HD 3 times/week for at least 6 months; ≥ 18 years; medical suitability to undergo graded ergometer exercise testing • Randomised number (intervention/control): 30/30 • Dialysis modality: HD • Mean age, range (years): intervention group (42, 19 to 76); control group (45, 23 to 64) • Sex (M/F): intervention group (16/12); control group (16/12) • Dialysis duration (mean, range) years: intervention group (4.1, 0.6 to 23.1); control group (3.8, 0.8 to 23.6) • Exclusion criteria: claudication; medical condition that precluded safe performance of maximal exercise testing; inability to cooperate with exercise testing; use of immunosuppressives, growth hormones, androgens, or anabolic steroids within the 3 months before study entry
Interventions	Study A Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Control group • Placebo Study B Intervention group 1 • L-carnitine (IV): 10 mg/kg at each dialysis session for 24 weeks Intervention group 2 • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Intervention group 3 • L-carnitine (IV): 40 mg/kg at each dialysis session for 24 weeks Control • Placebo
Outcomes	Outcomes relevant to this review • QoL: KDQ • Fatigue: KDQ-fatigue • Adverse events • Anaemia-related markers: Hb, HCT
Notes	Data were combined for QoL and fatigue and have been used in this combined study Funding source: supported in part by Sigma Tau Pharmaceuticals

Brass 2001a

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT (2-arm) • Study duration: not reported • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: USA • Setting: dialysis centres (12 sites) • Inclusion criteria: ESKD, HD 3 times/week for at least 6 months; > 18 years; medical suitability to undergo graded ergometer exercise testing • Randomised number (intervention/control): 30/30 • Dialysis modality: HD • Mean age, range (years): intervention group (42, 19 to 76); control group (45, 23 to 64) • Sex (M/F): intervention group (16/12); control group (16/12) • Dialysis duration (mean, range) years: intervention group (4.1, 0.6 to 23.1); control group (3.8, 0.8 to 23.6) • Exclusion criteria: claudication; medical condition that precluded safe performance of maximal exercise testing; inability to cooperate with exercise testing; use of immunosuppressives, growth hormones, androgens, or anabolic steroids within the 3 months before study entry
Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb, HCT
Notes	Funding source: Supported in part by Sigma Tau Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind placebo-controlled" study

Brass 2001a *(Continued)*

QoL

Blinding of outcome assessment (detection bias) Fatigue score	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Fatigue score	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Adverse events	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: Supported in part by Sigma Tau Pharmaceuticals

Brass 2001b

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT (4-arm) • Study duration: not reported • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: USA • Setting: dialysis centres (12 sites) • Inclusion criteria: ESKD; HD treatment 3 times/week for at least 6 months; > 18 years; medical suitability to undergo graded ergometer exercise testing • Randomised number (total): 133 • Analysed number (intervention 1/intervention 2/intervention 3/control): 32/30/32/33 • Dialysis modality: HD • Mean age, range (years): intervention group 1 (48, 27 to 76); intervention group 2 (48, 26 to 76); intervention group 3 (46, 25 to 79); control group (43, 24 to 67)

Brass 2001b *(Continued)*

- Sex (M/F): intervention group 1 (21/11); intervention group 2 (24/6); intervention group 3 (35/11); control group (20/13)
- Dialysis duration (mean, range) years: intervention groups (4.1, 0.6 to 23.1); control group (3.8, 0.8 to 23.6)
- Exclusion criteria: claudication; medical condition that precluded safe performance of maximal exercise testing; inability to cooperate with exercise testing; use of immunosuppressives, growth hormones, androgens, or anabolic steroids within the 3 months before study entry

Interventions	Intervention group 1 • L-carnitine (IV): 10 mg/kg at each dialysis session for 24 weeks Intervention group 2 • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Intervention group 3 • L-carnitine (IV): 40 mg/kg at each dialysis session for 24 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb, HCT
Notes	Funding source: Supported in part by Sigma Tau Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Fatigue score	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study

Brass 2001b *(Continued)*

Incomplete outcome data (attrition bias) QoL	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Fatigue score	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Adverse events	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: supported in part by Sigma Tau Pharmaceuticals

CARNIDIAL 2012

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: October 2006 to March 2010 • Study follow-up: 1 year
Participants	Baseline characteristics • Country: France • Setting: public hospital (1 site) • Inclusion criteria: started long-term HD < 6 months before the study started or afterwards; > 18 years • Randomised number (intervention/control): 46/46 • Dialysis modality: HD • Mean age ± SD (years): intervention group (61 ± 18); control group (61 ± 15) • Sex (M/F): not reported • Mean dialysis duration ± SD (days): intervention group (38 ± 25); control group (40 ± 29) • Exclusion criteria: pregnancy; cancer; expected life expectancy < 6 months; documented carnitine deficiency
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 1 year Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36 • Adverse events

CARNIDIAL 2012 *(Continued)*

- Anaemia-related markers: EPO resistance index
- Death (any cause)

Notes	Other information • Funding source: supported by a grant from the French Ministry of Health: CIRC 2005, P050316 • The first author received honoraria from Gambro and Hoffmann-La-Roche in 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned in a 1:1 ratio with a centralized randomization list stratified according to center"
Allocation concealment (selection bias)	Low risk	Quote: "randomly assigned in a 1:1 ratio with a centralized randomization list stratified according to center"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Adverse events	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported

CARNIDIAL 2012 *(Continued)*

Other bias	High risk	Funding source: supported by a grant from the French Ministry of Health, but Sigma-Tau provided L-carnitine and placebo without charge

Caruso 1998

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 9 months
Participants	Baseline characteristics • Country: Italy • Setting: dialysis centre (1 site) • Inclusion criteria: > 40 years; dialytic age > 1 year; rHuEPO therapy > 9 months; HCT 30% to 35%; normal iron status • Randomised number (intervention/control): 15/16 • Dialysis modality: HD • Mean age ± SD (years): intervention group (67.6 ± 13.43); control group (65.69 ± 14.54) • Sex (M/F): intervention group (11/4); control group (5/11) • Mean dialysis duration ± SD (years): intervention group (3.73 ± 2.49); control group (5.56 ± 4.38) • Exclusion criteria: L-carnitine intervention within 2 months; severe hyperparathyroidism (PTH > 150); signs of aluminium intoxication; uncontrolled hypertension; severe liver disease; causes of anaemia other than uremia; pregnancy
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 6 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, EPO dose • Death: any cause; cardiac
Notes	Funding source: not mentioned, but an author was from the Sigma Tau company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as "according to a randomization list"; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Caruso 1998 *(Continued)*

Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: not mentioned, but an author was from the Sigma Tau company

Catalano 1999

Study characteristics	
Methods	Study characteristics • Study design: cross-over RCT • Study duration: not reported • Study follow-up: 4 months
Participants	Baseline characteristics • Country: Italy • Setting: not reported • Inclusion criteria: patients undergoing HD • Randomised number (intervention/control): 5/5 • Dialysis modality: HD • Mean age, range (years): 68, 65 to 75 • Sex (M/F): 7/3 • Mean dialysis duration, range (years): 7.5 (1 to 18) • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 4 months Control group • Placebo

Catalano 1999 *(Continued)*

Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb
Notes	• Abstract-only publications • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Chazot 2003

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months
Participants	Baseline characteristics • Country: France • Setting: dialysis centre (1 site) • Inclusion criteria: BMI < 22 kg/m^2; HD • Randomised number (intervention/control): 28/25 • Dialysis modality: HD • Mean age, range (years): intervention group (66.7, 40.6 to 88); control group (65.2, 37.5 to 87.9) • Sex (M/F): intervention group (19/9); control group (14/11) • Mean dialysis duration, range (months): intervention group (110.8, 8.6 to 316); control group (112.7, 9.9 to 325.4)

Chazot 2003 *(Continued)*

	• Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 15 mg/kg at each dialysis session for 6 months Control group • Standard care
Outcomes	Outcomes relevant to this review • Anaemia-related markers: HCT, EPO dose • Death (any cause)
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Death	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data with similar reasons for missing data across groups
Incomplete outcome data (attrition bias) Death	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Chi 2021

Study characteristics

Methods	Study characteristics

Chi 2021 *(Continued)*

- Study design: parallel RCT
- Study duration: September 2017 to July 2019
- Study follow-up: 12 weeks

Participants	Baseline characteristics • Country: China • Setting: university hospital (1 site) • Inclusion criteria: maintenance HD patients; Hb < 120 g/L (male) and Hb < 110 g/L (female); able to undergo HD in hospital; ≥ 60 years; duration of HD ≥ 2 years; duration of low-flux HD ≥ 3 months; absence of severe infection or heart failure, antibiotic treatment, active diseases, and malignant tumours in the past 3 months; taking low-molecular-weight heparin calcium anticoagulation; undergoing 3 x 4-hour HD/week and blood flow 200 to 300 mL/min; smooth blood circulation during dialysis, reaching or approaching the dry body mass; good treatment compliance • Randomised number (intervention 1/intervention 2/intervention 3): 25/25/25 • Dialysis modality: HD • Mean age ± SD (years): intervention group 1 (71.08 ± 9.18); intervention group 2 (71.2 ± 6.31); intervention group 3 (71.32 ± 7.12) • Sex (M/F): intervention group 1 (14/11); intervention group 2 (15/10); intervention group 3 (13/12) • Dialysis duration: not reported • Exclusion criteria: use of glucocorticoids or immunosuppressants in the past 3 months; bleeding or blood transfusion or taking antibiotics in the past 3 months; haematologic disease; acute or chronic infection; severe malnutrition; malignant tumours; severe heart failure or multiple organ failure; sepsis, chronic hepatitis, tuberculosis, systemic lupus erythematosus, vasculitis, liver insufficiency, epilepsy, a family history of epilepsy; blood flow during dialysis < 200 mL/min
Interventions	Intervention group 1 • L-carnitine (IV): 1000 mg at each dialysis session for 12 weeks • High-flux: ultrafiltration coefficient 59 mL/(h·mm Hg) and an effective surface area of 1.8 m^2 Intervention group 2 • High-flux: ultrafiltration coefficient 59 mL/(h·mm Hg) and an effective surface area of 1.8 m^2 Intervention group 3 • Low-flux: ultrafiltration coefficient 12 mL/(h·mm Hg) and an effective surface area of 1.4 m^2
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb
Notes	Funding source: the Zhongshan Science and Technology Bureau Projects

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "divided by numeration table into three groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Chi 2021 *(Continued)*

Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Adverse events	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Adverse events	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	Funding source: the Zhongshan Science and Technology Bureau Projects

Cibulka 2005

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Czech Republic • Setting: dialysis centres (2 sites) • Inclusion criteria: all patients on dialysis who signed an informed consent form • Randomised number (total): 112 • Analysed number (intervention/control): 44/39 • Dialysis modality: HD • Mean age ± SD (years): intervention group (60.9 ± 12.1); control group (60.4 ± 13.3) • Sex (M/F): intervention group (31/13); control group (25/14) • Median dialysis duration, range (months): intervention group (16, 3 to 79); control group (16, 3 to 189) • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 15 mg/kg at each dialysis session for 6 months Control group • Placebo

Cibulka 2005 *(Continued)*

Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, EPO dose
Notes	Funding source: Internal Grant Agency (IGA) grant NB/7350-3 from the Ministry of Health, Czech Republic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "These subjects were randomly divided by computer"; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	The number of drop-outs per group is unknown Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Low risk	Funding source: Internal Grant Agency (IGA) grant NB/7350-3 from the Ministry of Health, Czech Republic

Cui 2016

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: March 2011 to June 2014 • Study follow-up: 28 weeks
Participants	Baseline characteristics • Country: China • Setting: dialysis centre (1 site) • Inclusion criteria: patients undergoing HD with renal anaemia; stable disease conditions for at least 1 month; HD 2 or 3 times/week; Hb < 90 g/L; serum ferritin level < 200 ng/mL, or transferrin saturation < 20% • Randomised number (intervention/control): 78/78 • Dialysis modality: HD • Mean age ± SD (years): intervention group (49.46 ± 10.13); control group (49.57 ± 9.97)

Cui 2016 *(Continued)*

- Sex (M/F): intervention group (40/38); control group (42/36)
- Dialysis duration range (months): intervention group (17.6 to 43.3); control group (18.2 to 43.6)
- Exclusion criteria: suffered from other severe complications or endocrine diseases or who had been treated with chalybeate

Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 28 weeks Control group • Placebo Co-interventions • EPO + iron saccharate
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, HCT, EPO dose
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using the random number table method"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Fagher 1985

Study characteristics

Methods	Study characteristics • Study design: parallel RCT

Fagher 1985 *(Continued)*

- Study duration: January 1982 to February 1983
- Study follow-up: 6 weeks

Participants	Baseline characteristics • Country: Sweden • Setting: university hospital (1 site) • Inclusion criteria: clinically steady HD patients • Randomised number (intervention/control): 14/14 • Dialysis modality: HD • Median age, range (years): intervention group (48, 28 to 65); control group (42, 24 to 62) • Sex (M/F): intervention group (9/5); control group (8/6) • Median dialysis duration, range (months): intervention group (37, 14 to 157); control group (35, 12 to 238) • Exclusion criteria: on any drug treatment; had concomitant metabolic diseases
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 6 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Myocardial function: ejection fraction
Notes	Funding source: Sigma-Tau, Italy supplied L-carnitine; grants from the Crafoord Foundation, Lund, Sweden, the Swedish Medical Society and the Swedish Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Myocardial function	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source was not commercial funding, but Sigma-Tau, Italy supplied L-carnitine

Fu 2010

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: April 2009 to October 2009 • Study follow-up: 3 months
Participants	Baseline characteristics • Country: China • Setting: university hospital dialysis centre (1 site) • Inclusion criteria: maintenance HD > 6 months • Randomised number (intervention/control): 20/20 • Dialysis modality: HD • Mean age ± SD (years): 53.5 ± 7.1 • Sex (M/F): 22/18 • Mean dialysis duration ± SD (months): 31.5 ± 20.5 • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 3 months Control group • Standard care
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb
Notes	Funding source: supported by Science and Technology Fund of Xi'an

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	No missing outcome data

Fu 2010 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Low risk	Funding source: supported by Science and Technology Fund of Xi'an

Fukami 2013

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: unclear
Participants	Baseline characteristics • Country: Japan • Setting: university hospital (1 site) • Inclusion criteria: HD patients • Randomised number (intervention/control): 32/38 • Dialysis modality: HD • Mean age ± SD (years): intervention group (68 ± 12.4); control group (67 ± 13.2) • Sex (M/F): intervention group (22/10); control group (22/16) • Mean dialysis duration, range (months): intervention group (109.2, 2 to 371); control group (91.3, 2 to 442) • Exclusion criteria: severe infection; pregnancy; chronic heart failure; acute kidney injury; severe liver dysfunction
Interventions	Intervention group • L-carnitine (oral): 900 mg/day for 6 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Death (any cause) • Vascular access failure
Notes	Funding source: a Grant-in-Aid for Welfare, and Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by Grants of MEXT-Supported Program for the Strategic Research Foundation at Private Universities, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported

Fukami 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Adverse events	High risk	The outcome measurement is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Death	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Vascular access failure	High risk	The outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Adverse events	High risk	Imbalance in numbers for missing data across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Vascular access failure	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Low risk	Funding source: a Grant-in-Aid for Welfare, and Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by Grants of MEXT-Supported Program for the Strategic Research Foundation at Private Universities, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan

Fukuda 2015

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: March to August 2008 • Study follow-up: 12 weeks
Participants	Baseline characteristics • Country: Japan • Setting: dialysis centres (4 sites) • Inclusion criteria: 30 to 70 years; ESKD for at least 1 year with afternoon HD 3 times/week • Randomised number (intervention/control): 103/99

Fukuda 2015 *(Continued)*

	• Dialysis modality: HD • Mean age ± SD (years): intervention group (55.6 ± 10); control group (56.2 ± 8.9) • Sex (M/F): intervention group (71/16); control group (72/15) • Mean dialysis duration ± SD (years): intervention group (10.6 ± 8.26); control group (11.0 ± 7.74) • Exclusion criteria: active malignant tumour; pregnancy or lactation
Interventions	Intervention group • L-carnitine (oral): 500 mg at each dialysis session for 12 weeks • Vitamin B1 10 mg; vitamin B2 1.8 mg; niacin 15 mg; vitamin B6 10 mg; vitamin B12 30 µg; folic acid 0.5 mg; vitamin C 60 mg; CoQ10 30 mg; naive galacto-oligosaccharide 5 g; zinc 8 mg Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36 • Fatigue score: questionnaire associated with chronic fatigue • Adverse events • Anaemia-related markers: Hb
Notes	Funding source: supported by grants from the Asahi Kasei Kuraray Medical Cooperation, 21st Century COE Program and Grant-in Aid for Scientific Research by Ministry of Education, Culture, Sports, Science and Technology (Japan), and grants from Health Labour Sciences Research Grant (Comprehensive Research on Disability Health and Welfare), Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization by means of a computer-generated random number table (1:1)"
Allocation concealment (selection bias)	Low risk	Quote: "Originally assigned code numbers were kept in closed envelopes within the coordinating center."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Fatigue score	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study

Fukuda 2015 *(Continued)*

Incomplete outcome data (attrition bias) QoL	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Fatigue score	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Adverse events	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	High risk	Funding source: supported by grants from the Asahi Kasei Kuraray Medical Cooperation, 21st Century COE Program and Grant-in Aid for Scientific Research by Ministry of Education, Culture, Sports, Science and Technology (Japan), and grants from Health Labour Sciences Research Grant (Comprehensive Research on Disability Health and Welfare), Japan

Garneata 2005

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Romania • Setting: not reported • Inclusion criteria: stable patients undergoing chronic HD for at least 6 months; Hb < 10.5 g/dL despite EPO administration in an unmodified dose (106.8 ± 35.4 IU/kg/week) at least 3 months prior to enrolment, without iron deficiency or known causes of EPO hyper-responsiveness • Analysed number (intervention/control): 20/20 • Dialysis modality: HD • Age: not reported • Dialysis duration: not reported • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (oral): 6 g/day for 6 months Control group • Standard care

Garneata 2005 *(Continued)*

Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, EPO dose
Notes	Other information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Hamedi-Kalajahi 2021

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: August 2019 to October 2019 • Study follow-up: 10 weeks
Participants	Baseline characteristics • Country: Iran • Setting: Children's Hospital and University Hospital (2 sites) • Inclusion criteria: CKD patients aged 6 to 18 years; at least 2 dialysis sessions/week; HD for at least 3 months • Randomised number (intervention/control): 15/15 • Dialysis modality: HD • Mean age ± SD (years): intervention group (12.92 ± 4.17); control group (13.25 ± 3.11)

Hamedi-Kalajahi 2021 *(Continued)*

- Sex (M/F): intervention group (10/5); control group (9/6)
- Dialysis duration: not reported
- Exclusion criteria: pregnancy; autoimmune, infectious, and cardiovascular disease; thyroid disorders; thrombocytopenia; nutritional support (central and parental nutrition)

Interventions	Intervention group • L-carnitine (oral): 50 mg/kg/day for 10 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL (PedsQL)
Notes	• Funding source: the Faculty of Nutrition and Dietetics, Tehran University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "based on random assignment in SPSS"
Allocation concealment (selection bias)	Low risk	Quote: "sealed and uniform envelopes were then elicited by an independent coworker"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Low risk	Missing outcome data balanced in numbers across intervention groups.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Funding source: the Faculty of Nutrition and Dietetics, Tehran University of Medical Sciences

Harmankaya 2002a

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months

Harmankaya 2002a *(Continued)*

Participants	Baseline characteristics • Country: Turkey • Setting: not reported • Inclusion criteria: chronic HD; receiving rHuEPO for at least 6 months • Number (intervention/control): 15/15 • Dialysis modality: HD • Mean age ± SD (years): intervention group (52 ± 11); control group (54 ± 13) • Sex (M/F): intervention group (8/7); control group (7/8) • Mean dialysis duration ± SD (months): intervention group (25 ± 18); control group (23 ± 16) • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 6 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: HCT, EPO dose
Notes	Other information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Higuchi 2014

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: June 2012 to December 2014 • Study follow-up: 12 months
Participants	Baseline characteristics • Country: Japan • Setting: multicentre (number of sites not reported) • Inclusion criteria: ≥ 20 years and ≤ 85 years; HD > 6 months at enrolment; free carnitine plasma concentration < 40 µmol/L • Randomised number (intervention/control): 110/112 • Dialysis modality: HD • Mean age ± SD (years): intervention group (66 ± 10); control group (67 ± 9) • Sex (females): intervention group (20%); control group (20%) • Median dialysis duration, IQR (years): intervention group (45, 17 to 60); control group (47, 24 to 66) • Exclusion criteria: history of severe heart failure, angina, MI, or stroke within the past 6 months; presence of infectious disease, thyroid disease, malignant tumours, or intervention with steroids or immunosuppressants; current hospitalisation; atrial fibrillation; L-carnitine therapy or supplementation within the past 6 months
Interventions	Intervention group • L-carnitine (oral): 20 mg/kg/day for 12 months Control group • Standard care
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb, EPO resistance index • Myocardial function: LVM, ejection fraction • Death (any cause)
Notes	Funding source: self-funding, but one of the authors has received honoraria from Kyowa Hakko Kirin, Daiichi Sankyo, and Otsuka Pharmaceutical

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Dynamic balancing randomization was carried out based on age, sex, HD vintage, hemoglobin level, and presence or absence of diabetes mellitus."
Allocation concealment (selection bias)	Low risk	Quote: "An independent investigator with no previous knowledge of the subjects before commencement of the trial monitored randomization of subject entry order."
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Higuchi 2014 *(Continued)*

Blinding of outcome assessment (detection bias) Adverse events	High risk	The outcome measurement is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Death	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Adverse events	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Myocardial function	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	High risk	Patients (intervention 19, control 18) were excluded after randomisation as "unsuitable for echography". Funding source: self-funding, but one of the authors has received honoraria from Kyowa Hakko Kirin, Daiichi Sankyo, and Otsuka Pharmaceutical

Ibarra-Sifuentes 2017

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: 1 April to 21 May 2016 • Study follow-up: 12 weeks
Participants	Baseline characteristics • Country: Mexico • Setting: university hospital (1 site)

Ibarra-Sifuentes 2017 *(Continued)*

- Inclusion criteria: men and non-pregnant women, not breastfeeding; 18 to 85 years; regular attendance to HD sessions, at least twice/week; previous 6 months on HD treatment; 2 or more intradialytic hypotension episodes in the past 6 months
- Randomised number (intervention/control): 18/15
- Dialysis modality: HD
- Mean age ± SD (years): intervention group (44.9 ± 16.9); control group (49 ± 12.1)
- Sex (M/F): intervention group (7/11); control group (8/7)
- Dialysis duration: not reported
- Exclusion criteria: treated with L-carnitine in the previous 6 months; septic stock history in the previous 6 months; pregnancy; lactation; and history of hypersensitivity or contraindication to L-carnitine

Interventions	Intervention group • L-carnitine (IV): 30 mg/kg at dialysis session for 12 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Myocardiac function: intradialytic hypotension
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized random number generator and allocated into L- carnitine and placebo groups"
Allocation concealment (selection bias)	Low risk	Quote: "computerized random number generator and allocated into L-carnitine and placebo groups"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Funding source: not reported

Khodaverdi 2010

Study characteristics

Khodaverdi 2010 *(Continued)*

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 3 months
Participants	Baseline characteristics • Country: Iran • Setting: dialysis centre • Inclusion criteria: ESKD; HD ≥ 1 year, Hb ≤ 10 mg/dL; adequate iron stores (ferritin > 100, SI/TIBC > 20%); normal liver tests • Randomised number (intervention/control): 14/15 • Dialysis modality: HD • Mean age ± SD (years): intervention group (49 ± 19); control group (52.4 ± 19.3) • Exclusion criteria: carnitine intake within 2 months; pregnancy; liver disease; ferritin < 100 and SI/TIBC < 20%; PTH > 150 or > 2 times normal; other causes of anaemia
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 3 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, HCT
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Funding source: not reported

Kletzmayr 1999

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 8 months
Participants	Baseline characteristics • Country: Austria • Setting: not reported • Inclusion criteria: maintenance HD > 6 months; stable rHuEPO user • Number (intervention/control): 20/20 • Dialysis modality: HD • Mean age ± SD (years): intervention group (54.3 ± 17); control group (51.3 ± 15.2) • Sex (M/F): intervention group (7/11); control group (8/7) • Mean dialysis duration ± SD (months): intervention group (30 ± 17.5); control group (43.2 ± 49.8) • Exclusion criteria: blood loss for any reason
Interventions	Intervention group 1 • L-carnitine (IV): 5 mg/kg at each dialysis session for 8 months Intervention group 2 • L-carnitine (IV): 25 mg/kg at each dialysis session for 8 months Control group • Placebo Co-intervention • IV iron during the run-in phase
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: EPO resistance index
Notes	Funding source: not reported, but "Leopold Pharma, Austria, for providing study drug and randomization procedure, and Fresenius Austria for financial support"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Kletzmayr 1999 *(Continued)*

Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: not reported, but "Leopold Pharma, Austria, for providing study drug and randomization procedure, and Fresenius Austria for financial support"

Kudoh 2013

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 3 months
Participants	Baseline characteristics • Country: Japan • Setting: private hospital (1 site) • Inclusion criteria: chronic HD > 2 years, dialysis frequency or duration unchanged for the previous 3 months; stable laboratory data without severe anaemia or hyperparathyroidism • Randomised number (total): 20 • Analysed number (intervention/control): 10/8 • Dialysis modality: HD • Mean age ± SD (years): intervention group (65.9 ± 6.4); control group (67.8 ± 9.4) • Sex (M/F): intervention group (4/6); control group (4/4) • Mean dialysis duration ± SD (months): intervention group (157.4 ± 115.3); control group (109 ± 62.5) • Exclusion criteria: prior MI or valvular heart disease
Interventions	Intervention group • L-carnitine (oral): 900 mg/day for 3 months

Kudoh 2013 *(Continued)*

	Control group • Placebo
Outcomes	Outcomes relevant to this review • Myocardial function: intradialytic hypotension, LVM, ejection fraction
Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Funding source: not reported

Labonia 1995

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Argentina • Setting: not reported • Inclusion criteria: HD > 1 year; dialysis frequency or duration unchanged for 6 months with a defined maintenance dose, either IV or SC; HCT 28% to 33% for the previous 3 months, normal iron status; usual treatment with folic acid and vitamin B12; no carnitine administration for the previous 6 months; absence of severe clinical hyperthyroidism • Randomised number (intervention/control): 13/11

Labonia 1995 *(Continued)*

	• Dialysis modality: HD • Mean age ± SD (years): intervention group (41.8 ± 18.6); control group (62.5 ± 7.2) • Sex (M/F): intervention group (6/7); control group (6/5) • Exclusion criteria: received transfusion within the last 6 months; under ACEi treatment
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 6 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: EPO dose
Notes	Other information • Patients were treated to maintain normal iron levels throughout the study, which were defined as follows: serum iron > 70 µg/dL, serum ferritin > 100 ng/mL, serum transferrin saturation > 20% • Funding source: supported by Sigma-Tau SpA, Pomezia, Roma, Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; the method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: supported by Sigma-Tau SpA, Pomezia, Roma, Italy

Maruyama 2017

Study characteristics

Methods	Study characteristics • Study design: parallel RCT

Maruyama 2017 *(Continued)*

- Study duration: not reported
- Study follow-up: 12 months

Participants	Baseline characteristics • Country: Japan • Setting: private hospital (1 site) • Inclusion criteria: patients with renal anaemia on maintenance HD • Randomised number (intervention/control): 30/30 • Dialysis modality: HD • Mean age ± SD (years): intervention group (70 ± 10); control group (69 ± 11) • Sex (M/F): intervention group (21/9); control group (17/13) • Mean dialysis duration ± SD (months): intervention group (48 ± 77); control group (52 ± 54) • Exclusion criteria: previously taken L-carnitine in either oral or injected form; taking any carnitine preparation as a supplement; difficulty communicating owing to dementia or other factors; acute inflammation; taking an immunosuppressive drug, steroid, or antibiotic; history of blood transfusion within the past 6 months
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 12 months Control group • Standard care
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb, EPO dose, EPO resistance index • Myocardial function: ejection function • Death (any cause)
Notes	Funding source: not reported, but one of the authors has received honoraria from Otsuka Pharmaceuticals Co. Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out by dynamic allocation based on age, sex, hemodialysis vintage, haemoglobin level, and presence or absence of diabetes mellitus"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out by dynamic allocation based on age, sex, hemodialysis vintage, haemoglobin level, and presence or absence of diabetes mellitus"
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Adverse events	High risk	The outcome measurement is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	The outcome measurement is not likely to be influenced by lack of blinding

Maruyama 2017 *(Continued)*

Anaemia-related markers		
Blinding of outcome assessment (detection bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Death	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Adverse events	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Myocardial function	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Death	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	High risk	Funding source: not reported, but one of the authors has received honoraria from Otsuka Pharmaceuticals Co. Ltd

Mettang 1997

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 4 months
Participants	Baseline characteristics • Country: Germany • Setting: dialysis centre (1 site) • Inclusion criteria: HD ≥ 6 months before the onset of the study period were screened • Randomised number (intervention/control): 9/8 • Dialysis modality: HD • Mean age ± SD (years): intervention group (64.6 ± 14.2); control group (59.5 ± 13.7) • Sex (M/F): intervention group (3/6); control group (3/5) • Mean dialysis duration ± SD (years): intervention group (6.0 ± 8.5); control group (6.5 ± 7.0) • Exclusion criteria: DM; malignant disease; autoimmune disease necessitating immunosuppressive or steroid therapy

Mettang 1997 *(Continued)*

Interventions	Intervention group • L-carnitine (IV): 10 mg/kg at each dialysis session for 4 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Muscle symptoms: cramps, weakness • Anaemia-related markers: Hb, HCT
Notes	Funding source: Supported in part by research grants from Fresenius AG, Oberursel; the Khalil Foundation; the Robert-Bosch Foundation, Stuttgart; and Fa Medice, Iserlohn, Germany. Fa Medice, Iserlohn, Germany, for generously providing L-carnitine and placebo for the randomized trial and supporting the determination of carnitine in serum samples, as well as the statistical analyses; Fresenius AG, Oberursel, Germany, for generally supporting this research.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Adverse events	Low risk	Missing outcome data balanced in numbers across intervention groups

Mettang 1997 *(Continued)*

Incomplete outcome data (attrition bias) Muscle symptoms	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Fa Medice, Iserlohn, Germany, for generously providing L-carnitine and placebo for the randomized trial and supporting the determination of carnitine in serum samples, as well as the statistical analyses; Fresenius AG, Oberursel, Germany, for generally supporting this research

Mitwalli 2005

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: July 2002 to December 2002 • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Saudi Arabia • Setting: university hospital (1 site) • Inclusion criteria: HD • Randomised number (intervention/control): 18/18 • Dialysis modality: HD • Mean age ± SD (years): intervention group (54 ± 15); control group (42 ± 14) • Sex: not reported • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 15 mg/kg at each dialysis session for 6 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, HCT
Notes	Funding source: not reported

Mitwalli 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Quote: "in a single blind manner to receive L-Carnitine or placebo"
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Mortazavi 2011a

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: September 2008 to May 2009 • Study follow-up: 9 months
Participants	Baseline characteristics • Country: Iran • Setting: dialysis centre (1 site) • Inclusion criteria: > 21 years; PD at least for 1 month prior; informed consent; no history of carnitine used in the previous 8 weeks; no history of infectious disease or fever in the previous month; KT/V > 0.9 • Randomised number (intervention/control): 28/27 • Dialysis modality: PD • Mean ± SD (years): intervention group (50.66 ± 17); control group (57.91 ± 13) • Mean dialysis duration ± SD (years): intervention group (23 ± 13); control group (28 ± 18) • Exclusion criteria: carnitine in the last 8 months; antibiotics for the past month due to an infection
Interventions	Intervention group • L-carnitine (oral): 750 mg/day for 9 months Control group

Mortazavi 2011a *(Continued)*

	• Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb • Death (any cause)
Notes	Funding: Isfahan University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were divided into carnitine and placebo groups by a computer-generated random number table."
Allocation concealment (selection bias)	Low risk	Quote: "The carnitine and placebo were coded by project colleagues and delivered to the project manager in similar packages."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Adverse events	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Death	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Low risk	Funding: Isfahan University of Medical Sciences

Mortazavi 2012

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT (3-arm) • Study duration: October 2008 to April 2010 • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Iran • Setting: dialysis centre (1 site) • Inclusion criteria: > 21 years; HD at least for one month; informed consent; no history of carnitine used in the previous 8 weeks; no history of infectious diseases or fever in the previous month • Randomised number (intervention/control 1/control 2): 17/19/18 • Dialysis modality: HD • Mean age ± SD (years): 54 ± 17 • Sex (M/F): 28/26 • Mean dialysis duration ± SD (months): 36 ± 33 • Exclusion criteria: experiencing side effects (hypertension, dizziness, blurred vision, decreased mini-mental state score, and diarrhoea) after taking tablets; not willing to cooperate; an infectious problem or antibiotic usage; changed dialysis method; continuing treatment in another centre; having kidney transplantation
Interventions	Intervention group • L-carnitine (oral): 750 mg/day for 9 months Control group 1 • Placebo Control group 2 • No treatment
Outcomes	Outcomes relevant to this review • Adverse events • Anaemia-related markers: Hb, EPO dose • Death (any cause)
Notes	Funding source: Source of Support: Isfahan University of Medical Sciences, Isfahan, Iran

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study

Mortazavi 2012 *(Continued)*

Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Adverse events	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Death	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Low risk	Funding source: Source of Support: Isfahan University of Medical Sciences, Isfahan, Iran

Naini 2011

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 16 weeks
Participants	Baseline characteristics • Country: Iran • Setting: university hospital • Inclusion criteria: 18 to 75 years; HD > 12 weeks, 3 times/week 4 hours/session; serum triglycerides or total cholesterol > 200 mg/dL or serum HDL concentration < 40 mg/dL • Randomised number (intervention/control): 27/27 • Dialysis modality: HD • Mean age ± SD (years): intervention group (53.9 ± 17.2); control group (51.8 ± 13.5) • Sex (M/F): intervention group (12/12); control group (14/13) • Mean dialysis duration ± SD (months): intervention group (32.5 ± 25.9); control group (28.1 ± 13.3) • Exclusion criteria: taking carnitine supplement or any drug that interacts with carnitine (anticoagulant medication or those lowering the seizure threshold (e.g. tricyclic antidepressants) in the last month; other drugs influencing lipid metabolism during the previous 8 weeks; liver dysfunction; hy-

Naini 2011 *(Continued)*

	pothyroidism; chronic infectious diseases; active source of infection; inflammatory diseases; history of seizure; known cases of any brain mass
Interventions	Intervention group • L-carnitine (oral): 1000 mg/day for 16 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36 • Anaemia-related markers: Hb • Death (any cause)
Notes	Funding source: This study was supported by the Isfahan University of Medical Sciences, Isfahan, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were assigned to either carnitine or placebo groups based on the random number table, generated by random allocation software."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Quote: "In the carnitine group, three patients were excluded; one underwent kidney transplantation, one died because of myocardial infarction, and one was not willing to continue the study."
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Quote: "In the carnitine group, three patients were excluded; one underwent kidney transplantation, one died because of myocardial infarction, and one was not willing to continue the study."
Incomplete outcome data (attrition bias) Death	Low risk	No missing outcome data

Naini 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Low risk	Funding source: this study was supported by the Isfahan University of Medical Sciences, Isfahan, Iran

Pacheco 2008

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 12 weeks
Participants	Baseline characteristics • Country: Chile • Setting: university hospital (1 site) • Inclusion criteria: chronic HD; 20 to 50 years • Randomised number (intervention/control): 15/15 • Dialysis modality: HD • Mean age ± SD (years): intervention group (38.8 ± 9.5); control group (35.8 ± 11.4) • Sex (M/F): intervention group (7/6); control group (4/4) • Exclusion criteria: DM; COPD; CAD; HCT < 25%; BMI > 30
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis for 12 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: HCT
Notes	Funding: Labomed Chile provided carnitine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random number table"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study

Pacheco 2008 *(Continued)*

Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	High risk	Imbalance in numbers for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding: Labomed Chile provided carnitine

Rathod 2006

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: January 2005 to October 2005 • Study follow-up: 8 weeks
Participants	Baseline characteristics • Country: India • Setting: HD unit at a university hospital (1 site) • Inclusion criteria: ESKD patients attending the HD unit; clinically stable, male and non-pregnant, non-lactating female patients; 18 to 65 years; undergoing maintenance HD at least twice/week for a minimum duration of 6 months; having at least 2 of the following dialysis-related symptoms: inter- or intradialytic hypotension, muscle cramping, lack of energy or generalised weakness, muscle weakness, myopathy • Randomised number (intervention/control): 10/10 • Dialysis modality: HD • Mean age ± SD (years): intervention group (40.3 ± 13.58); control group (47.3 ± 11.69) • Sex (M/F): intervention group (10/0); control group (8/2) • Mean dialysis duration ± SD (months): intervention group (9.2 ± 2.25); control group (9.6 ± 2.5) • Exclusion criteria: received L-carnitine therapy in the previous 6 months or blood transfusion in the previous 4 weeks; history of seizure disorder; requiring/taking concomitant hypolipidaemic agents; history suggestive of hypersensitivity to or any contraindication to L-carnitine
Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 8 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36 • Muscle symptoms: cramps, weakness • Anaemia-related markers: Hb • Myocardial function: intradialytic hypotension

Rathod 2006 *(Continued)*

Notes	Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomization chart for simple randomization in blocks of 4"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Quote: "a patient-blind, randomized, placebo-controlled clinical trial"
Blinding of outcome assessment (detection bias) QoL	High risk	The outcome measurement is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Muscle symptoms	High risk	The outcome measurement is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Myocardial function	High risk	The outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) QoL	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Muscle symptoms	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Myocardial function	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Roozbeh 2007

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 8 week
Participants	Baseline characteristics • Country: Iran • Setting: not reported • Inclusion criteria: ESKD patients • Randomised number (intervention/control): 30/30 • Dialysis modality: HD • Age: not reported • Sex: not reported • Dialysis duration: not reported • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (oral): 500 mg/day for 8 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • Muscle symptoms: weakness
Notes	Other information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data

Roozbeh 2007 *(Continued)*

Muscle symptoms

Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Saxena 2004

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 4 weeks
Participants	Baseline characteristics • Country: India • Setting: not reported • Inclusion criteria: chronic HD • Randomised number (intervention/control): 10/10 • Dialysis modality: HD • Mean age ± SD (years): intervention group (61 ± 14.04); control group (59 ± 6.41) • Sex: not reported • Mean dialysis duration ± SD (months): 9 ± 2 • Exclusion criteria: active infection; gastrointestinal bleed
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 4 weeks Control group • Standard care
Outcomes	Outcomes relevant to this review • Muscle symptoms: weakness • Anaemia-related markers: Hb
Notes	Other information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported

Saxena 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Fatigue score	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Muscle symptoms	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Fatigue score	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Muscle symptoms	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Semeniuk 2000

Study characteristics	
Methods	Study characteristics • Study design: cross-over RCT • Study duration: November 1997 to June 1998 • Study follow-up: 12 weeks
Participants	Baseline characteristics • Country: India • Setting: not reported • Inclusion criteria: chronic HD • Randomised number (intervention/control): 10/10 • Dialysis modality: HD • Mean age ± SD (years): intervention group (61 ± 14.04); control group (59 ± 6.41) • Sex: not reported

Semeniuk 2000 *(Continued)*

- Mean dialysis duration ± SD (months): 9 ± 2
- Exclusion criteria: active infection; gastrointestinal bleeding

Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 12 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: KD-QOL • Muscle symptoms: muscle cramp • Anaemia-related markers: Hb, EPO dose • Myocardial function: intradialytic hypotension
Notes	Funding source: not reported in detail, but Sigma-Tau Pharmaceuticals supplied L-carnitine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Muscle symptoms	Unclear risk	Insufficient information to permit judgement

Semeniuk 2000 *(Continued)*

Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Funding source: not reported in detail, but Sigma-Tau Pharmaceuticals supplied L-carnitine

Signorelli 2006

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 12 months
Participants	Baseline characteristics • Country: Italy • Setting: university hospital (1 site) • Inclusion criteria: HD; clinical diagnosis of peripheral arterial disease at the 2nd stage according to the Leriche-Fontaine classification; ankle/brachial index ≤ 0.9 • Randomised number (intervention/control): 32/32 • Dialysis modality: HD • Mean age ± SD (years): intervention group (66.7 ± 6.6); control group (66 ± 2.7) • Sex: not reported • Dialysis duration: not reported • Exclusion criteria: coronary ischaemic disease; congestive heart failure; active hepatic disease; active inflammatory disease; arterial hypertension
Interventions	Intervention group • L-carnitine (IV): 600 mg at each dialysis session for 12 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Adverse events • Death: any cause, cardiovascular
Notes	Funding source: not reported
Risk of bias	

Signorelli 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Adverse events	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Adverse events	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Death	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Funding source: the authors have provided no information on sources of funding

Sloan 1998a

Study characteristics	
Methods	Study A characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 6 months Study B characteristics • Study design: cross-over RCT • Study duration: not reported • Study follow-up: 6 months
Participants	Baseline characteristics • Country: USA • Setting: dialysis centres (2 sites) • Inclusion criteria: chronic HD patients • Number (intervention/control)

Sloan 1998a *(Continued)*

- Study A: 2-arm parallel RCT (30/33)
- Study B: cross-over RCT (19/19)

- Dialysis modality: HD
- Mean age, range (years): 52.2, 23 to 82
- Sex: 40% female
- Dialysis duration: not reported
- Exclusion criteria: not reported

Interventions	Study A and B Intervention group • L-carnitine (oral): 2000 mg at each dialysis session for 3 months Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36
Notes	Funding source: not reported, but Sigma Tau Pharmaceuticals provided L-carnitine and placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Equal numbers of eligible patients were assigned by a computer randomization code to one of three double-blind treatment groups."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: not reported, but Sigma Tau Pharmaceuticals provided L-carnitine and placebo

Sloan 1998b

Study characteristics

Sloan 1998b *(Continued)*

Methods	Study B* • Study design: cross-over RCT • Study duration: not reported • Study follow-up: 6 months *Cross-over 'arm' is part of Sloan 1998a
Participants	Baseline characteristics • Country: USA • Setting: dialysis centres (2 sites) • Inclusion criteria: chronic HD patients • Number (intervention/control) ○ Study B: cross-over RCT (19/19) • Dialysis modality: HD • Mean age, range (years): 52.2, 23 to 82 • Sex: 40% female • Dialysis duration: not reported • Exclusion criteria: not reported
Interventions	Study A and Study B Intervention group • L-carnitine (oral): 2000 mg at each dialysis session for 3 months Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36
Notes	Funding source: not reported, but Sigma Tau Pharmaceuticals provided L-carnitine and placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Equal numbers of eligible patients were assigned by a computer randomization code to one of three double-blind treatment groups."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Unclear risk	Insufficient information to permit judgement

Sloan 1998b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Funding source: not reported, but Sigma Tau Pharmaceuticals provided L-carnitine and placebo

Song 2013a

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 8 months
Participants	Baseline characteristics • Country: China • Setting: Affiliated Hospital of Logistics College of Chinese People's Armed Police Forces • Inclusion criteria: maintenance HD > 6 months; maintenance use of rHuEPO 120 U/kg; low-flux dialysis within 1 month before the trial • Randomised number (intervention/control): 163/163 • Dialysis modality: HD • Mean age ±SD (years): intervention group (52.5 ± 10.2); control group (53.6 ± 11.7) • Sex (M/F): intervention group (80/83); control group (81/82) • Mean dialysis duration ± SD (months): intervention group (14.02 ± 5.55); control group (13.87 ± 5.75) • Exclusion criteria: severe liver disease; peptic ulcer; asthma; infection; tumour; fever; heart failure; autoimmune diseases; other causes of anaemia; blood transfusion; use of steroids within 3 months
Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 8 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb, HCT, EPO dose
Notes	Funding: Natural Science Foundation of Tianjin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Song 2013a *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Low risk	Funding: Natural Science Foundation of Tianjin

Sorge-Haedicke 2001

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: Germany • Setting: not reported • Inclusion criteria: chronic HD; HCT < 36; chronic rHuEPO therapy • Randomised number (intervention/control): 43/40 • Dialysis modality: HD • Age: not reported • Sex (M/F): not reported • Dialysis duration: not reported • Other relevant information • Exclusion criteria: mechanical haemolysis; serum albumin > 50 µg/L; iron overload; intact PTH > 50 pmol/L; any change of treatment modality during the study; HCT > 40
Interventions	Intervention group • L-carnitine (IV): 28.5 mg/kg at each dialysis session for 24 weeks Control group • Placebo Co-interventions • During run in-phase (last 4 weeks pre-study) and during the study, all patients were iron-replaced with IV ferrum (III)-gluconate Ferrlecit according to the DOQI-Anemia-Guidelines
Outcomes	Outcomes relevant to this review

Sorge-Haedicke 2001 *(Continued)*

- Anaemia-related markers: Hb, EPO dose

Notes	Other information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Steiber 2006

Study characteristics

Methods	Study characteristics • Study design: parallel RCT • Study duration: September 2001 to March 2002 • Study follow-up: 24 weeks
Participants	Baseline characteristics • Country: USA • Setting: dialysis centre (1 site) • Inclusion criteria: ≥ 18 years; at least 1 year's duration of treatment; 2 more of the following risk factors: ≥ 85 years; female sex; use of aspirin or mannitol; presence of type 2 DM; left atrial dilation, or left ventricular hypertrophy • Number (total): 48; intervention group (15); control group (19) • Dialysis modality: HD • Mean age ± SD (years): intervention group (67.6 ± 15.1); control group (69.4 ± 14.8) • Sex (M/F): intervention group (7/8); control group (15/4)

Steiber 2006 *(Continued)*

- Mean dialysis duration ± SD (years): intervention group (3.8 ± 2.3); control group (4.0 ± 2.2)
- Exclusion criteria: current or previous treatment (within the last 2 months) with L-carnitine; severe blood loss; disease affecting skeletal muscle function; severe liver disease; pregnancy; free carnitine > 40 µmol/L

Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 24 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: SF-36 • Anaemia-related markers: Hb, HCT, EPO dose
Notes	Funding source: Sigma Tau Pharmaceuticals donation of levocarnitine and ROIP Grant, Michigan State University. One of the author was supported by a grant from the Blodgett Butterworth Health Care Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomization was used, using random numbers generated from an Excel spreadsheet."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) QoL	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	High risk	Insufficient information to permit judgement Quote: "Twenty-one patients dropped out before completion of the study due to various reasons: 7 voluntarily withdrew, 7 died from causes unrelated to carnitine, and 7 declined to complete the final SF-36 survey."
Incomplete outcome data (attrition bias) Anaemia-related markers	High risk	Insufficient information to permit judgement Quote: "Twenty-one patients dropped out before completion of the study due to various reasons: 7 voluntarily withdrew, 7 died from causes unrelated to carnitine, and 7 declined to complete the final SF-36 survey."
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	The study had an extreme baseline imbalance

Steiber 2006 *(Continued)*

	Funding source: Sigma Tau Pharmaceuticals donation of levocarnitine and ROIP Grant, Michigan State University. One of the author was supported by a grant from the Blodgett Butterworth Health Care Foundation

Sugiyama 2021

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: December 2018 to June 2020 • Study follow-up: 6 months
Participants	Baseline characteristics • Country: Japan • Setting: multicentre (21 sites) • Inclusion criteria: > 20 years; ESKD undergoing HD; diagnosed with dialysis-associated secondary carnitine deficiency and had been administered IV L-carnitine at a dose of 1000 mg/HD session 3 times weekly for at least 3 months • Randomised number (intervention group 1/intervention group 2 /control): 19/18/20 • Dialysis modality: HD • Mean age ± SD (years): intervention group 1 (64.5 ± 13.3); intervention group 2 (69.4 ± 12.7); control group (69.5 ± 9.8) • Sex (M/F): intervention group 1 (13/6); intervention group 2 (12/6); control group (10/7) • Dialysis duration: not reported • Exclusion criteria: unstable lower limb cramps and general fatigue; Hb < 10 g/dL; deemed to have inadequate information by a physician
Interventions	Intervention group 1 • L-carnitine (IV): 1000 mg 3 times/week at each dialysis session for 12 months Intervention group 2 • L-carnitine (IV): 1000 mg once/week at dialysis session for 12 months • Placebo: saline twice/week Control group • Placebo: saline 3 times/week
Outcomes	Outcomes relevant to this review • Anaemia-related markers: Hb • Myocardial function: LVM, ejection fraction • Death (any cause)
Notes	Funding source: a Grant-in-Aid for Welfare and Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. One of the authors has received honoraria, including lecture fees, from Otsuka Pharmaceutical Co., Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement

Sugiyama 2021 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "using simple randomization procedures (computer-generated list of random numbers) by the clinical research coordinator"
Allocation concealment (selection bias)	Low risk	Quote: "using simple randomization procedures (computer-generated list of random numbers) by the clinical research coordinator"
Blinding of participants and personnel (performance bias)	High risk	Quote: "single-blind, placebo-controlled, randomized clinical"
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) Death	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Myocardial function	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes of interest to this review were reported
Other bias	High risk	Funding source: a Grant-in-Aid for Welfare and Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. One of the authors has received honoraria, including lecture fees, from Otsuka Pharmaceutical Co., Ltd

Trovato 1983

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 18 months
Participants	Baseline characteristics • Country: Italy • Setting: not reported

Trovato 1983 *(Continued)*

- Inclusion criteria: maintenance HD
- Randomised number (intervention/control): 13/13
- Dialysis modality: HD
- Mean age ± SD (years): 45.54 ± 13.16
- Sex (M/F): 13/13
- Dialysis duration: not reported
- Exclusion criteria: not reported

Interventions	Intervention group • L-carnitine (oral): 1500 mg/day for 18 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Anaemia-related markers: HCT, EPO dose
Notes	Other information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Quote: "single-blind"
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Anaemia-related markers	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Insufficient information to permit judgement

Vaux 2004

Study characteristics

Vaux 2004 *(Continued)*

Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 16 weeks
Participants	Baseline characteristics • Country: UK • Setting: not reported • Inclusion criteria: ESKD on HD; proven carnitine deficiency (acylcarnitine/free carnitine ratio > 0.4); Hb > 10 g/dL • Randomised number (total): 30 • Analysed number (intervention/control): 13/13 • Dialysis modality: HD • Mean age ± SD (years): intervention group (58.8 ± 19.2); control group (63.8 ± 16.4) • Sex (M/F): intervention group (10/3); control group (9/4) • Mean dialysis duration ± SD (months): intervention group (26 ± 25); control group (50 ± 44) • Exclusion criteria: severe medical condition (e,g, severe cardiovascular disease or malignancy); severe pre-dialysis uncontrolled hypertension (SBP >180 mm Hg or DBP > 105 mm Hg); type 1 diabetes; life expectancy of < 4 months; history of drug or alcohol abuse in the previous 6 months; immunosuppressant therapy in the previous 4 weeks; any investigational drug in the previous 3 months or carnitine in the previous 4 months
Interventions	Intervention group • L-carnitine (IV): 20 mg/kg at each dialysis session for 16 weeks Control group • Placebo
Outcomes	Outcomes relevant to this review • QoL: VAS • Anaemia-related markers: Hb, EPO dose • Myocardial function: intradialytic hypotension • Death: any cause, cardiovascular
Notes	Funding source: Sigma Tau for providing the *L*-carnitine and for additional financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind placebo-controlled" study

Vaux 2004 *(Continued)*

QoL		
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Death	Low risk	Quote: "double-blind placebo-controlled" study
Incomplete outcome data (attrition bias) QoL	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Myocardial function	Low risk	Missing outcome data balanced in numbers across intervention groups
Incomplete outcome data (attrition bias) Death	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	High risk	Sigma Tau for providing the L-carnitine and for additional financial support

Yano 2021

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: November 2015 to June 2016 • Study follow-up: 3 months
Participants	Baseline characteristics • Country: Japan • Setting: university hospital (1 site) • Inclusion criteria: stable HD patients; > 20 years; ESKD undergoing HD; carnitine deficiency, defined as having both free carnitine levels < 36 µmoL/L, and acylcarnitine free/carnitine ratio < 0.4 • Randomised number (intervention group/control): 10/10 • Dialysis modality: HD • Mean age ± SD (years): intervention group (57.1 ± 11.1); control group (53.9 ± 16.5) • Sex (M/F): intervention group (6/4); control group (6/4) • Dialysis duration: not reported

Yano 2021 *(Continued)*

	• Exclusion criteria: contraindications for L-carnitine; pregnant women, or those possibly pregnant; patients deemed inadequate by a physician; or those suffering from symptomatic CVD or musculoskeletal disorders interfering with exercise training
Interventions	Intervention group • L-carnitine (IV): 1000 mg at each dialysis session for 3 months Control group • Cycle ergometer exercise during HD sessions
Outcomes	Outcomes relevant to this review • Muscle weakness: 10-minute walk test, chair-stand test • Anaemia-related markers: Hb
Notes	Funding source: a Grant-in-Aid for Welfare and Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. One of the authors has received honoraria, including lecture fees, from Otsuka Pharmaceutical Co., Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned using simple randomization procedures (computer-generated list of random numbers) "
Allocation concealment (selection bias)	Low risk	Quote: "the allocation was concealed by finishing the randomization"
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label" study
Blinding of outcome assessment (detection bias) Muscle symptoms	High risk	Quote: "open-label" study
Blinding of outcome assessment (detection bias) Anaemia-related markers	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) Muscle symptoms	Low risk	All patient outcome data reported
Incomplete outcome data (attrition bias) Anaemia-related markers	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes of interest to this review were reported
Other bias	High risk	Funding source: a Grant-in-Aid for Welfare and Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. One of the authors has received honoraria, including lecture fees, from Otsuka Pharmaceutical Co., Ltd

Zilleruelo 1993

Study characteristics	
Methods	Study characteristics • Study design: parallel RCT • Study duration: not reported • Study follow-up: 3 months
Participants	Baseline characteristics • Country: USA • Setting: not reported • Inclusion criteria: patients undergoing either bicarbonate or acetate HD • Number (total): 33 • Dialysis modality: HD • Mean age, range (years): 37, 12 to 72 • Sex (M/F): not reported • Mean dialysis duration, range (months): 39, 6 to 192 • Exclusion criteria: not reported
Interventions	Intervention group • L-carnitine (IV): 2000 mg at each dialysis session for 3 months Control group • Placebo
Outcomes	Outcomes relevant to this review • Myocardial function: intradialytic hypotension
Notes	Funding source: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind placebo-controlled" study
Blinding of outcome assessment (detection bias) Muscle symptoms	Low risk	Quote: "double-blind" study
Blinding of outcome assessment (detection bias) Myocardial function	Low risk	Quote: "double-blind" study

Zilleruelo 1993 *(Continued)*

Incomplete outcome data (attrition bias) Muscle symptoms	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) Myocardial function	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

ACEi: angiotensin-converting enzyme inhibitor; BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CAPD: continuous ambulatory peritoneal dialysis; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; EPO: erythropoietin; ESKD: end-stage kidney disease; Hb: haemoglobin; HCT: haematocrit; HD: haemodialysis; HDL: high density lipoprotein; IP: intraperitoneal; IQR: interquartile range; IV: intravenous; KDQ: Kidney Disease Questionnaire; LVM: left ventricular mass; M/F: male/female; MI: myocardial infarction; NYHA: New York Heart Association; PD: peritoneal dialysis; PTH: parathyroid hormone; RCT: randomised controlled trial; rHuEPO: recombinant human erythropoietin; SBP: systolic blood pressure; SC: subcutaneous; SD: standard deviation; SF-36: Short Form 36; SI: serum iron; TIBC: total iron binding capacity; URR: urea reduction ratio; VAS: visual analogue scale; w/v: weight/volume

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alattiya 2016	Not designed to measure our outcomes of interest: serum albumin, ALP, WBC, monocyte counts
Al-Madani 2000	Wrong intervention: cellulose acetate and polysulfone HD
Bellinghieri 1990	Not designed to measure the outcomes of interest: platelet aggregation; lipid profiles
Bizzi 1978	Wrong intervention: single dose of L-carnitine was administered
Bonomini 2007	Not designed to measure the outcomes of interest: platelet activation responses
Bonomini 2020	Wrong comparison: control group also received L-carnitine
Candan 2001	Not designed to measure the outcomes of interest: respiratory functions
Duranay 2006	Not designed to measure the outcomes of interest: inflammatory and nutritional markers
Fatouros 2010	Not designed to measure the outcomes of interest: oxidative stress responses
Gahl 1993	Wrong participants: patients with nephropathic cystinosis
Guarnieri 1980a	Not designed to measure the outcomes of interest: lipid profiles
Gunal 1999	Wrong intervention: a single dose of L-carnitine was administered
Hakeshzadeh 2010	Not designed to measure the outcomes of interest: serum amyloid A, vascular inflammation markers
Iranian 2009	Not designed to measure the outcomes of interest: inflammation markers

Study	Reason for exclusion
IRCT2013042913160N1	Not designed to measure the outcomes of interest: pre-albumin, transferrin, total lymphocyte count, CRP
IRCT2014030516848N1	Not designed to measure the outcomes of interest: sleep quality
IRCT2015112224645N2	Not designed to measure the outcomes of interest: oxidized LDL, serum malondialdehyde
Ito 2019b	Not designed to measure the outcomes of interest: residual kidney function
Liu 2020	Not designed to measure the outcomes of interest: kidney function, immunity, inflammatory response, oxidative stress
Owen 2007	Not designed to measure the outcomes of interest: cardiac parameters (blood pressure, stroke volume, cardiac output, peripheral resistance, heart rate), muscle biopsy
Sabri 2012	Not designed to measure the outcomes of interest: endothelial function
Sakurabayashi 2001	Wrong control: compared different doses (L-carnitine 5 mg/kg versus 10 mg/kg versus 15 mg/kg)
Shakeri 2010	Not designed to measure the outcomes of interest: inflammation markers, lipoprotein, oxidative stress
Shojaei 2011	Not designed to measure the outcomes of interest: serum lipoprotein
Siami 1991	Not designed to measure the outcomes of interest: fatty acid metabolism
Sja'bani 2005	Not designed to measure the outcomes of interest: maximum voluntary contraction of quadriceps femoral muscle
Suchitra 2011	Not designed to measure the outcomes of interest: lipid parameters, inflammatory, nutritional markers
Vacha 1989	Wrong control: compared at different doses (L-carnitine 4 g versus 2 g)
Warady 1990	Not designed to measure the outcomes of interest: serum triglyceride
Weschler 1984	Not designed to measure the outcomes of interest: platelet aggregation, serum triglyceride
Yassari 2020	Not designed to measure the outcomes of interest: ergospirometry parameters (VE Max, VO2-Max and VCO2 Max, AT, VE/VCO2 slope)
Yderstraede 1987	Not designed to measure the outcomes of interest: carnitine, triglycerides, cholesterol, apolipoprotein
Zilleruelo 1989	Not designed to measure the outcomes of interest: lipid profiles

ALP: alkaline phosphatase; CRP: C-reactive protein; LDL: low-density lipoprotein; WBC: white blood cells

Characteristics of studies awaiting classification *[ordered by study ID]*

ACCORD 2009

Methods	Parallel RCT (blinded)
Participants	HD patients

ACCORD 2009 *(Continued)*

Interventions	L-carnitine (IV): 1000 mg at each dialysis session for 6 months
Outcomes	Primary outcome: EPO resistance index Secondary outcome: muscle fatigue, QoL (SF-36), dialytic symptoms, and plasma lipid profiles
Notes	The study has been completed. A publication has been prepared, but not yet published

EudraCT2006-005298-23

Methods	Parallel RCT (open label)
Participants	Adult PD patients
Interventions	L-carnitine containing PD solution
Outcomes	Insulin sensitivity
Notes	Protocol registration only; current status is unknown

EudraCT2006-005300-13

Methods	Parallel RCT (open label)
Participants	Adults PD patients with diabetes type 2
Interventions	L-carnitine containing PD solution
Outcomes	Insulin sensitivity
Notes	Protocol registration only; current status is prematurely ended

IRCT138811212779N2

Methods	Parallel RCT (double blind)
Participants	HD patients
Interventions	L-carnitine (IV): 1000 mg at each dialysis session/ubiquinone (oral) 100 mg/day
Outcomes	Cardiovascular risk factors
Notes	Protocol registration only; current status is unknown

IRCT20180921041080N1

Methods	Parallel RCT (double blind)
Participants	HD participants

IRCT20180921041080N1 *(Continued)*

Interventions	L-carnitine
Outcomes	Anaemia related-markers
Notes	Protocol registration only; current status is unknown

ISRCTN96315193

Methods	Parallel RCT (3-arm)
Participants	HD patients
Interventions	1. rHuEPO 2. L-carnitine (IV) 3. rHuEPO + L-carnitine (IV)
Outcomes	Hb
Notes	Protocol registration only; current status is completed, the results is unknown

Jack 2000

Methods	Parallel RCT
Participants	ESKD patients
Interventions	L-carnitine (IV)
Outcomes	QoL (SF-36), anaemia-related markers (Hb, ESA dose)
Notes	Study was not described as randomised. More information was needed from the original authors, but their contact details were not available

RENACARE 2019

Methods	Parallel RCT (double-blind)
Participants	HD patients
Interventions	Oral nutritional supplement specifically developed for undernourished HD patients enriched with functional nutrients (extra virgin olive oil, omega 3 fatty acids, whey protein, antioxidants and carnitine), with probiotics
Outcomes	• Nutritional status: anthropometric measurements, handgrip strength measured by a Jamar hand dynamometer, body composition assessed by bioelectrical impedance analysis, and a 5-day dietary record • Functional status assessed by the "Barthel" test, the "Short Physical Performance Battery" and the "International Physical Activity Questionnaire" • QoL assessed by the "12-item short form health survey", and the presence of symptoms of depression and anxiety by the "Hospital Anxiety and Depression Scale"

RENACARE 2019 *(Continued)*

	• Inflammatory markers • Oxidative markers • Gut microbiota • Circulating miRNAs and the expression of it's target genes on cells
Notes	Protocol registration only; current status is completed, the results is unknown

UMIN000011208

Methods	Cross-over RCT (single blind)
Participants	HD patients
Interventions	L-carnitine
Outcomes	Anaemia, cardiac function, muscle wasting
Notes	Protocol registration only; this study has been completed. A publication has been prepared, but not yet published

UMIN000012222

Methods	Cross-over RCT (single blind)
Participants	HD patients
Interventions	L-carnitine
Outcomes	cardiac function, anaemia, exercise tolerance
Notes	Protocol registration only; this study is terminated

UMIN000013009

Methods	Cross-over RCT (single blind)
Participants	HD patients
Interventions	L-carnitine
Outcomes	Questionnaire survey (physical weariness, muscle condition), regular blood test and chest X-ray, test of physical strength, muscle mass, EPO resistance index, differential count of carnitine
Notes	Protocol registration only; current status is terminated

UMIN000031514

Methods	Parallel RCT (open label)

UMIN000031514 *(Continued)*

Participants	PD patients
Interventions	L-carnitine
Outcomes	Peritoneal membrane function, residual kidney function, cardiac function, EPO resistant anaemia, insulin resistance
Notes	Protocol registration only; current status is completed. A publication has been prepared, but not yet published

Unsal 2006

Methods	Cross-over study
Participants	HD patients
Interventions	L-carnitine
Outcomes	Intradialytic hypotension, muscle cramps
Notes	Study was not described as randomised. More information was needed from the original authors, but their contact details were not available

EPO: erythropoietin; ESA: erythropoietin stimulating agents; ESKD: end-stage kidney disease; Hb: haemoglobin; HD: haemodialysis; PD: peritoneal dialysis; QoL: quality of life; RCT: randomised controlled trial; rHuEPO: recombinant human erythropoietin; SF-36: Short form 36

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20200225046620N1

Study name	The effect of L-carnitine and erythropoietin on anemia in hemodialysis patients
Methods	Parallel RCT
Participants	Inclusion criteria: < 30 years, history of at least 6 months of dialysis Exclusion criteria: active infectious or inflammatory disease
Interventions	Intervention group 1 • EPO (SC): 2000 IU 3 times/week • L-carnitine placebo (oral): daily for 3 months Intervention group 2 • EPO (SC): 2000 IU 3 times/week • L-carnitine (oral tablet): 20 mg/kg/day
Outcomes	Hb
Starting date	20 Feb 2020
Contact information	Fatemeh Attaran Kakhk Zahedan University of Medical Sciences

IRCT20200225046620N1 *(Continued)*

Notes	Status: recruitment complete (last updated: 24 March 2020). The current status is unknown

IRCT20201027049166N1

Study name	Effect of oral L–carnitine and omega 3 supplementation separately and in combination on quality of life, quality of sleep, lipid profile and CRP in renal failure patients under hemodialysis _A randomized clinical trial
Methods	RCT
Participants	Inclusion criteria: >18 years; HD > twice/week for 3 months; negative history of allergy to L-carnitine and omega 3 Exclusion criteria: use of supplementation with L-carnitine or omega 3; unpredictable drug complication; uncooperative; planned kidney transplantation
Interventions	Intervention 1 • L-carnitine (oral tablet): 250 mg (Poursina Pharmaceutical Company) twice/day for 3 months Intervention 2 • Omega 3 (oral capsule): 1000 mg/day (GMV Pharmaceutical Company) for 3 months Intervention 3 • L-carnitine (oral tablet): 250 mg (Poursina Pharmaceutical Company) twice/day for 3 months • Omega 3 (oral capsule): 1000 mg/day (GMV Pharmaceutical Company) for 3 months
Outcomes	Profile lipid Questionnaire score of sleep quality Questionnaire score QoL in HD
Starting date	8 July 2021
Contact information	Alireza Dehghan Yasouj University of Medical Sciences
Notes	Status: recruitment complete (last updated: 6 April 2021). The current status is unknown

EPO: erythropoietin; Hb: haemoglobin; HD: haemodialysis; QoL: quality of life; RCT: randomised controlled trial; SC: subcutaneous

DATA AND ANALYSES

Comparison 1. L-carnitine versus placebo

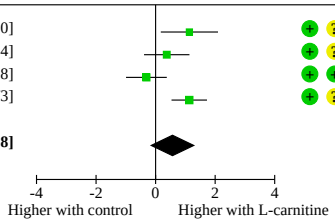
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 QoL (SF-36 PCS)	4	134	Std. Mean Difference (IV, Random, 95% CI)	0.57 [-0.15, 1.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 QoL (SF-36 MCS)	4	134	Std. Mean Difference (IV, Random, 95% CI)	0.70 [0.22, 1.18]
1.3 QoL (total)	3	230	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.29, 0.25]
1.4 Fatigue score	2	353	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.20, 0.23]
1.5 Adverse events	12	1041	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.86, 1.51]
1.6 Muscle symptoms	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Cramps	2	102	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.18, 1.09]
1.6.2 Weakness	2	102	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.47, 1.25]
1.7 Anaemia-related markers (Hb)	26	1795	Mean Difference (IV, Random, 95% CI)	0.46 [0.18, 0.74]
1.8 Anaemia-related markers (HCT)	14	950	Mean Difference (IV, Random, 95% CI)	1.78 [0.38, 3.18]
1.9 Anaemia-related markers (EPO dose)	13	965	Mean Difference (IV, Random, 95% CI)	-0.97 [-1.59, -0.34]
1.10 Anaemia-related markers (EPO resistance index)	5	343	Mean Difference (IV, Random, 95% CI)	-1.56 [-3.59, 0.46]
1.11 Myocardial function (intradialytic hypotension)	3	128	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.34, 1.69]
1.12 Myocardial function (LVM)	3	217	Mean Difference (IV, Random, 95% CI)	-7.18 [-14.24, -0.13]
1.13 Myocardial function (ejection fraction)	6	410	Mean Difference (IV, Random, 95% CI)	2.26 [-0.26, 4.79]
1.14 Death (any cause)	13	857	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.68, 2.43]
1.15 Death (cardiovascular)	5	445	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.30, 3.19]
1.16 Vascular access failure	1	102	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.06, 15.56]
1.17 Peritoneal dialysis infection	1	35	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.13, 13.34]

Analysis 1.1. Comparison 1: L-carnitine versus placebo, Outcome 1: QoL (SF-36 PCS)

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Rathod 2006	48.12	12.48	10	34.08	11.18	10	21.2%	1.13 [0.17 , 2.10]	+ ? − − + ? ?
Steiber 2006	39.7	8.29	13	35.7	11.97	14	24.8%	0.37 [-0.39 , 1.14]	+ ? + + − ? −
CARNIDIAL 2012	26.91	1.85	13	27.48	1.78	23	26.2%	-0.31 [-0.99 , 0.38]	+ + + + ? + −
Naini 2011	52.5	18	24	34.5	13.3	27	27.8%	1.13 [0.53 , 1.73]	+ ? + + ? + +
Total (95% CI)			**60**			**74**	**100.0%**	**0.57 [-0.15 , 1.28]**	

Heterogeneity: Tau² = 0.39; Chi² = 11.32, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable

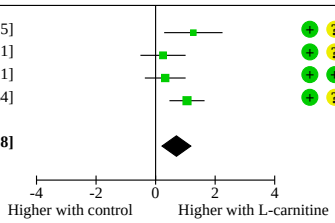


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): QoL
(E) Incomplete outcome data (attrition bias): QoL
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: L-carnitine versus placebo, Outcome 2: QoL (SF-36 MCS)

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Rathod 2006	50.17	11.1	10	34.41	12.66	10	17.2%	1.27 [0.29 , 2.25]	+ ? − − + ? ?
Steiber 2006	54.2	7.93	13	51.8	10.48	14	24.1%	0.25 [-0.51 , 1.01]	+ ? + + − ? −
CARNIDIAL 2012	17.8	1.81	13	17.18	1.91	23	27.1%	0.32 [-0.36 , 1.01]	+ + + + ? + −
Naini 2011	58.2	21.2	24	37.6	17.3	27	31.5%	1.05 [0.47 , 1.64]	+ ? + + ? + +
Total (95% CI)			**60**			**74**	**100.0%**	**0.70 [0.22 , 1.18]**	

Heterogeneity: Tau² = 0.10; Chi² = 5.20, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Not applicable

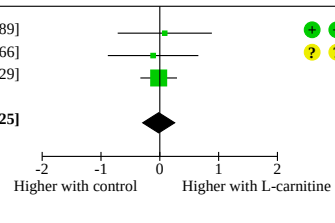


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): QoL
(E) Incomplete outcome data (attrition bias): QoL
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: L-carnitine versus placebo, Outcome 3: QoL (total)

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Hamedi-Kalajahi 2021	67.33	8.12	12	66.67	6.88	12	11.5%	0.08 [-0.72 , 0.89]	+ + + + + + +
Vaux 2004	0.75	1.5	13	1	2.6	13	12.4%	-0.11 [-0.88 , 0.66]	? ? + + + ? −
Brass 2001 (A+B)	5.27	1.03	121	5.29	1.08	59	76.1%	-0.02 [-0.33 , 0.29]	
Total (95% CI)			**146**			**84**	**100.0%**	**-0.02 [-0.29 , 0.25]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

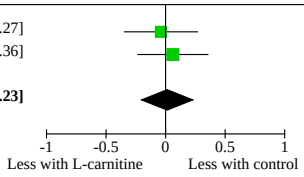


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): QoL
(E) Incomplete outcome data (attrition bias): QoL
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: L-carnitine versus placebo, Outcome 4: Fatigue score

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brass 2001 (A+B)	5.09	1.28	121	5.14	1.22	59	47.8%	-0.04 [-0.35 , 0.27]
Fukuda 2015	5.59	4.56	87	5.31	4.52	86	52.2%	0.06 [-0.24 , 0.36]
Total (95% CI)			**208**			**145**	**100.0%**	**0.01 [-0.20 , 0.23]**

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable

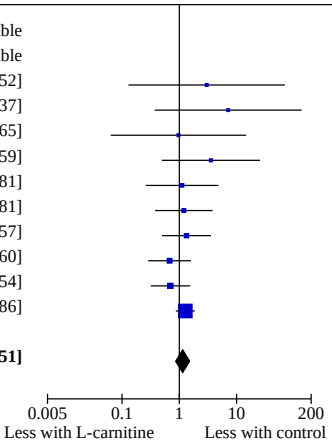


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Fatigue score
(E) Incomplete outcome data (attrition bias): Fatigue score
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: L-carnitine versus placebo, Outcome 5: Adverse events

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Signorelli 2006	0	32	0	32		Not estimable
Maruyama 2017	0	30	0	30		Not estimable
Kletzmayr 1999	1	20	0	20	0.8%	3.00 [0.13 , 69.52]
Higuchi 2014	3	110	0	112	0.9%	7.13 [0.37 , 136.37]
Mortazavi 2011a	1	28	1	27	1.1%	0.96 [0.06 , 14.65]
Mettang 1997	4	9	1	8	2.0%	3.56 [0.49 , 25.59]
Mortazavi 2012	3	17	3	19	3.7%	1.12 [0.26 , 4.81]
Fukuda 2015	6	103	5	103	5.9%	1.20 [0.38 , 3.81]
Fukami 2013	8	51	6	51	8.1%	1.33 [0.50 , 3.57]
Ahmad 1990	7	47	11	50	10.6%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	12.6%	0.70 [0.32 , 1.54]
CARNIDIAL 2012	28	46	22	46	54.3%	1.27 [0.87 , 1.86]
Total (95% CI)		**518**		**523**	**100.0%**	**1.14 [0.86 , 1.51]**
Total events:	68		59			

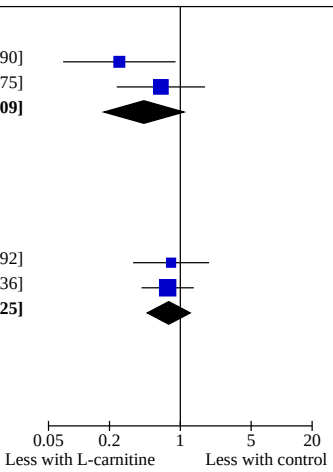
Heterogeneity: Tau² = 0.00; Chi² = 6.44, df = 9 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable

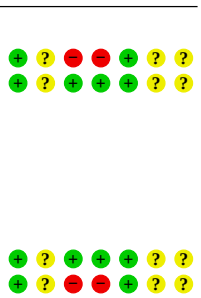


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Adverse events
(E) Incomplete outcome data (attrition bias): Adverse events
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: L-carnitine versus placebo, Outcome 6: Muscle symptoms

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Cramps						
Rathod 2006	2	10	8	10	40.9%	0.25 [0.07 , 0.90]
Ahmad 1990	5	38	9	44	59.1%	0.64 [0.24 , 1.75]
Subtotal (95% CI)		**48**		**54**	**100.0%**	**0.44 [0.18 , 1.09]**
Total events:	7		17			
Heterogeneity: Tau² = 0.10; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%						
Test for overall effect: Z = 1.78 (P = 0.07)						
1.6.2 Weakness						
Ahmad 1990	7	38	10	44	32.1%	0.81 [0.34 , 1.92]
Rathod 2006	6	10	8	10	67.9%	0.75 [0.41 , 1.36]
Subtotal (95% CI)		**48**		**54**	**100.0%**	**0.77 [0.47 , 1.25]**
Total events:	13		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: Chi² = 1.15, df = 1 (P = 0.28), I² = 12.8%						





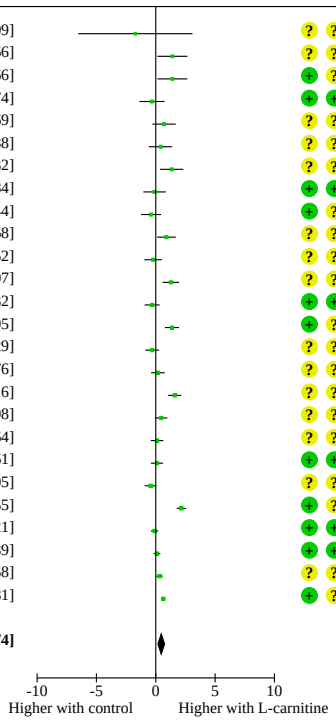
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Muscle symptoms
(E) Incomplete outcome data (attrition bias): Muscle symptoms
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: L-carnitine versus placebo, Outcome 7: Anaemia-related markers (Hb)

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Mettang 1997	10.21	6	8	11.93	3.27	7	0.3%	-1.72 [-6.53 , 3.09]	? ? + + + ? -
Mitwalli 2005	11.3	2.1	24	9.9	2.5	27	2.5%	1.40 [0.14 , 2.66]	? ? - + - ? ?
Naini 2011	11.3	2.1	24	9.9	2.5	27	2.5%	1.40 [0.14 , 2.66]	+ ? + + + + +
Mortazavi 2011a	11.08	2	28	11.4	2	27	3.0%	-0.32 [-1.38 , 0.74]	+ + + + + + +
Khodaverdi 2010	1.2	1.2	14	0.5	1.5	15	3.2%	0.70 [-0.29 , 1.69]	? ? + + + + ?
Biolo 2008	12.9	1.2	9	12.5	0.949	10	3.2%	0.40 [-0.58 , 1.38]	? ? + + + ? -
Fu 2010	9.87	1.89	20	8.53	1.18	20	3.2%	1.34 [0.36 , 2.32]	? ? - + + ? +
Yano 2021	11.6	1.4	10	11.7	0.6	10	3.3%	-0.10 [-1.04 , 0.84]	+ + - + + + -
Steiber 2006	11.9	1.2	15	12.3	1.3	19	3.5%	-0.40 [-1.24 , 0.44]	+ ? + + - ? -
Arduini 2006	11.3	0.8	13	10.4	1.2	13	3.7%	0.90 [0.12 , 1.68]	? ? + + + ? -
Cibulka 2005	11.484	1.702	44	11.705	1.726	39	3.8%	-0.22 [-0.96 , 0.52]	? ? + + ? ? +
Mortazavi 2012	11.6	1.05	17	10.33	1.08	19	3.9%	1.27 [0.57 , 1.97]	? ? + + ? + +
Sugiyama 2021	11.094	0.8	34	11.4	1.2	17	4.1%	-0.31 [-0.94 , 0.32]	+ + - + + + -
Rathod 2006	0.89	0.56	10	-0.47	0.77	10	4.2%	1.36 [0.77 , 1.95]	+ ? - + + ? ?
Brass 2001a	11	1.3	28	11.3	0.9	28	4.3%	-0.30 [-0.89 , 0.29]	? ? + + + ? -
Vaux 2004	-0.08	0.9	13	-0.26	0.56	13	4.3%	0.18 [-0.40 , 0.76]	? ? + + + ? -
Garneata 2005	10.2	0.9	20	8.6	0.9	20	4.3%	1.60 [1.04 , 2.16]	? ? ? + ? ? ?
Saxena 2004	9.68	0.844	10	9.23	0.13	10	4.4%	0.45 [-0.08 , 0.98]	? ? ? + ? ? ?
Sorge-Haedicke 2001	10.89	1.19	43	10.78	1.26	40	4.4%	0.11 [-0.42 , 0.64]	? ? + + ? ? ?
Maruyama 2017	11.1	1	30	11	1	30	4.5%	0.10 [-0.41 , 0.61]	+ + - + + + -
Brass 2001b	11.16	1.07	94	11.6	1.3	33	4.5%	-0.44 [-0.93 , 0.05]	? ? + + + ? -
Cui 2016	11.436	1.227	78	9.272	1.251	78	4.8%	2.16 [1.78 , 2.55]	+ ? - + + ? ?
Fukuda 2015	10.5	0.99	87	10.6	1.06	86	4.9%	-0.10 [-0.41 , 0.21]	+ + + + + + -
Higuchi 2014	11.1	0.6	75	11	1.1	73	5.0%	0.10 [-0.19 , 0.39]	+ + - + + + -
Song 2013a	11.534	1.166	163	11.22	1.323	163	5.0%	0.31 [0.04 , 0.58]	? ? - + + ? +
Chi 2021	8.798	0.266	25	8.172	0.385	25	5.1%	0.63 [0.44 , 0.81]	+ ? ? + + ? +
Total (95% CI)			**936**			**859**	**100.0%**	**0.46 [0.18 , 0.74]**	

Heterogeneity: Tau² = 0.38; Chi² = 176.92, df = 25 (P < 0.00001); I² = 86%
Test for overall effect: Z = 3.24 (P = 0.001)
Test for subgroup differences: Not applicable

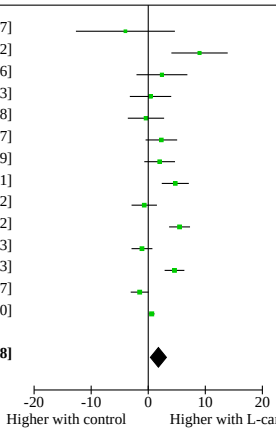


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Anaemia-related markers
(E) Incomplete outcome data (attrition bias): Anaemia-related markers
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: L-carnitine versus placebo, Outcome 8: Anaemia-related markers (HCT)

Study or Subgroup	L-carnitine Mean [%]	L-carnitine SD [%]	L-carnitine Total	Control Mean [%]	Control SD [%]	Control Total	Weight	Mean Difference IV, Random, 95% CI [%]	Risk of Bias A B C D E F G
Mettang 1997	32	8	8	36	9	7	2.1%	-4.00 [-12.67 , 4.67]	? ? + + + ? -
Trovato 1983	36.35	7.22	13	27.36	5.5	13	4.5%	8.99 [4.06 , 13.92]	? ? - + ? ? ?
Pacheco 2008	32.2	5.6	13	29.8	4.7	8	5.0%	2.40 [-2.06 , 6.86]	+ ? + + - ? -
Chazot 2003	32.5	6.6	23	32.1	5.8	22	6.0%	0.40 [-3.23 , 4.03]	? ? - + + ? ?
Khodaverdi 2010	3.3	3.8	14	3.7	4.9	15	6.7%	-0.40 [-3.58 , 2.78]	? ? + + + + ?
Mitwalli 2005	32.5	3.7	18	30.2	4	13	7.3%	2.30 [-0.47 , 5.07]	? ? - + - ? ?
Arduini 2006	34.3	3.6	13	32.3	3.4	13	7.4%	2.00 [-0.69 , 4.69]	? ? + + + ? -
Caruso 1998	32.84	2.26	12	28.1	4.07	16	7.9%	4.74 [2.37 , 7.11]	? ? + + + ? -
Steiber 2006	37	2.7	15	37.7	3.9	19	8.1%	-0.70 [-2.92 , 1.52]	+ ? + + - ? -
Cui 2016	40.23	5.78	78	34.74	5.89	78	8.7%	5.49 [3.66 , 7.32]	+ ? - + + ? ?
Brass 2001b	32.8	4	28	33.9	2.9	28	8.7%	-1.10 [-2.93 , 0.73]	? ? + + + ? -
Harmankaya 2002a	32.4	3.1	15	27.8	1.44	15	8.8%	4.60 [2.87 , 6.33]	? ? ? + ? ? ?
Brass 2001a	33.6	3.18	94	35.1	4.2	33	9.0%	-1.50 [-3.07 , 0.07]	? ? + + + ? -
Song 2013a	34.5	2.4	163	33.9	2.2	163	10.0%	0.60 [0.10 , 1.10]	? ? - + + ? +
Total (95% CI)			**507**			**443**	**100.0%**	**1.78 [0.38 , 3.18]**	

Heterogeneity: Tau² = 5.02; Chi² = 82.76, df = 13 (P < 0.00001); I² = 84%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable

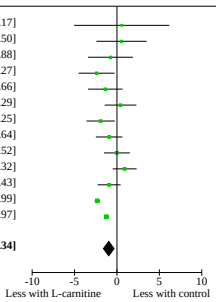


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Anaemia-related markers
(E) Incomplete outcome data (attrition bias): Anaemia-related markers
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: L-carnitine versus placebo, Outcome 9: Anaemia-related markers (EPO dose)

Study or Subgroup	L-carnitine Mean [×1000 U/week]	L-carnitine SD [×1000 U/week]	L-carnitine Total	Control Mean [×1000 U/week]	Control SD [×1000 U/week]	Control Total	Weight	Mean Difference IV, Random, 95% CI [×1000 U/week]	Risk of Bias A B C D E F G
Kletzmayr 1999	12.4683	7.0863	12	11.9094	8.0178	16	1.2%	0.56 [-5.05 , 6.17]	? ? + + ? ? -
Mortazavi 2012	6.666	4.618	17	6.125	4.421	19	3.5%	0.54 [-2.42 , 3.50]	? ? + + ? + +
Caruso 1998	6.364	3.557	12	7.125	3.5	16	4.2%	-0.76 [-3.41 , 1.88]	? ? + + + ? -
Harmankaya 2002a	4.8	3.3	15	7.2	2.6	15	5.6%	-2.40 [-4.53 , -0.27]	? ? ? + ? ? ?
Labonia 1995	3.5385	1.898	13	4.9091	2.9681	11	6.0%	-1.37 [-3.41 , 0.66]	? ? + + ? ? -
Sorge-Haedicke 2001	6.0828	4.3956	43	5.661	4.2846	40	6.6%	0.42 [-1.45 , 2.29]	? ? + + ? ? ?
Maruyama 2017	4.078	2.467	30	5.995	3.96	30	7.5%	-1.92 [-3.59 , -0.25]	+ + - + + + -
Garneata 2005	7.67173	2.43741	20	8.59205	2.60997	20	8.0%	-0.92 [-2.49 , 0.64]	? ? ? + ? ? ?
Cibulka 2005	4.5	3.557	44	4.5	3.5	39	8.3%	0.00 [-1.52 , 1.52]	? ? + + ? ? +
Chazot 2003	1.934	2.728	23	1.029	2.073	22	8.9%	0.91 [-0.51 , 2.32]	? ? - + + ? ?
Vaux 2004	-0.769	1.739	13	0.153	1.772	13	9.2%	-0.92 [-2.27 , 0.43]	? ? + + + ? -
Song 2013a	7.261	1.37	163	9.5685	1.5755	163	15.4%	-2.31 [-2.63 , -1.99]	? ? - + + ? +
Cui 2016	9.73385	0.85625	78	10.9737	0.84255	78	15.6%	-1.24 [-1.51 , -0.97]	+ ? - + + ? ?
Total (95% CI)			**483**			**482**	**100.0%**	**-0.97 [-1.59 , -0.34]**	

Heterogeneity: Tau² = 0.64; Chi² = 51.62, df = 12 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.03 (P = 0.002)
Test for subgroup differences: Not applicable

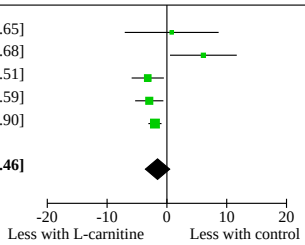


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Anaemia-related markers
(E) Incomplete outcome data (attrition bias): Anaemia-related markers
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: L-carnitine versus placebo, Outcome 10: Anaemia-related markers (EPO resistance index)

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Kletzmayr 1999	17.2	10	12	16.4	11.1	16	5.7%	0.80 [-7.05 , 8.65]	? ? + + ? ? −
CARNIDIAL 2012	15.6	15.9	35	9.5	5.8	38	9.9%	6.10 [0.52 , 11.68]	+ + + + + + −
Maruyama 2017	6.4	3.8	30	9.6	6.5	30	23.3%	-3.20 [-5.89 , -0.51]	+ + − + + + −
Steiber 2006	-1.62	3.52	15	1.33	3.44	19	25.7%	-2.95 [-5.31 , -0.59]	+ ? + + − ? −
Higuchi 2014	6.9	3.5	75	8.9	3.3	73	35.5%	-2.00 [-3.10 , -0.90]	+ + − + + + −
Total (95% CI)			**167**			**176**	**100.0%**	**-1.56 [-3.59 , 0.46]**	

Heterogeneity: Tau² = 2.69; Chi² = 9.96, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable

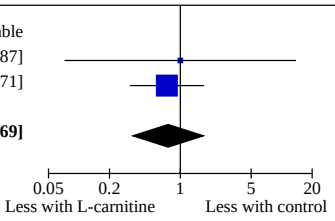


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Anaemia-related markers
(E) Incomplete outcome data (attrition bias): Anaemia-related markers
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.11. Comparison 1: L-carnitine versus placebo, Outcome 11: Myocardial function (intradialytic hypotension)

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Vaux 2004	0	13	0	13		Not estimable	? ? + + + ? −
Rathod 2006	1	10	1	10	9.3%	1.00 [0.07 , 13.87]	+ ? − − + ? ?
Ahmad 1990	7	38	11	44	90.7%	0.74 [0.32 , 1.71]	+ ? + + + ? ?
Total (95% CI)		**61**		**67**	**100.0%**	**0.76 [0.34 , 1.69]**	
Total events:	8		12				

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

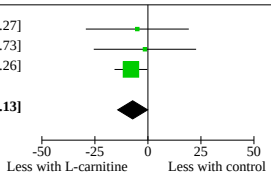


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Myocardial function
(E) Incomplete outcome data (attrition bias): Myocardial function
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.12. Comparison 1: L-carnitine versus placebo, Outcome 12: Myocardial function (LVM)

Study or Subgroup	L-carnitine Mean [g/m²]	L-carnitine SD [g/m²]	L-carnitine Total	Control Mean [g/m²]	Control SD [g/m²]	Control Total	Weight	Mean Difference IV, Random, 95% CI [g/m²]	Risk of Bias A B C D E F G
Kudoh 2013	97.1	30.2	10	102.1	22.3	8	8.5%	-5.00 [-29.27 , 19.27]	? ? + + ? ? ?
Sugiyama 2021	118.6	35.8	34	120	44	17	8.6%	-1.40 [-25.53 , 22.73]	+ + − ? + + −
Higuchi 2014	104	23	75	112	25	73	83.0%	-8.00 [-15.74 , -0.26]	+ + − ? + + −
Total (95% CI)			**119**			**98**	**100.0%**	**-7.18 [-14.24 , -0.13]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)
Test for subgroup differences: Not applicable

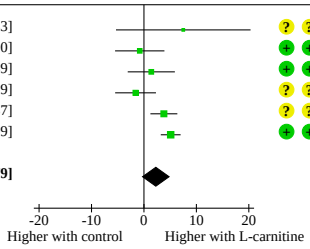


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Myocardial function
(E) Incomplete outcome data (attrition bias): Myocardial function
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.13. Comparison 1: L-carnitine versus placebo, Outcome 13: Myocardial function (ejection fraction)

Study or Subgroup	L-carnitine Mean [%]	L-carnitine SD [%]	L-carnitine Total	Control Mean [%]	Control SD [%]	Control Total	Weight	Mean Difference IV, Random, 95% CI [%]	Risk of Bias A B C D E F G
Kudoh 2013	64.4	13.8	10	56.9	13.8	8	3.4%	7.50 [-5.33 , 20.33]	? ? + + ? ? ?
Sugiyama 2021	64.5	9.29	34	65.3	7.4	17	14.7%	-0.80 [-5.50 , 3.90]	+ + − ? + + −
Maruyama 2017	58.7	8.1	30	57.3	9.6	30	15.4%	1.40 [-3.09 , 5.89]	+ + − ? + + −
Fagher 1985	-0.6	5.2	14	1	5.3	14	17.6%	-1.60 [-5.49 , 2.29]	? ? + ? + ? −
Abdul-Hassan Mahdi 2021	52.3	5.91	70	48.5	6.53	35	23.0%	3.80 [1.23 , 6.37]	? ? ? ? ? ? +
Higuchi 2014	58.6	5.5	75	53.5	6.2	73	25.8%	5.10 [3.21 , 6.99]	+ + − ? + + −
Total (95% CI)			**233**			**177**	**100.0%**	**2.26 [-0.26 , 4.79]**	

Heterogeneity: Tau² = 5.50; Chi² = 13.74, df = 5 (P = 0.02); I² = 64%
Test for overall effect: Z = 1.76 (P = 0.08)
Test for subgroup differences: Not applicable

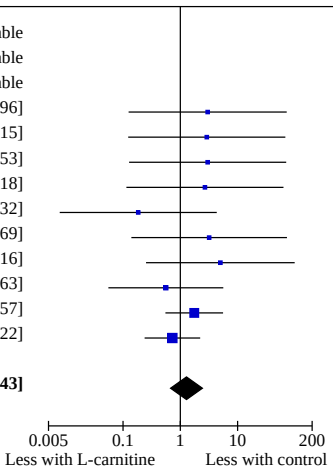


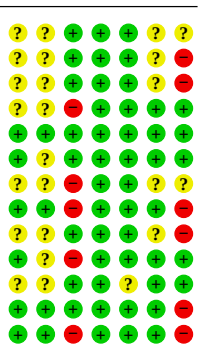
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Myocardial function
(E) Incomplete outcome data (attrition bias): Myocardial function
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.14. Comparison 1: L-carnitine versus placebo, Outcome 14: Death (any cause)

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Signorelli 2006	0	32	0	32		Not estimable
Vaux 2004	0	13	0	13		Not estimable
Mettang 1997	0	8	0	7		Not estimable
Fukami 2013	1	51	0	51	4.0%	3.00 [0.13 , 71.96]
Mortazavi 2011a	1	28	0	27	4.1%	2.90 [0.12 , 68.15]
Naini 2011	1	27	0	27	4.1%	3.00 [0.13 , 70.53]
Chazot 2003	1	28	0	25	4.1%	2.69 [0.11 , 63.18]
Sugiyama 2021	0	37	1	20	4.1%	0.18 [0.01 , 4.32]
Caruso 1998	1	15	0	16	4.2%	3.19 [0.14 , 72.69]
Ahmadi 2016	2	25	0	25	4.6%	5.00 [0.25 , 99.16]
Mortazavi 2012	1	17	2	19	7.7%	0.56 [0.06 , 5.63]
CARNIDIAL 2012	7	46	4	46	30.4%	1.75 [0.55 , 5.57]
Higuchi 2014	5	110	7	112	32.7%	0.73 [0.24 , 2.22]
Total (95% CI)		**437**		**420**	**100.0%**	**1.28 [0.68 , 2.43]**
Total events:	20		14			

Heterogeneity: Tau² = 0.00; Chi² = 5.37, df = 9 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



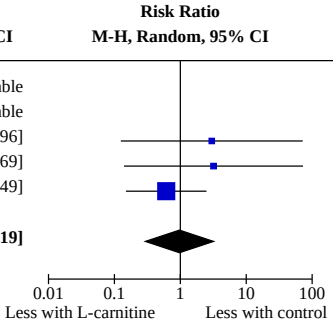


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Death
(E) Incomplete outcome data (attrition bias): Death
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.15. Comparison 1: L-carnitine versus placebo, Outcome 15: Death (cardiovascular)

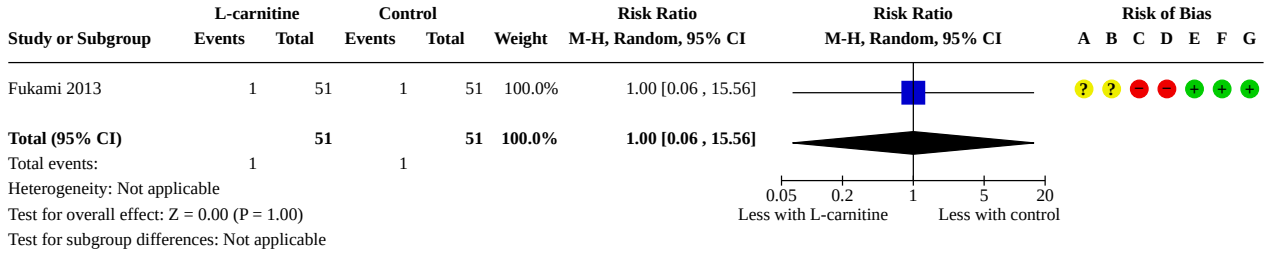
Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Vaux 2004	0	13	0	13		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Fukami 2013	1	51	0	51	14.0%	3.00 [0.13 , 71.96]
Caruso 1998	1	15	0	16	14.5%	3.19 [0.14 , 72.69]
Higuchi 2014	3	110	5	112	71.5%	0.61 [0.15 , 2.49]
Total (95% CI)		**221**		**224**	**100.0%**	**0.97 [0.30 , 3.19]**
Total events:	5		5			

Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



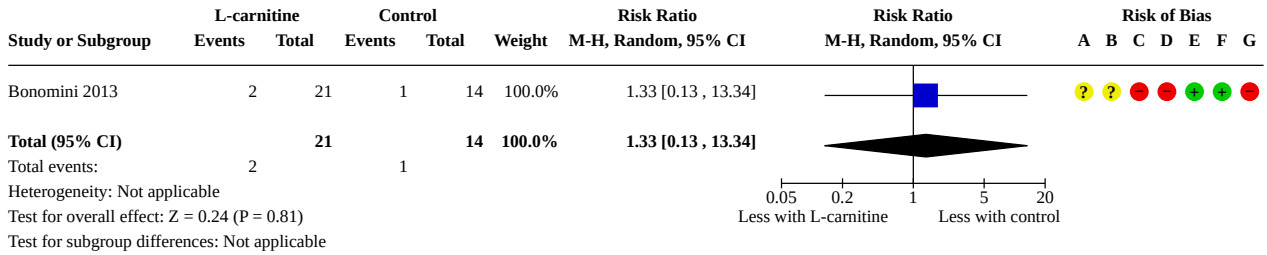
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Death
(E) Incomplete outcome data (attrition bias): Death
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.16. Comparison 1: L-carnitine versus placebo, Outcome 16: Vascular access failure



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Vascular access failure
(E) Incomplete outcome data (attrition bias): Vascular access failure
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.17. Comparison 1: L-carnitine versus placebo, Outcome 17: Peritoneal dialysis infection



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Peritoneal dialysis infection
(E) Incomplete outcome data (attrition bias): Peritoneal dialysis infection
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 QoL (SF-36 PCS): average dose	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 Dose ≥ 10 mg/kg/day	1	51	Std. Mean Difference (IV, Random, 95% CI)	1.13 [0.53, 1.73]
2.1.2 Dose < 10 mg/kg/day	3	83	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.45, 1.13]
2.2 QoL (SF-36 PCS): intervention duration	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 ≤ 6 months	3	98	Std. Mean Difference (IV, Random, 95% CI)	0.89 [0.39, 1.38]
2.2.2 > 6 months	1	36	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.99, 0.38]
2.3 QoL (SF-36 PCS): route of administration	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 Intravenous	3	83	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.45, 1.13]
2.3.2 Oral	1	51	Std. Mean Difference (IV, Random, 95% CI)	1.13 [0.53, 1.73]
2.4 QoL (SF-36 MCS): average dose	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 Dose ≥ 10 mg/kg/day	1	51	Std. Mean Difference (IV, Random, 95% CI)	1.05 [0.47, 1.64]
2.4.2 Dose < 10 mg/kg/day	3	83	Std. Mean Difference (IV, Random, 95% CI)	0.53 [-0.03, 1.10]
2.5 QoL (SF-36 MCS): intervention duration	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.5.1 ≤ 6 months	3	98	Std. Mean Difference (IV, Random, 95% CI)	0.84 [0.25, 1.42]
2.5.2 > 6 months	1	36	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.36, 1.01]
2.6 QoL (SF-36 MCS): route of administration	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.6.1 Intravenous	3	83	Std. Mean Difference (IV, Random, 95% CI)	0.53 [-0.03, 1.10]
2.6.2 Oral	1	51	Std. Mean Difference (IV, Random, 95% CI)	1.05 [0.47, 1.64]
2.7 QoL (total): average dose	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 Dose ≥ 10 mg/kg/day	2	204	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.30, 0.28]
2.7.2 Dose < 10 mg/day	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.88, 0.66]
2.8 QoL (total): route of administration	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8.1 Intravenous	2	206	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.32, 0.26]
2.8.2 Oral	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.72, 0.89]
2.9 QoL (total): age	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.9.1 Age ≥ 18 years	2	206	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.32, 0.26]
2.9.2 Age < 18 years	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.72, 0.89]
2.10 Fatigue score: route of administration	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.10.1 Intravenous	1	180	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.35, 0.27]
2.10.2 Oral	1	173	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.24, 0.36]
2.11 Fatigue score: single agent alone or multi-component	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.11.1 single agent alone	1	180	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.35, 0.27]
2.11.2 multi-component	1	173	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.24, 0.36]
2.12 Adverse events: dialysis modality	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.12.1 HD patients only	11	986	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.86, 1.52]
2.12.2 PD patients only	1	55	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.65]
2.13 Adverse events: average dose	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.13.1 Dose ≥ 10 mg/kg/day	4	415	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.65, 2.95]
2.13.2 Dose < 10 mg/kg/day	7	586	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.75, 1.52]
2.14 Adverse events: intervention duration	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.14.1 ≤ 6 months	5	472	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.46]
2.14.2 > 6 months	7	569	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.91, 1.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.15 Adverse events: route of administration	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.15.1 Intravenous	7	420	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.59]
2.15.2 Oral	5	621	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.70, 2.50]
2.16 Adverse events: single agent alone or multi-component	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.16.1 Single agent	11	835	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.85, 1.52]
2.16.2 Multi-component	1	206	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.38, 3.81]
2.17 Anaemia-related markers (Hb): dialysis modality	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.17.1 HD	25	1740	Mean Difference (IV, Random, 95% CI)	0.48 [0.20, 0.77]
2.17.2 PD	1	55	Mean Difference (IV, Random, 95% CI)	-0.32 [-1.38, 0.74]
2.18 Anaemia-related markers (Hb): average dose	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.18.1 Dose ≥ 10 mg/kg/day	8	596	Mean Difference (IV, Random, 95% CI)	0.39 [-0.14, 0.92]
2.18.2 Dose < 10 mg/kg/day	18	1199	Mean Difference (IV, Random, 95% CI)	0.50 [0.16, 0.83]
2.19 Anaemia-related markers (Hb): intervention duration	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.19.1 ≤ 6 months	20	1119	Mean Difference (IV, Random, 95% CI)	0.55 [0.19, 0.91]
2.19.2 > 6 months	6	676	Mean Difference (IV, Random, 95% CI)	0.21 [-0.11, 0.54]
2.20 Anaemia-related markers (Hb): route of administration	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.20.1 Intravenous	20	1292	Mean Difference (IV, Random, 95% CI)	0.41 [0.09, 0.74]
2.20.2 Oral	6	503	Mean Difference (IV, Random, 95% CI)	0.62 [0.00, 1.23]
2.21 Anaemia-related markers (Hb): single agent alone or multi-component	26		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.21.1 Single-agent	25	1622	Mean Difference (IV, Random, 95% CI)	0.49 [0.20, 0.78]
2.21.2 Multi component	1	173	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.41, 0.21]
2.22 Anaemia-related markers (HCT): average of dose	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.22.1 Dose ≥ 10 mg/kg/day	3	209	Mean Difference (IV, Random, 95% CI)	1.18 [-2.59, 4.96]
2.22.2 Dose < 10 mg/kg/day	11	741	Mean Difference (IV, Random, 95% CI)	2.07 [0.52, 3.62]
2.23 Anaemia-related markers (HCT): intervention duration	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.23.1 ≤ 6 months	12	598	Mean Difference (IV, Random, 95% CI)	1.50 [-0.26, 3.27]
2.23.2 > 6 months	2	352	Mean Difference (IV, Random, 95% CI)	4.42 [-3.77, 12.61]
2.24 Anaemia-related markers (HCT): route of administration	14		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.24.1 intravenous	13	924	Mean Difference (IV, Random, 95% CI)	1.45 [0.08, 2.81]
2.24.2 oral	1	26	Mean Difference (IV, Random, 95% CI)	8.99 [4.06, 13.92]
2.25 Anaemia-related markers (EPO dose): average of dose	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.25.1 Dose ≥ 10 mg/kg/day	5	247	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.67, 0.28]
2.25.2 Dose < 10 mg/kg/day	8	720	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.84, -0.35]
2.26 Anaemia-related markers (EPO dose): intervention duration	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.26.1 ≤ 6 months	9	517	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.34, -0.07]
2.26.2 > 6 months	4	450	Mean Difference (IV, Random, 95% CI)	-1.81 [-2.87, -0.76]
2.27 Anaemia-related markers (EPO dose): route of administration	13		Mean Difference (IV, Random, 95% CI)	Subtotals only

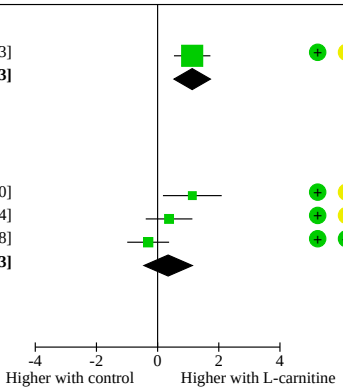
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.27.1 Intravenous	11	891	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.70, -0.35]
2.27.2 Oral	2	76	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.99, 0.78]
2.28 Anaemia-related markers (EPO resistance index): average of dose	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.28.1 Dose ≧ 10 mg/kg/day	2	208	Mean Difference (IV, Random, 95% CI)	-2.17 [-3.19, -1.16]
2.28.2 Dose < 10 mg/kg/day	2	107	Mean Difference (IV, Random, 95% CI)	1.21 [-7.63, 10.05]
2.29 Anaemia-related markers (EPO resistance index): route of administration	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.29.1 Intravenous	4	195	Mean Difference (IV, Random, 95% CI)	-0.71 [-4.25, 2.83]
2.29.2 Oral	1	148	Mean Difference (IV, Random, 95% CI)	-2.00 [-3.10, -0.90]
2.30 Myocardial function (intradialytic hypotension): average dose	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.30.1 Dose ≥ 10 mg/kg/day	1	26	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.30.2 Dose < 10 mg/kg/day	2	102	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.34, 1.69]
2.31 Myocardial function (intradialytic hypotension): route of administration	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.31.1 Intravenous	3	128	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.34, 1.69]
2.32 Myocardial function (LVM): average dose	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.32.1 Dose ≥ 10 mg/kg/day	2	166	Mean Difference (IV, Random, 95% CI)	-7.72 [-15.10, -0.34]
2.32.2 Dose < 10 mg/kg/day	1	51	Mean Difference (IV, Random, 95% CI)	-1.40 [-25.53, 22.73]
2.33 Myocardial function (LVM): intervention duration	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.33.1 ≤ 6 months	1	18	Mean Difference (IV, Random, 95% CI)	-5.00 [-29.27, 19.27]

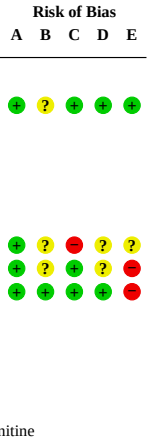
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.33.2 > 6 months	2	199	Mean Difference (IV, Random, 95% CI)	-7.38 [-14.76, -0.01]
2.34 Myocardial function (LVM): route of administration	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.34.1 Intravenous	1	51	Mean Difference (IV, Random, 95% CI)	-1.40 [-25.53, 22.73]
2.34.2 Oral	2	166	Mean Difference (IV, Random, 95% CI)	-7.72 [-15.10, -0.34]
2.35 Myocardial function (ejection fraction): average dose	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.35.1 Dose ≧ 10 mg/kg/day	3	271	Mean Difference (IV, Random, 95% CI)	4.68 [3.17, 6.19]
2.35.2 Dose < 10 mg/kg/day	3	139	Mean Difference (IV, Random, 95% CI)	-0.45 [-2.95, 2.04]
2.36 Myocardial function (ejection fraction): intervention duration	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.36.1 ≤ 6 months	3	151	Mean Difference (IV, Random, 95% CI)	1.99 [-2.64, 6.62]
2.36.2 > 6 months	3	259	Mean Difference (IV, Random, 95% CI)	2.39 [-1.41, 6.19]
2.37 Myocardial function (ejection fraction): route of administration	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.37.1 Intravenous	4	244	Mean Difference (IV, Random, 95% CI)	1.03 [-1.76, 3.81]
2.37.2 Oral	2	166	Mean Difference (IV, Random, 95% CI)	5.15 [3.28, 7.02]
2.38 Death (any cause): dialysis modality	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.38.1 HD patients only	12	802	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.64, 2.38]
2.38.2 PD patients only	1	55	Risk Ratio (M-H, Random, 95% CI)	2.90 [0.12, 68.15]
2.39 Death (any cause): average dose	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.39.1 Dose ≧ 10 mg/kg/day	5	469	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.40, 2.34]
2.39.2 Dose < 10 mg/kg/day	8	388	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.69, 4.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.40 Death (any cause): intervention duration	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.40.1 ≤ 6 months	8	395	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.82, 13.40]
2.40.2 > 6 months	5	462	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.48, 2.04]
2.41 Death (any cause): route of administration	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.41.1 Intravenous	7	335	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.59, 4.17]
2.41.2 Oral	6	519	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.48, 2.58]
2.42 Death (cardiovascular): average dose	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.42.1 Dose ≥ 10 mg/kg/day	2	324	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.87]
2.42.2 Dose < 10 mg/kg/day	3	121	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.14, 72.69]
2.43 Death (cardiovascular): intervention duration	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.43.1 ≤ 6 months	3	159	Risk Ratio (M-H, Random, 95% CI)	3.09 [0.33, 28.74]
2.43.2 > 6 months	2	286	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.15, 2.49]
2.44 Death (cardiovascular): route of administration	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.44.1 Intravenous	3	121	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.14, 72.69]
2.44.2 Oral	2	324	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.87]

Analysis 2.1. Comparison 2: Subgroup analyses, Outcome 1: QoL (SF-36 PCS): average dose

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Dose ≥ 10 mg/kg/day								
Naini 2011	52.5	18	24	34.5	13.3	27	100.0%	1.13 [0.53 , 1.73]
Subtotal (95% CI)			**24**			**27**	**100.0%**	**1.13 [0.53 , 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.72 (P = 0.0002)								
2.1.2 Dose < 10 mg/kg/day								
Rathod 2006	48.12	12.48	10	34.08	11.18	10	28.9%	1.13 [0.17 , 2.10]
Steiber 2006	39.7	8.29	13	35.7	11.97	14	34.4%	0.37 [-0.39 , 1.14]
CARNIDIAL 2012	26.91	1.85	13	27.48	1.78	23	36.7%	-0.31 [-0.99 , 0.38]
Subtotal (95% CI)			**36**			**47**	**100.0%**	**0.34 [-0.45 , 1.13]**
Heterogeneity: Tau² = 0.32; Chi² = 5.92, df = 2 (P = 0.05); I² = 66%								
Test for overall effect: Z = 0.85 (P = 0.39)								
Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.8%								

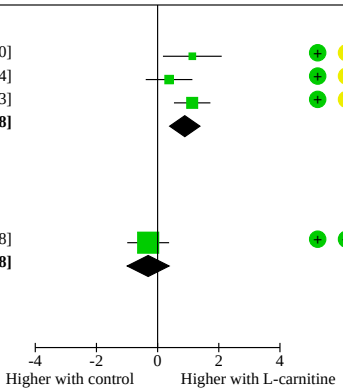


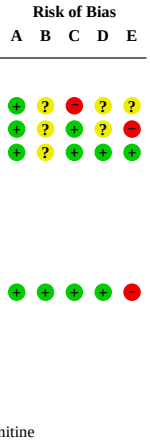


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.2. Comparison 2: Subgroup analyses, Outcome 2: QoL (SF-36 PCS): intervention duration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 ≤ 6 months								
Rathod 2006	48.12	12.48	10	34.08	11.18	10	22.2%	1.13 [0.17 , 2.10]
Steiber 2006	39.7	8.29	13	35.7	11.97	14	32.1%	0.37 [-0.39 , 1.14]
Naini 2011	52.5	18	24	34.5	13.3	27	45.7%	1.13 [0.53 , 1.73]
Subtotal (95% CI)			**47**			**51**	**100.0%**	**0.89 [0.39 , 1.38]**
Heterogeneity: Tau² = 0.05; Chi² = 2.63, df = 2 (P = 0.27); I² = 24%								
Test for overall effect: Z = 3.52 (P = 0.0004)								
2.2.2 > 6 months								
CARNIDIAL 2012	26.91	1.85	13	27.48	1.78	23	100.0%	-0.31 [-0.99 , 0.38]
Subtotal (95% CI)			**13**			**23**	**100.0%**	**-0.31 [-0.99 , 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.88 (P = 0.38)								
Test for subgroup differences: Chi² = 7.72, df = 1 (P = 0.005), I² = 87.0%								

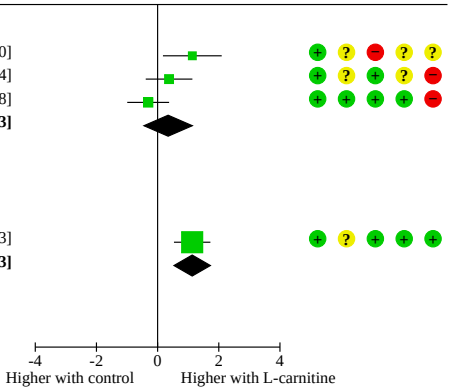




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.3. Comparison 2: Subgroup analyses, Outcome 3: QoL (SF-36 PCS): route of administration

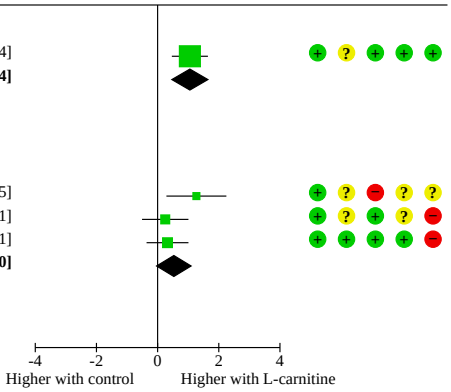
Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.3.1 Intravenous								
Rathod 2006	48.12	12.48	10	34.08	11.18	10	28.9%	1.13 [0.17 , 2.10]
Steiber 2006	39.7	8.29	13	35.7	11.97	14	34.4%	0.37 [-0.39 , 1.14]
CARNIDIAL 2012	26.91	1.85	13	27.48	1.78	23	36.7%	-0.31 [-0.99 , 0.38]
Subtotal (95% CI)			**36**			**47**	**100.0%**	**0.34 [-0.45 , 1.13]**
Heterogeneity: Tau² = 0.32; Chi² = 5.92, df = 2 (P = 0.05); I² = 66%								
Test for overall effect: Z = 0.85 (P = 0.39)								
2.3.2 Oral								
Naini 2011	52.5	18	24	34.5	13.3	27	100.0%	1.13 [0.53 , 1.73]
Subtotal (95% CI)			**24**			**27**	**100.0%**	**1.13 [0.53 , 1.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.72 (P = 0.0002)								
Test for subgroup differences: Chi² = 2.43, df = 1 (P = 0.12), I² = 58.8%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.4. Comparison 2: Subgroup analyses, Outcome 4: QoL (SF-36 MCS): average dose

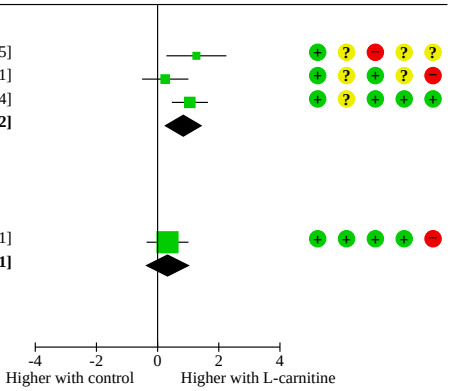
Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.4.1 Dose ≥ 10 mg/kg/day								
Naini 2011	58.2	21.2	24	37.6	17.3	27	100.0%	1.05 [0.47 , 1.64]
Subtotal (95% CI)			**24**			**27**	**100.0%**	**1.05 [0.47 , 1.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.51 (P = 0.0005)								
2.4.2 Dose < 10 mg/kg/day								
Rathod 2006	50.17	11.1	10	34.41	12.66	10	24.7%	1.27 [0.29 , 2.25]
Steiber 2006	54.2	7.93	13	51.8	10.48	14	35.3%	0.25 [-0.51 , 1.01]
CARNIDIAL 2012	17.8	1.81	13	17.18	1.91	23	40.0%	0.32 [-0.36 , 1.01]
Subtotal (95% CI)			**36**			**47**	**100.0%**	**0.53 [-0.03 , 1.10]**
Heterogeneity: Tau² = 0.09; Chi² = 3.03, df = 2 (P = 0.22); I² = 34%								
Test for overall effect: Z = 1.84 (P = 0.07)								
Test for subgroup differences: Chi² = 1.58, df = 1 (P = 0.21), I² = 36.8%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.5. Comparison 2: Subgroup analyses, Outcome 5: QoL (SF-36 MCS): intervention duration

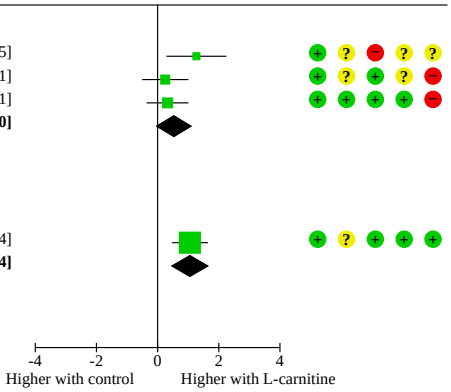
Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.5.1 ≤ 6 months								
Rathod 2006	50.17	11.1	10	34.41	12.66	10	24.2%	1.27 [0.29 , 2.25]
Steiber 2006	54.2	7.93	13	51.8	10.48	14	33.2%	0.25 [-0.51 , 1.01]
Naini 2011	58.2	21.2	24	37.6	17.3	27	42.6%	1.05 [0.47 , 1.64]
Subtotal (95% CI)			**47**			**51**	**100.0%**	**0.84 [0.25 , 1.42]**
Heterogeneity: Tau² = 0.12; Chi² = 3.57, df = 2 (P = 0.17); I² = 44%								
Test for overall effect: Z = 2.81 (P = 0.005)								
2.5.2 > 6 months								
CARNIDIAL 2012	17.8	1.81	13	17.18	1.91	23	100.0%	0.32 [-0.36 , 1.01]
Subtotal (95% CI)			**13**			**23**	**100.0%**	**0.32 [-0.36 , 1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.6%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.6. Comparison 2: Subgroup analyses, Outcome 6: QoL (SF-36 MCS): route of administration

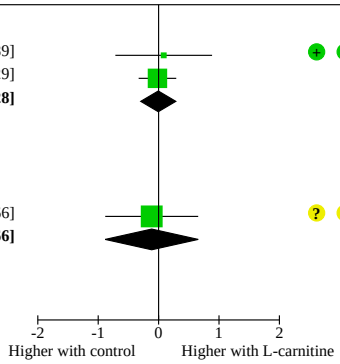
Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.6.1 Intravenous								
Rathod 2006	50.17	11.1	10	34.41	12.66	10	24.7%	1.27 [0.29 , 2.25]
Steiber 2006	54.2	7.93	13	51.8	10.48	14	35.3%	0.25 [-0.51 , 1.01]
CARNIDIAL 2012	17.8	1.81	13	17.18	1.91	23	40.0%	0.32 [-0.36 , 1.01]
Subtotal (95% CI)			**36**			**47**	**100.0%**	**0.53 [-0.03 , 1.10]**
Heterogeneity: Tau² = 0.09; Chi² = 3.03, df = 2 (P = 0.22); I² = 34%								
Test for overall effect: Z = 1.84 (P = 0.07)								
2.6.2 Oral								
Naini 2011	58.2	21.2	24	37.6	17.3	27	100.0%	1.05 [0.47 , 1.64]
Subtotal (95% CI)			**24**			**27**	**100.0%**	**1.05 [0.47 , 1.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.51 (P = 0.0005)								
Test for subgroup differences: Chi² = 1.58, df = 1 (P = 0.21), I² = 36.8%								



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.7. Comparison 2: Subgroup analyses, Outcome 7: QoL (total): average dose

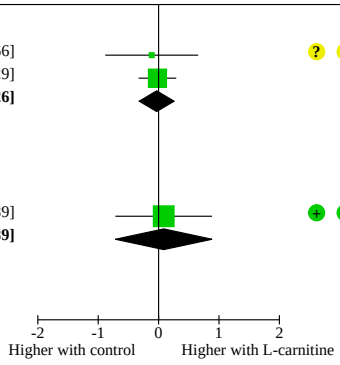
Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E
2.7.1 Dose ≥ 10 mg/kg/day									
Hamedi-Kalajahi 2021	67.33	8.12	12	66.67	6.88	12	13.1%	0.08 [-0.72 , 0.89]	+ + + + +
Brass 2001 (A+B)	5.27	1.03	121	5.29	1.08	59	86.9%	-0.02 [-0.33 , 0.29]	
Subtotal (95% CI)			**133**			**71**	**100.0%**	**-0.01 [-0.30 , 0.28]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%									
Test for overall effect: Z = 0.04 (P = 0.97)									
2.7.2 Dose < 10 mg/day									
Vaux 2004	0.75	1.5	13	1	2.6	13	100.0%	-0.11 [-0.88 , 0.66]	? ? + ? −
Subtotal (95% CI)			**13**			**13**	**100.0%**	**-0.11 [-0.88 , 0.66]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.29 (P = 0.77)									
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.80), I² = 0%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

Analysis 2.8. Comparison 2: Subgroup analyses, Outcome 8: QoL (total): route of administration

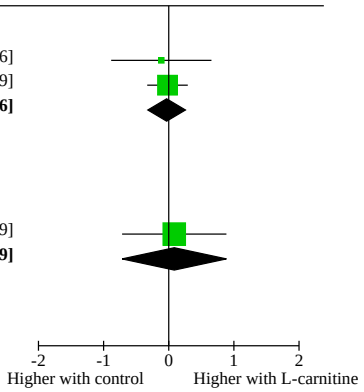
Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E
2.8.1 Intravenous									
Vaux 2004	0.75	1.5	13	1	2.6	13	14.1%	-0.11 [-0.88 , 0.66]	? ? + ? −
Brass 2001 (A+B)	5.27	1.03	121	5.29	1.08	59	85.9%	-0.02 [-0.33 , 0.29]	
Subtotal (95% CI)			**134**			**72**	**100.0%**	**-0.03 [-0.32 , 0.26]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%									
Test for overall effect: Z = 0.22 (P = 0.83)									
2.8.2 Oral									
Hamedi-Kalajahi 2021	67.33	8.12	12	66.67	6.88	12	100.0%	0.08 [-0.72 , 0.89]	+ + + + +
Subtotal (95% CI)			**12**			**12**	**100.0%**	**0.08 [-0.72 , 0.89]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.21 (P = 0.84)									
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%									



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Selective reporting (reporting bias)
(E) Other bias

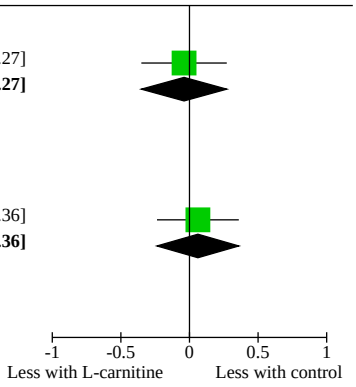
Analysis 2.9. Comparison 2: Subgroup analyses, Outcome 9: QoL (total): age

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.9.1 Age ≥ 18 years								
Vaux 2004	0.75	1.5	13	1	2.6	13	14.1%	-0.11 [-0.88 , 0.66]
Brass 2001 (A+B)	5.27	1.03	121	5.29	1.08	59	85.9%	-0.02 [-0.33 , 0.29]
Subtotal (95% CI)			**134**			**72**	**100.0%**	**-0.03 [-0.32 , 0.26]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.22 (P = 0.83)								
2.9.2 Age < 18 years								
Hamedi-Kalajahi 2021	67.33	8.12	12	66.67	6.88	12	100.0%	0.08 [-0.72 , 0.89]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**0.08 [-0.72 , 0.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%								



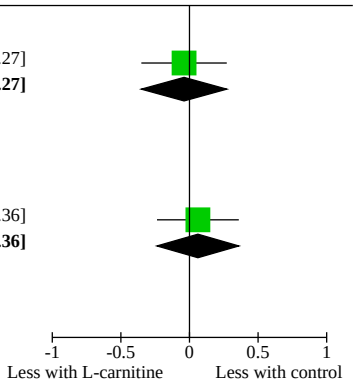
Analysis 2.10. Comparison 2: Subgroup analyses, Outcome 10: Fatigue score: route of administration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.10.1 Intravenous								
Brass 2001 (A+B)	5.09	1.28	121	5.14	1.22	59	100.0%	-0.04 [-0.35 , 0.27]
Subtotal (95% CI)			**121**			**59**	**100.0%**	**-0.04 [-0.35 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
2.10.2 Oral								
Fukuda 2015	5.59	4.56	87	5.31	4.52	86	100.0%	0.06 [-0.24 , 0.36]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**0.06 [-0.24 , 0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%								



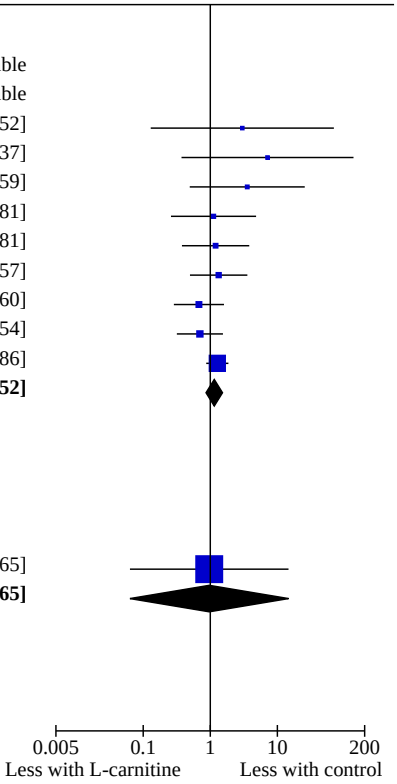
Analysis 2.11. Comparison 2: Subgroup analyses, Outcome 11: Fatigue score: single agent alone or multi-component

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.11.1 single agent alone								
Brass 2001 (A+B)	5.09	1.28	121	5.14	1.22	59	100.0%	-0.04 [-0.35 , 0.27]
Subtotal (95% CI)			**121**			**59**	**100.0%**	**-0.04 [-0.35 , 0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
2.11.2 multi-component								
Fukuda 2015	5.59	4.56	87	5.31	4.52	86	100.0%	0.06 [-0.24 , 0.36]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**0.06 [-0.24 , 0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%								



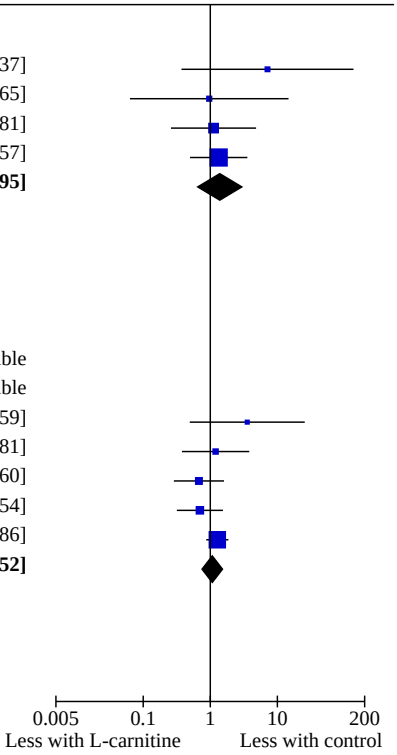
Analysis 2.12. Comparison 2: Subgroup analyses, Outcome 12: Adverse events: dialysis modality

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 HD patients only						
Maruyama 2017	0	30	0	30		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Kletzmayr 1999	1	20	0	20	0.8%	3.00 [0.13 , 69.52]
Higuchi 2014	3	110	0	112	0.9%	7.13 [0.37 , 136.37]
Mettang 1997	4	9	1	8	2.0%	3.56 [0.49 , 25.59]
Mortazavi 2012	3	17	3	19	3.7%	1.12 [0.26 , 4.81]
Fukuda 2015	6	103	5	103	6.0%	1.20 [0.38 , 3.81]
Fukami 2013	8	51	6	51	8.2%	1.33 [0.50 , 3.57]
Ahmad 1990	7	47	11	50	10.8%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	12.7%	0.70 [0.32 , 1.54]
CARNIDIAL 2012	28	46	22	46	54.9%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**490**		**496**	**100.0%**	**1.15 [0.86 , 1.52]**
Total events:	67		58			
Heterogeneity: Tau² = 0.00; Chi² = 6.43, df = 8 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
2.12.2 PD patients only						
Mortazavi 2011a	1	28	1	27	100.0%	0.96 [0.06 , 14.65]
Subtotal (95% CI)		**28**		**27**	**100.0%**	**0.96 [0.06 , 14.65]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%						



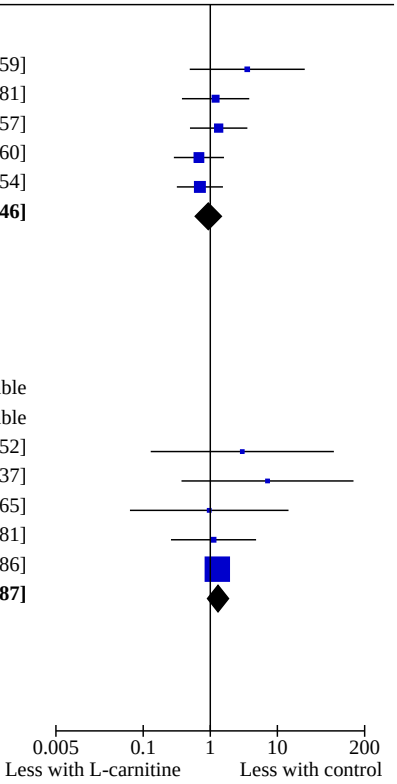
Analysis 2.13. Comparison 2: Subgroup analyses, Outcome 13: Adverse events: average dose

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Dose ≥ 10 mg/kg/day						
Higuchi 2014	3	110	0	112	6.6%	7.13 [0.37 , 136.37]
Mortazavi 2011a	1	28	1	27	7.7%	0.96 [0.06 , 14.65]
Mortazavi 2012	3	17	3	19	26.8%	1.12 [0.26 , 4.81]
Fukami 2013	8	51	6	51	58.9%	1.33 [0.50 , 3.57]
Subtotal (95% CI)		**206**		**209**	**100.0%**	**1.38 [0.65 , 2.95]**
Total events:	15		10			
Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
2.13.2 Dose < 10 mg/kg/day						
Maruyama 2017	0	30	0	30		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Mettang 1997	4	9	1	8	3.1%	3.56 [0.49 , 25.59]
Fukuda 2015	6	103	5	103	8.7%	1.20 [0.38 , 3.81]
Ahmad 1990	7	47	11	50	15.1%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	17.5%	0.70 [0.32 , 1.54]
CARNIDIAL 2012	28	46	22	46	55.6%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**292**		**294**	**100.0%**	**1.07 [0.75 , 1.52]**
Total events:	52		49			
Heterogeneity: Tau² = 0.02; Chi² = 4.46, df = 4 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.38 (P = 0.70)						
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%						



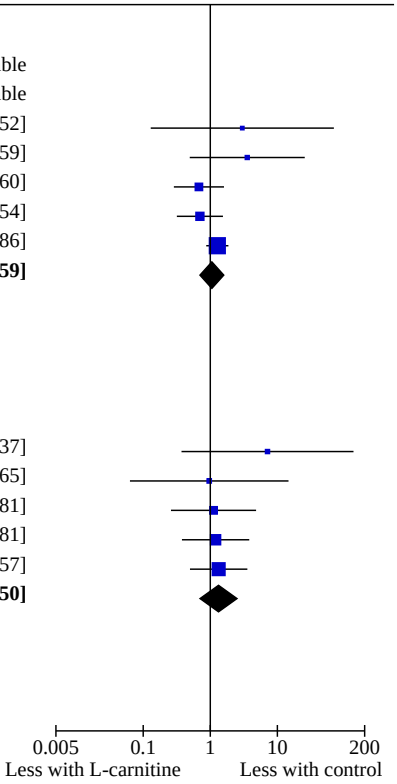
Analysis 2.14. Comparison 2: Subgroup analyses, Outcome 14: Adverse events: intervention duration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.14.1 ≤ 6 months						
Mettang 1997	4	9	1	8	5.1%	3.56 [0.49 , 25.59]
Fukuda 2015	6	103	5	103	15.0%	1.20 [0.38 , 3.81]
Fukami 2013	8	51	6	51	20.7%	1.33 [0.50 , 3.57]
Ahmad 1990	7	47	11	50	27.1%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	32.0%	0.70 [0.32 , 1.54]
Subtotal (95% CI)		**235**		**237**	**100.0%**	**0.93 [0.60 , 1.46]**
Total events:	32		33			
Heterogeneity: Tau² = 0.00; Chi² = 3.53, df = 4 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.77)						
2.14.2 > 6 months						
Maruyama 2017	0	30	0	30		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Kletzmayr 1999	1	20	0	20	1.3%	3.00 [0.13 , 69.52]
Higuchi 2014	3	110	0	112	1.5%	7.13 [0.37 , 136.37]
Mortazavi 2011a	1	28	1	27	1.7%	0.96 [0.06 , 14.65]
Mortazavi 2012	3	17	3	19	6.1%	1.12 [0.26 , 4.81]
CARNIDIAL 2012	28	46	22	46	89.4%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**283**		**286**	**100.0%**	**1.30 [0.91 , 1.87]**
Total events:	36		26			
Heterogeneity: Tau² = 0.00; Chi² = 1.76, df = 4 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Chi² = 1.29, df = 1 (P = 0.26), I² = 22.6%						



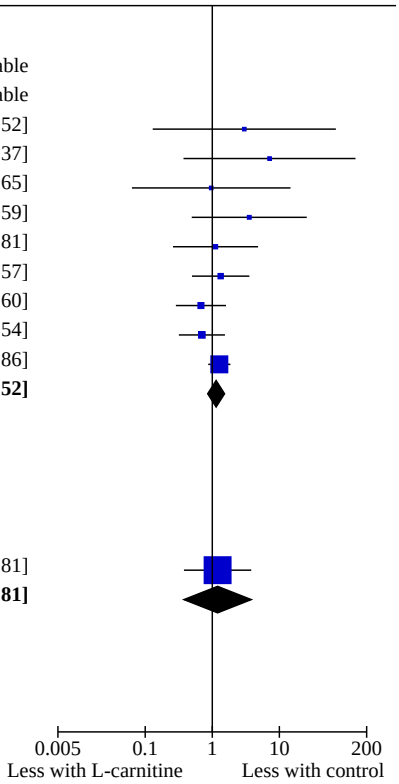
Analysis 2.15. Comparison 2: Subgroup analyses, Outcome 15: Adverse events: route of administration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 Intravenous						
Maruyama 2017	0	30	0	30		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Kletzmayr 1999	1	20	0	20	1.7%	3.00 [0.13 , 69.52]
Mettang 1997	4	9	1	8	4.1%	3.56 [0.49 , 25.59]
Ahmad 1990	7	47	11	50	18.5%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	21.2%	0.70 [0.32 , 1.54]
CARNIDIAL 2012	28	46	22	46	54.5%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**209**		**211**	**100.0%**	**1.06 [0.70 , 1.59]**
Total events:	47		44			
Heterogeneity: Tau² = 0.04; Chi² = 4.82, df = 4 (P = 0.31); I² = 17%						
Test for overall effect: Z = 0.26 (P = 0.79)						
2.15.2 Oral						
Higuchi 2014	3	110	0	112	4.6%	7.13 [0.37 , 136.37]
Mortazavi 2011a	1	28	1	27	5.4%	0.96 [0.06 , 14.65]
Mortazavi 2012	3	17	3	19	18.8%	1.12 [0.26 , 4.81]
Fukuda 2015	6	103	5	103	30.0%	1.20 [0.38 , 3.81]
Fukami 2013	8	51	6	51	41.3%	1.33 [0.50 , 3.57]
Subtotal (95% CI)		**309**		**312**	**100.0%**	**1.33 [0.70 , 2.50]**
Total events:	21		15			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 4 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%						



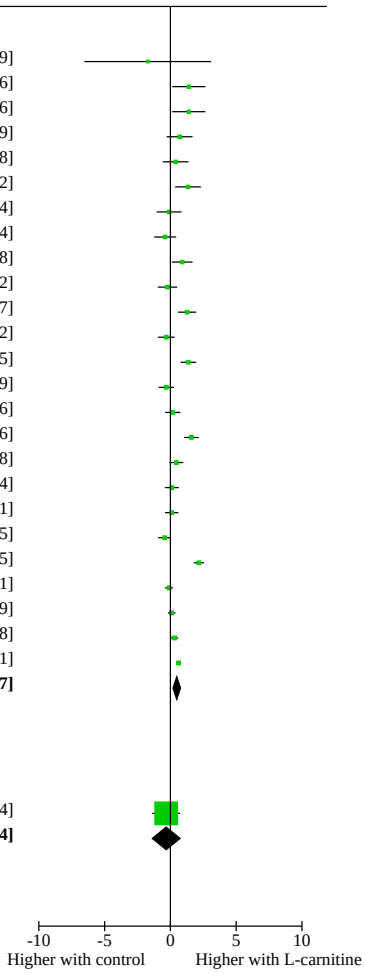
Analysis 2.16. Comparison 2: Subgroup analyses, Outcome 16: Adverse events: single agent alone or multi-component

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.16.1 Single agent						
Maruyama 2017	0	30	0	30		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Kletzmayr 1999	1	20	0	20	0.8%	3.00 [0.13 , 69.52]
Higuchi 2014	3	110	0	112	1.0%	7.13 [0.37 , 136.37]
Mortazavi 2011a	1	28	1	27	1.1%	0.96 [0.06 , 14.65]
Mettang 1997	4	9	1	8	2.1%	3.56 [0.49 , 25.59]
Mortazavi 2012	3	17	3	19	3.9%	1.12 [0.26 , 4.81]
Fukami 2013	8	51	6	51	8.6%	1.33 [0.50 , 3.57]
Ahmad 1990	7	47	11	50	11.3%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	13.4%	0.70 [0.32 , 1.54]
CARNIDIAL 2012	28	46	22	46	57.7%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**415**		**420**	**100.0%**	**1.14 [0.85 , 1.52]**
Total events:	62		54			
Heterogeneity: Tau² = 0.00; Chi² = 6.44, df = 8 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
2.16.2 Multi-component						
Fukuda 2015	6	103	5	103	100.0%	1.20 [0.38 , 3.81]
Subtotal (95% CI)		**103**		**103**	**100.0%**	**1.20 [0.38 , 3.81]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						



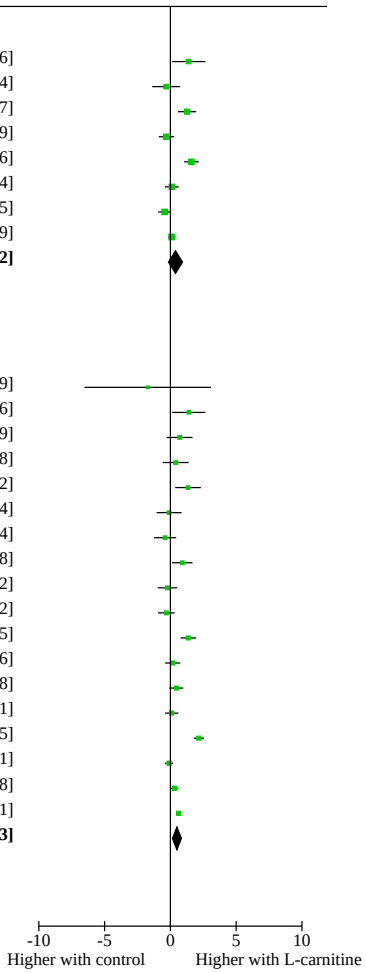
Analysis 2.17. Comparison 2: Subgroup analyses, Outcome 17: Anaemia-related markers (Hb): dialysis modality

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.17.1 HD								
Mettang 1997	10.21	6	8	11.93	3.27	7	0.3%	-1.72 [-6.53 , 3.09]
Naini 2011	11.3	2.1	24	9.9	2.5	27	2.6%	1.40 [0.14 , 2.66]
Mitwalli 2005	11.3	2.1	24	9.9	2.5	27	2.6%	1.40 [0.14 , 2.66]
Khodaverdi 2010	1.2	1.2	14	0.5	1.5	15	3.3%	0.70 [-0.29 , 1.69]
Biolo 2008	12.9	1.2	9	12.5	0.949	10	3.3%	0.40 [-0.58 , 1.38]
Fu 2010	9.87	1.89	20	8.53	1.18	20	3.3%	1.34 [0.36 , 2.32]
Yano 2021	11.6	1.4	10	11.7	0.6	10	3.4%	-0.10 [-1.04 , 0.84]
Steiber 2006	11.9	1.2	15	12.3	1.3	19	3.7%	-0.40 [-1.24 , 0.44]
Arduini 2006	11.3	0.8	13	10.4	1.2	13	3.8%	0.90 [0.12 , 1.68]
Cibulka 2005	11.484	1.702	44	11.705	1.726	39	3.9%	-0.22 [-0.96 , 0.52]
Mortazavi 2012	11.6	1.05	17	10.33	1.08	19	4.1%	1.27 [0.57 , 1.97]
Sugiyama 2021	11.094	0.8	34	11.4	1.2	17	4.3%	-0.31 [-0.94 , 0.32]
Rathod 2006	0.89	0.56	10	-0.47	0.77	10	4.4%	1.36 [0.77 , 1.95]
Brass 2001a	11	1.3	28	11.3	0.9	28	4.4%	-0.30 [-0.89 , 0.29]
Vaux 2004	-0.08	0.9	13	-0.26	0.56	13	4.4%	0.18 [-0.40 , 0.76]
Garneata 2005	10.2	0.9	20	8.6	0.9	20	4.5%	1.60 [1.04 , 2.16]
Saxena 2004	9.68	0.844	10	9.23	0.13	10	4.5%	0.45 [-0.08 , 0.98]
Sorge-Haedicke 2001	10.89	1.19	43	10.78	1.26	40	4.5%	0.11 [-0.42 , 0.64]
Maruyama 2017	11.1	1	30	11	1	30	4.6%	0.10 [-0.41 , 0.61]
Brass 2001b	11.16	1.07	94	11.6	1.3	33	4.6%	-0.44 [-0.93 , 0.05]
Cui 2016	11.436	1.227	78	9.272	1.251	78	4.9%	2.16 [1.78 , 2.55]
Fukuda 2015	10.5	0.99	87	10.6	1.06	86	5.1%	-0.10 [-0.41 , 0.21]
Higuchi 2014	11.1	0.6	75	11	1.1	73	5.1%	0.10 [-0.19 , 0.39]
Song 2013a	11.534	1.166	163	11.22	1.323	163	5.2%	0.31 [0.04 , 0.58]
Chi 2021	8.798	0.266	25	8.172	0.385	25	5.3%	0.63 [0.44 , 0.81]
Subtotal (95% CI)			**908**			**832**	**100.0%**	**0.48 [0.20 , 0.77]**
Heterogeneity: Tau² = 0.38; Chi² = 174.83, df = 24 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 3.36 (P = 0.0008)								
2.17.2 PD								
Mortazavi 2011a	11.08	2	28	11.4	2	27	100.0%	-0.32 [-1.38 , 0.74]
Subtotal (95% CI)			**28**			**27**	**100.0%**	**-0.32 [-1.38 , 0.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.59 (P = 0.55)								
Test for subgroup differences: Chi² = 2.07, df = 1 (P = 0.15), I² = 51.8%								



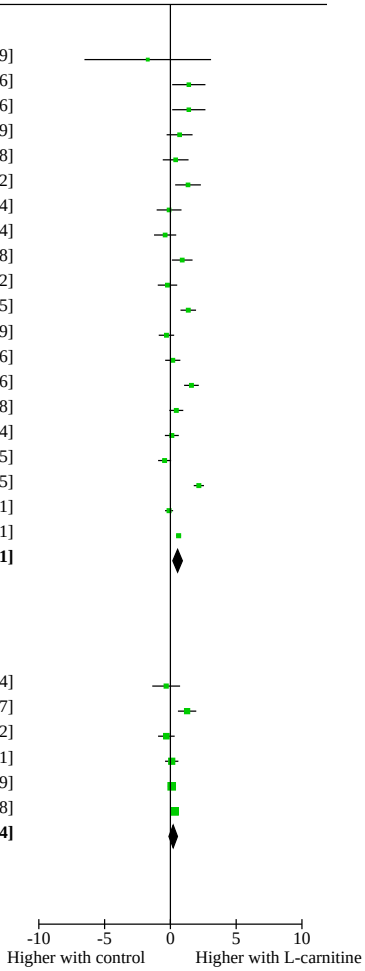
Analysis 2.18. Comparison 2: Subgroup analyses, Outcome 18: Anaemia-related markers (Hb): average dose

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.18.1 Dose ≥ 10 mg/kg/day								
Naini 2011	11.3	2.1	24	9.9	2.5	27	8.3%	1.40 [0.14 , 2.66]
Mortazavi 2011a	11.08	2	28	11.4	2	27	9.7%	-0.32 [-1.38 , 0.74]
Mortazavi 2012	11.6	1.05	17	10.33	1.08	19	12.4%	1.27 [0.57 , 1.97]
Brass 2001b	11	1.3	28	11.3	0.9	28	13.3%	-0.30 [-0.89 , 0.29]
Garneata 2005	10.2	0.9	20	8.6	0.9	20	13.5%	1.60 [1.04 , 2.16]
Sorge-Haedicke 2001	10.89	1.19	43	10.78	1.26	40	13.7%	0.11 [-0.42 , 0.64]
Brass 2001a	11.16	1.07	94	11.6	1.3	33	13.9%	-0.44 [-0.93 , 0.05]
Higuchi 2014	11.1	0.6	75	11	1.1	73	15.1%	0.10 [-0.19 , 0.39]
Subtotal (95% CI)			**329**			**267**	**100.0%**	**0.39 [-0.14 , 0.92]**
Heterogeneity: Tau² = 0.46; Chi² = 47.26, df = 7 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 1.44 (P = 0.15)								
2.18.2 Dose < 10 mg/kg/day								
Mettang 1997	10.21	6	8	11.93	3.27	7	0.5%	-1.72 [-6.53 , 3.09]
Mitwalli 2005	11.3	2.1	24	9.9	2.5	27	3.7%	1.40 [0.14 , 2.66]
Khodaverdi 2010	1.2	1.2	14	0.5	1.5	15	4.7%	0.70 [-0.29 , 1.69]
Biolo 2008	12.9	1.2	9	12.5	0.949	10	4.7%	0.40 [-0.58 , 1.38]
Fu 2010	9.87	1.89	20	8.53	1.18	20	4.7%	1.34 [0.36 , 2.32]
Yano 2021	11.6	1.4	10	11.7	0.6	10	4.8%	-0.10 [-1.04 , 0.84]
Steiber 2006	11.9	1.2	15	12.3	1.3	19	5.2%	-0.40 [-1.24 , 0.44]
Arduini 2006	11.3	0.8	13	10.4	1.2	13	5.4%	0.90 [0.12 , 1.68]
Cibulka 2005	11.484	1.702	44	11.705	1.726	39	5.6%	-0.22 [-0.96 , 0.52]
Sugiyama 2021	11.094	0.8	34	11.4	1.2	17	6.1%	-0.31 [-0.94 , 0.32]
Rathod 2006	0.89	0.56	10	-0.47	0.77	10	6.2%	1.36 [0.77 , 1.95]
Vaux 2004	-0.08	0.9	13	-0.26	0.56	13	6.3%	0.18 [-0.40 , 0.76]
Saxena 2004	9.68	0.844	10	9.23	0.13	10	6.5%	0.45 [-0.08 , 0.98]
Maruyama 2017	11.1	1	30	11	1	30	6.6%	0.10 [-0.41 , 0.61]
Cui 2016	11.436	1.227	78	9.272	1.251	78	7.0%	2.16 [1.78 , 2.55]
Fukuda 2015	10.5	0.99	87	10.6	1.06	86	7.2%	-0.10 [-0.41 , 0.21]
Song 2013a	11.534	1.166	163	11.22	1.323	163	7.3%	0.31 [0.04 , 0.58]
Chi 2021	8.798	0.266	25	8.172	0.385	25	7.5%	0.63 [0.44 , 0.81]
Subtotal (95% CI)			**607**			**592**	**100.0%**	**0.50 [0.16 , 0.83]**
Heterogeneity: Tau² = 0.39; Chi² = 122.96, df = 17 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 2.88 (P = 0.004)								
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%								



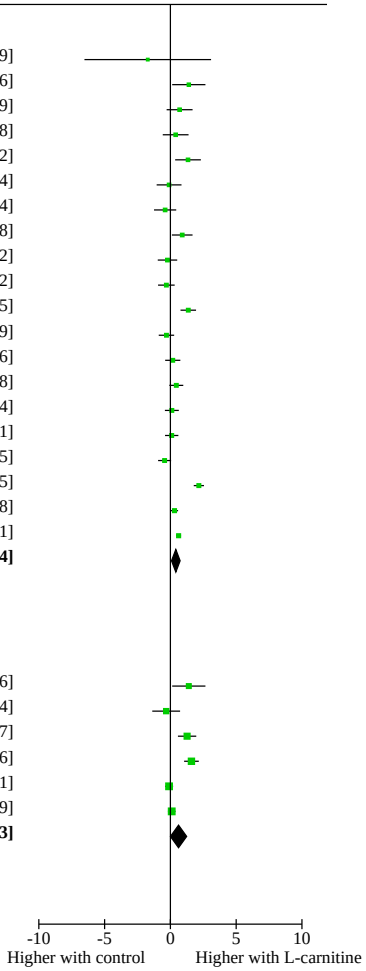
Analysis 2.19. Comparison 2: Subgroup analyses, Outcome 19: Anaemia-related markers (Hb): intervention duration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.19.1 ≤ 6 months								
Mettang 1997	10.21	6	8	11.93	3.27	7	0.5%	-1.72 [-6.53 , 3.09]
Mitwalli 2005	11.3	2.1	24	9.9	2.5	27	3.7%	1.40 [0.14 , 2.66]
Naini 2011	11.3	2.1	24	9.9	2.5	27	3.7%	1.40 [0.14 , 2.66]
Khodaverdi 2010	1.2	1.2	14	0.5	1.5	15	4.4%	0.70 [-0.29 , 1.69]
Biolo 2008	12.9	1.2	9	12.5	0.949	10	4.5%	0.40 [-0.58 , 1.38]
Fu 2010	9.87	1.89	20	8.53	1.18	20	4.5%	1.34 [0.36 , 2.32]
Yano 2021	11.6	1.4	10	11.7	0.6	10	4.6%	-0.10 [-1.04 , 0.84]
Steiber 2006	11.9	1.2	15	12.3	1.3	19	4.9%	-0.40 [-1.24 , 0.44]
Arduini 2006	11.3	0.8	13	10.4	1.2	13	5.1%	0.90 [0.12 , 1.68]
Cibulka 2005	11.484	1.702	44	11.705	1.726	39	5.2%	-0.22 [-0.96 , 0.52]
Rathod 2006	0.89	0.56	10	-0.47	0.77	10	5.6%	1.36 [0.77 , 1.95]
Brass 2001b	11	1.3	28	11.3	0.9	28	5.6%	-0.30 [-0.89 , 0.29]
Vaux 2004	-0.08	0.9	13	-0.26	0.56	13	5.7%	0.18 [-0.40 , 0.76]
Garneata 2005	10.2	0.9	20	8.6	0.9	20	5.7%	1.60 [1.04 , 2.16]
Saxena 2004	9.68	0.844	10	9.23	0.13	10	5.8%	0.45 [-0.08 , 0.98]
Sorge-Haedicke 2001	10.89	1.19	43	10.78	1.26	40	5.8%	0.11 [-0.42 , 0.64]
Brass 2001a	11.16	1.07	94	11.6	1.3	33	5.9%	-0.44 [-0.93 , 0.05]
Cui 2016	11.436	1.227	78	9.272	1.251	78	6.1%	2.16 [1.78 , 2.55]
Fukuda 2015	10.5	0.99	87	10.6	1.06	86	6.3%	-0.10 [-0.41 , 0.21]
Chi 2021	8.798	0.266	25	8.172	0.385	25	6.5%	0.63 [0.44 , 0.81]
Subtotal (95% CI)			**589**			**530**	**100.0%**	**0.55 [0.19 , 0.91]**
Heterogeneity: Tau² = 0.52; Chi² = 151.62, df = 19 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 2.96 (P = 0.003)								
2.19.2 > 6 months								
Mortazavi 2011a	11.08	2	28	11.4	2	27	7.1%	-0.32 [-1.38 , 0.74]
Mortazavi 2012	11.6	1.05	17	10.33	1.08	19	12.6%	1.27 [0.57 , 1.97]
Sugiyama 2021	11.094	0.8	34	11.4	1.2	17	14.0%	-0.31 [-0.94 , 0.32]
Maruyama 2017	11.1	1	30	11	1	30	17.3%	0.10 [-0.41 , 0.61]
Higuchi 2014	11.1	0.6	75	11	1.1	73	24.2%	0.10 [-0.19 , 0.39]
Song 2013a	11.534	1.166	163	11.22	1.323	163	24.7%	0.31 [0.04 , 0.58]
Subtotal (95% CI)			**347**			**329**	**100.0%**	**0.21 [-0.11 , 0.54]**
Heterogeneity: Tau² = 0.09; Chi² = 13.75, df = 5 (P = 0.02); I² = 64%								
Test for overall effect: Z = 1.29 (P = 0.20)								
Test for subgroup differences: Chi² = 1.82, df = 1 (P = 0.18), I² = 45.1%								



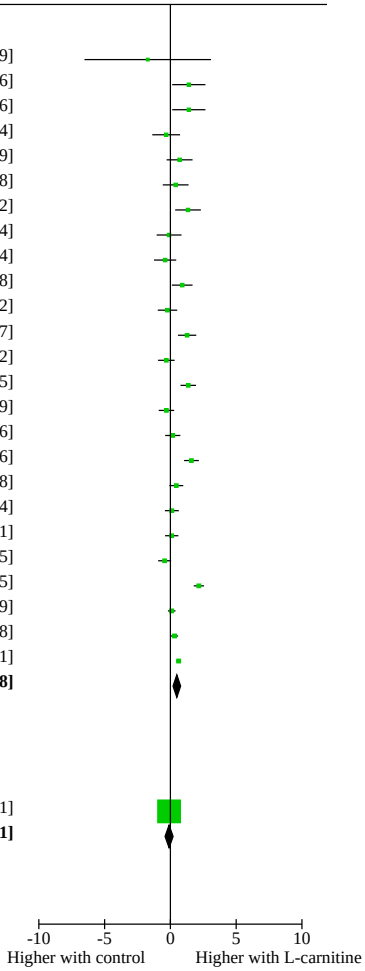
Analysis 2.20. Comparison 2: Subgroup analyses, Outcome 20: Anaemia-related markers (Hb): route of administration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.20.1 Intravenous								
Mettang 1997	10.21	6	8	11.93	3.27	7	0.4%	-1.72 [-6.53 , 3.09]
Mitwalli 2005	11.3	2.1	24	9.9	2.5	27	3.4%	1.40 [0.14 , 2.66]
Khodaverdi 2010	1.2	1.2	14	0.5	1.5	15	4.2%	0.70 [-0.29 , 1.69]
Biolo 2008	12.9	1.2	9	12.5	0.949	10	4.2%	0.40 [-0.58 , 1.38]
Fu 2010	9.87	1.89	20	8.53	1.18	20	4.2%	1.34 [0.36 , 2.32]
Yano 2021	11.6	1.4	10	11.7	0.6	10	4.3%	-0.10 [-1.04 , 0.84]
Steiber 2006	11.9	1.2	15	12.3	1.3	19	4.7%	-0.40 [-1.24 , 0.44]
Arduini 2006	11.3	0.8	13	10.4	1.2	13	4.9%	0.90 [0.12 , 1.68]
Cibulka 2005	11.484	1.702	44	11.705	1.726	39	5.0%	-0.22 [-0.96 , 0.52]
Sugiyama 2021	11.094	0.8	34	11.4	1.2	17	5.4%	-0.31 [-0.94 , 0.32]
Rathod 2006	0.89	0.56	10	-0.47	0.77	10	5.6%	1.36 [0.77 , 1.95]
Brass 2001b	11	1.3	28	11.3	0.9	28	5.6%	-0.30 [-0.89 , 0.29]
Vaux 2004	-0.08	0.9	13	-0.26	0.56	13	5.6%	0.18 [-0.40 , 0.76]
Saxena 2004	9.68	0.844	10	9.23	0.13	10	5.8%	0.45 [-0.08 , 0.98]
Sorge-Haedicke 2001	10.89	1.19	43	10.78	1.26	40	5.8%	0.11 [-0.42 , 0.64]
Maruyama 2017	11.1	1	30	11	1	30	5.8%	0.10 [-0.41 , 0.61]
Brass 2001a	11.16	1.07	94	11.6	1.3	33	5.9%	-0.44 [-0.93 , 0.05]
Cui 2016	11.436	1.227	78	9.272	1.251	78	6.2%	2.16 [1.78 , 2.55]
Song 2013a	11.534	1.166	163	11.22	1.323	163	6.5%	0.31 [0.04 , 0.58]
Chi 2021	8.798	0.266	25	8.172	0.385	25	6.7%	0.63 [0.44 , 0.81]
Subtotal (95% CI)			**685**			**607**	**100.0%**	**0.41 [0.09 , 0.74]**
Heterogeneity: Tau² = 0.41; Chi² = 131.55, df = 19 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 2.48 (P = 0.01)								
2.20.2 Oral								
Naini 2011	11.3	2.1	24	9.9	2.5	27	11.2%	1.40 [0.14 , 2.66]
Mortazavi 2011a	11.08	2	28	11.4	2	27	13.1%	-0.32 [-1.38 , 0.74]
Mortazavi 2012	11.6	1.05	17	10.33	1.08	19	16.8%	1.27 [0.57 , 1.97]
Garneata 2005	10.2	0.9	20	8.6	0.9	20	18.2%	1.60 [1.04 , 2.16]
Fukuda 2015	10.5	0.99	87	10.6	1.06	86	20.3%	-0.10 [-0.41 , 0.21]
Higuchi 2014	11.1	0.6	75	11	1.1	73	20.4%	0.10 [-0.19 , 0.39]
Subtotal (95% CI)			**251**			**252**	**100.0%**	**0.62 [0.00 , 1.23]**
Heterogeneity: Tau² = 0.46; Chi² = 40.98, df = 5 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 1.97 (P = 0.05)								
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%								



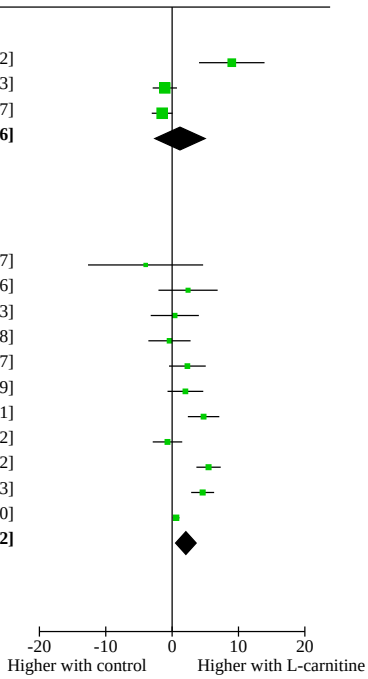
Analysis 2.21. Comparison 2: Subgroup analyses, Outcome 21: Anaemia-related markers (Hb): single agent alone or multi-component

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.21.1 Single-agent								
Mettang 1997	10.21	6	8	11.93	3.27	7	0.3%	-1.72 [-6.53 , 3.09]
Mitwalli 2005	11.3	2.1	24	9.9	2.5	27	2.7%	1.40 [0.14 , 2.66]
Naini 2011	11.3	2.1	24	9.9	2.5	27	2.7%	1.40 [0.14 , 2.66]
Mortazavi 2011a	11.08	2	28	11.4	2	27	3.2%	-0.32 [-1.38 , 0.74]
Khodaverdi 2010	1.2	1.2	14	0.5	1.5	15	3.3%	0.70 [-0.29 , 1.69]
Biolo 2008	12.9	1.2	9	12.5	0.949	10	3.4%	0.40 [-0.58 , 1.38]
Fu 2010	9.87	1.89	20	8.53	1.18	20	3.4%	1.34 [0.36 , 2.32]
Yano 2021	11.6	1.4	10	11.7	0.6	10	3.5%	-0.10 [-1.04 , 0.84]
Steiber 2006	11.9	1.2	15	12.3	1.3	19	3.7%	-0.40 [-1.24 , 0.44]
Arduini 2006	11.3	0.8	13	10.4	1.2	13	3.9%	0.90 [0.12 , 1.68]
Cibulka 2005	11.484	1.702	44	11.705	1.726	39	4.0%	-0.22 [-0.96 , 0.52]
Mortazavi 2012	11.6	1.05	17	10.33	1.08	19	4.2%	1.27 [0.57 , 1.97]
Sugiyama 2021	11.094	0.8	34	11.4	1.2	17	4.3%	-0.31 [-0.94 , 0.32]
Rathod 2006	0.89	0.56	10	-0.47	0.77	10	4.5%	1.36 [0.77 , 1.95]
Brass 2001b	11	1.3	28	11.3	0.9	28	4.5%	-0.30 [-0.89 , 0.29]
Vaux 2004	-0.08	0.9	13	-0.26	0.56	13	4.5%	0.18 [-0.40 , 0.76]
Garneata 2005	10.2	0.9	20	8.6	0.9	20	4.6%	1.60 [1.04 , 2.16]
Saxena 2004	9.68	0.844	10	9.23	0.13	10	4.6%	0.45 [-0.08 , 0.98]
Sorge-Haedicke 2001	10.89	1.19	43	10.78	1.26	40	4.6%	0.11 [-0.42 , 0.64]
Maruyama 2017	11.1	1	30	11	1	30	4.7%	0.10 [-0.41 , 0.61]
Brass 2001a	11.16	1.07	94	11.6	1.3	33	4.7%	-0.44 [-0.93 , 0.05]
Cui 2016	11.436	1.227	78	9.272	1.251	78	5.0%	2.16 [1.78 , 2.55]
Higuchi 2014	11.1	0.6	75	11	1.1	73	5.2%	0.10 [-0.19 , 0.39]
Song 2013a	11.534	1.166	163	11.22	1.323	163	5.2%	0.31 [0.04 , 0.58]
Chi 2021	8.798	0.266	25	8.172	0.385	25	5.4%	0.63 [0.44 , 0.81]
Subtotal (95% CI)			**849**			**773**	**100.0%**	**0.49 [0.20 , 0.78]**
Heterogeneity: Tau² = 0.39; Chi² = 162.93, df = 24 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 3.33 (P = 0.0009)								
2.21.2 Multi component								
Fukuda 2015	10.5	0.99	87	10.6	1.06	86	100.0%	-0.10 [-0.41 , 0.21]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.10 [-0.41 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								
Test for subgroup differences: Chi² = 7.57, df = 1 (P = 0.006), I² = 86.8%								



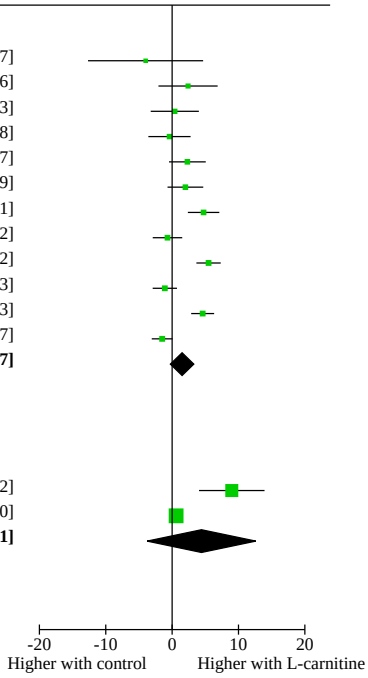
Analysis 2.22. Comparison 2: Subgroup analyses, Outcome 22: Anaemia-related markers (HCT): average of dose

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.22.1 Dose ≥ 10 mg/kg/day								
Trovato 1983	36.35	7.22	13	27.36	5.5	13	24.2%	8.99 [4.06 , 13.92]
Brass 2001b	32.8	4	28	33.9	2.9	28	37.5%	-1.10 [-2.93 , 0.73]
Brass 2001a	33.6	3.18	94	35.1	4.2	33	38.4%	-1.50 [-3.07 , 0.07]
Subtotal (95% CI)			**135**			**74**	**100.0%**	**1.18 [-2.59 , 4.96]**
Heterogeneity: Tau² = 9.04; Chi² = 15.99, df = 2 (P = 0.0003); I² = 87%								
Test for overall effect: Z = 0.61 (P = 0.54)								
2.22.2 Dose < 10 mg/kg/day								
Mettang 1997	32	8	8	36	9	7	2.6%	-4.00 [-12.67 , 4.67]
Pacheco 2008	32.2	5.6	13	29.8	4.7	8	6.3%	2.40 [-2.06 , 6.86]
Chazot 2003	32.5	6.6	23	32.1	5.8	22	7.7%	0.40 [-3.23 , 4.03]
Khodaverdi 2010	3.3	3.8	14	3.7	4.9	15	8.5%	-0.40 [-3.58 , 2.78]
Mitwalli 2005	32.5	3.7	18	30.2	4	13	9.3%	2.30 [-0.47 , 5.07]
Arduini 2006	34.3	3.6	13	32.3	3.4	13	9.5%	2.00 [-0.69 , 4.69]
Caruso 1998	32.84	2.26	12	28.1	4.07	16	10.1%	4.74 [2.37 , 7.11]
Steiber 2006	37	2.7	15	37.7	3.9	19	10.4%	-0.70 [-2.92 , 1.52]
Cui 2016	40.23	5.78	78	34.74	5.89	78	11.2%	5.49 [3.66 , 7.32]
Harmankaya 2002a	32.4	3.1	15	27.8	1.44	15	11.4%	4.60 [2.87 , 6.33]
Song 2013a	34.5	2.4	163	33.9	2.2	163	13.1%	0.60 [0.10 , 1.10]
Subtotal (95% CI)			**372**			**369**	**100.0%**	**2.07 [0.52 , 3.62]**
Heterogeneity: Tau² = 4.73; Chi² = 56.55, df = 10 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 2.62 (P = 0.009)								
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%								



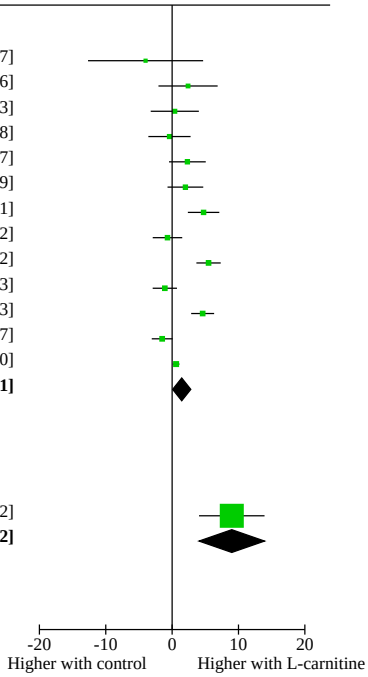
Analysis 2.23. Comparison 2: Subgroup analyses, Outcome 23: Anaemia-related markers (HCT): intervention duration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.23.1 ≤ 6 months								
Mettang 1997	32	8	8	36	9	7	3.0%	-4.00 [-12.67 , 4.67]
Pacheco 2008	32.2	5.6	13	29.8	4.7	8	6.4%	2.40 [-2.06 , 6.86]
Chazot 2003	32.5	6.6	23	32.1	5.8	22	7.5%	0.40 [-3.23 , 4.03]
Khodaverdi 2010	3.3	3.8	14	3.7	4.9	15	8.0%	-0.40 [-3.58 , 2.78]
Mitwalli 2005	32.5	3.7	18	30.2	4	13	8.6%	2.30 [-0.47 , 5.07]
Arduini 2006	34.3	3.6	13	32.3	3.4	13	8.7%	2.00 [-0.69 , 4.69]
Caruso 1998	32.84	2.26	12	28.1	4.07	16	9.1%	4.74 [2.37 , 7.11]
Steiber 2006	37	2.7	15	37.7	3.9	19	9.3%	-0.70 [-2.92 , 1.52]
Cui 2016	40.23	5.78	78	34.74	5.89	78	9.7%	5.49 [3.66 , 7.32]
Brass 2001b	32.8	4	28	33.9	2.9	28	9.8%	-1.10 [-2.93 , 0.73]
Harmankaya 2002a	32.4	3.1	15	27.8	1.44	15	9.9%	4.60 [2.87 , 6.33]
Brass 2001a	33.6	3.18	94	35.1	4.2	33	10.0%	-1.50 [-3.07 , 0.07]
Subtotal (95% CI)			**331**			**267**	**100.0%**	**1.50 [-0.26 , 3.27]**
Heterogeneity: Tau² = 7.44; Chi² = 67.07, df = 11 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 1.67 (P = 0.10)								
2.23.2 > 6 months								
Trovato 1983	36.35	7.22	13	27.36	5.5	13	45.5%	8.99 [4.06 , 13.92]
Song 2013a	34.5	2.4	163	33.9	2.2	163	54.5%	0.60 [0.10 , 1.10]
Subtotal (95% CI)			**176**			**176**	**100.0%**	**4.42 [-3.77 , 12.61]**
Heterogeneity: Tau² = 32.00; Chi² = 11.00, df = 1 (P = 0.0009); I² = 91%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%								



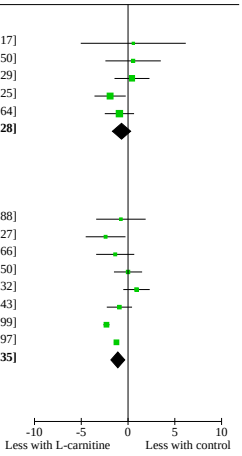
Analysis 2.24. Comparison 2: Subgroup analyses, Outcome 24: Anaemia-related markers (HCT): route of administration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.24.1 intravenous								
Mettang 1997	32	8	8	36	9	7	2.0%	-4.00 [-12.67 , 4.67]
Pacheco 2008	32.2	5.6	13	29.8	4.7	8	5.1%	2.40 [-2.06 , 6.86]
Chazot 2003	32.5	6.6	23	32.1	5.8	22	6.2%	0.40 [-3.23 , 4.03]
Khodaverdi 2010	3.3	3.8	14	3.7	4.9	15	6.9%	-0.40 [-3.58 , 2.78]
Mitwalli 2005	32.5	3.7	18	30.2	4	13	7.6%	2.30 [-0.47 , 5.07]
Arduini 2006	34.3	3.6	13	32.3	3.4	13	7.7%	2.00 [-0.69 , 4.69]
Caruso 1998	32.84	2.26	12	28.1	4.07	16	8.2%	4.74 [2.37 , 7.11]
Steiber 2006	37	2.7	15	37.7	3.9	19	8.5%	-0.70 [-2.92 , 1.52]
Cui 2016	40.23	5.78	78	34.74	5.89	78	9.1%	5.49 [3.66 , 7.32]
Brass 2001b	32.8	4	28	33.9	2.9	28	9.1%	-1.10 [-2.93 , 0.73]
Harmankaya 2002a	32.4	3.1	15	27.8	1.44	15	9.3%	4.60 [2.87 , 6.33]
Brass 2001a	33.6	3.18	94	35.1	4.2	33	9.6%	-1.50 [-3.07 , 0.07]
Song 2013a	34.5	2.4	163	33.9	2.2	163	10.8%	0.60 [0.10 , 1.10]
Subtotal (95% CI)			**494**			**430**	**100.0%**	**1.45 [0.08 , 2.81]**
Heterogeneity: Tau² = 4.43; Chi² = 72.65, df = 12 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 2.08 (P = 0.04)								
2.24.2 oral								
Trovato 1983	36.35	7.22	13	27.36	5.5	13	100.0%	8.99 [4.06 , 13.92]
Subtotal (95% CI)			**13**			**13**	**100.0%**	**8.99 [4.06 , 13.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.57 (P = 0.0004)								
Test for subgroup differences: Chi² = 8.34, df = 1 (P = 0.004), I² = 88.0%								



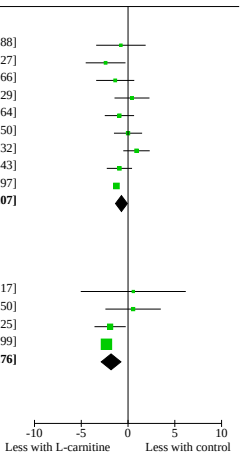
Analysis 2.25. Comparison 2: Subgroup analyses, Outcome 25: Anaemia-related markers (EPO dose): average of dose

Study or Subgroup	L-carnitine Mean [×1000 U/week]	L-carnitine SD [×1000 U/week]	L-carnitine Total	Control Mean [×1000 U/week]	Control SD [×1000 U/week]	Control Total	Weight	Mean Difference IV, Random, 95% CI [×1000 U/week]
2.25.1 Dose ≥ 10 mg/kg/day								
Kletzmayr 1999	12.4683	7.0863	12	11.9094	8.0178	16	3.0%	0.56 [-5.05 , 6.17]
Mortazavi 2012	6.666	4.618	17	6.125	4.421	19	10.3%	0.54 [-2.42 , 3.50]
Sorge-Haedicke 2001	6.0828	4.3956	43	5.661	4.2846	40	24.2%	0.42 [-1.45 , 2.29]
Maruyama 2017	4.078	2.467	30	5.995	3.96	30	29.5%	-1.92 [-3.59 , -0.25]
Garneata 2005	7.67173	2.43741	20	8.59205	2.60997	20	33.0%	-0.92 [-2.49 , 0.64]
Subtotal (95% CI)			**122**			**125**	**100.0%**	**-0.69 [-1.67 , 0.28]**
Heterogeneity: Tau² = 0.11; Chi² = 4.37, df = 4 (P = 0.36); I² = 8%								
Test for overall effect: Z = 1.40 (P = 0.16)								
2.25.2 Dose < 10 mg/kg/day								
Caruso 1998	6.364	3.557	12	7.125	3.5	16	5.8%	-0.76 [-3.41 , 1.88]
Harmankaya 2002a	4.8	3.3	15	7.2	2.6	15	7.8%	-2.40 [-4.53 , -0.27]
Labonia 1995	3.5385	1.898	13	4.9091	2.9681	11	8.2%	-1.37 [-3.41 , 0.66]
Cibulka 2005	4.5	3.558	46	4.5	3.5	39	11.5%	0.00 [-1.50 , 1.50]
Chazot 2003	1.934	2.728	23	1.029	2.073	22	12.2%	0.91 [-0.51 , 2.32]
Vaux 2004	-0.769	1.739	13	0.153	1.772	13	12.6%	-0.92 [-2.27 , 0.43]
Song 2013a	7.261	1.37	163	9.5685	1.5755	163	20.8%	-2.31 [-2.63 , -1.99]
Cui 2016	9.73385	0.85625	78	10.9737	0.84255	78	21.1%	-1.24 [-1.51 , -0.97]
Subtotal (95% CI)			**363**			**357**	**100.0%**	**-1.09 [-1.84 , -0.35]**
Heterogeneity: Tau² = 0.66; Chi² = 44.08, df = 7 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 2.88 (P = 0.004)								
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%								



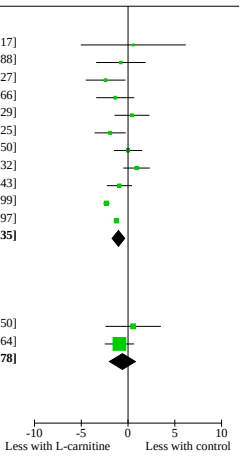
Analysis 2.26. Comparison 2: Subgroup analyses, Outcome 26: Anaemia-related markers (EPO dose): intervention duration

Study or Subgroup	L-carnitine Mean [×1000 U/week]	L-carnitine SD [×1000 U/week]	L-carnitine Total	Control Mean [×1000 U/week]	Control SD [×1000 U/week]	Control Total	Weight	Mean Difference IV, Random, 95% CI [×1000 U/week]
2.26.1 ≤ 6 months								
Caruso 1998	6.364	3.557	12	7.125	3.5	16	4.8%	-0.76 [-3.41 , 1.88]
Harmankaya 2002a	4.8	3.3	15	7.2	2.6	15	6.8%	-2.40 [-4.53 , -0.27]
Labonia 1995	3.5385	1.898	13	4.9091	2.968	11	7.2%	-1.37 [-3.41 , 0.66]
Sorge-Haedicke 2001	6.0828	4.3956	43	5.661	4.2846	40	8.2%	0.42 [-1.45 , 2.29]
Garneata 2005	7.67173	2.43741	20	8.59205	2.60997	20	10.4%	-0.92 [-2.49 , 0.64]
Cibulka 2005	4.5	3.557	46	4.5	3.5	39	11.0%	0.00 [-1.50 , 1.50]
Chazot 2003	1.934	2.728	23	1.029	2.073	22	11.8%	0.91 [-0.51 , 2.32]
Vaux 2004	-0.769	1.739	13	0.153	1.772	13	12.5%	-0.92 [-2.27 , 0.43]
Cui 2016	9.73385	0.85625	78	10.9737	0.84255	78	27.3%	-1.24 [-1.51 , -0.97]
Subtotal (95% CI)			**263**			**254**	**100.0%**	**-0.71 [-1.34 , -0.07]**
Heterogeneity: Tau² = 0.36; Chi² = 15.09, df = 8 (P = 0.06); I² = 47%								
Test for overall effect: Z = 2.18 (P = 0.03)								
2.26.2 > 6 months								
Kletzmayr 1999	12.4683	7.0863	12	11.9094	8.0178	16	3.3%	0.56 [-5.05 , 6.17]
Mortazavi 2012	6.666	4.618	17	6.125	4.421	19	10.6%	0.54 [-2.42 , 3.50]
Maruyama 2017	4.078	2.467	30	5.995	3.96	30	24.7%	-1.92 [-3.59 , -0.25]
Song 2013a	7.261	1.37	163	9.5685	1.5755	163	61.4%	-2.31 [-2.63 , -1.99]
Subtotal (95% CI)			**222**			**228**	**100.0%**	**-1.81 [-2.87 , -0.76]**
Heterogeneity: Tau² = 0.44; Chi² = 4.65, df = 3 (P = 0.20); I² = 35%								
Test for overall effect: Z = 3.38 (P = 0.0007)								
Test for subgroup differences: Chi² = 3.13, df = 1 (P = 0.08), I² = 68.0%								



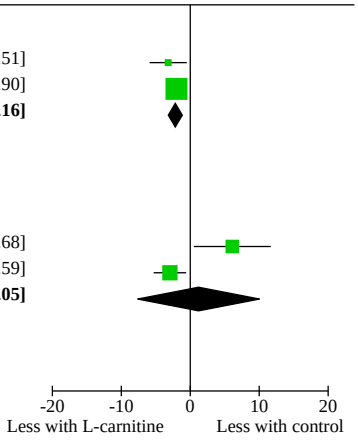
Analysis 2.27. Comparison 2: Subgroup analyses, Outcome 27: Anaemia-related markers (EPO dose): route of administration

Study or Subgroup	L-carnitine Mean [×1000 U/week]	L-carnitine SD [×1000 U/week]	L-carnitine Total	Control Mean [×1000 U/week]	Control SD [×1000 U/week]	Control Total	Weight	Mean Difference IV, Random, 95% CI [×1000 U/week]
2.27.1 Intravenous								
Kletzmayr 1999	12.4683	7.0863	12	11.9094	8.0178	16	1.3%	0.56 [-5.05 , 6.17]
Caruso 1998	6.364	3.557	12	7.125	3.5	16	4.8%	-0.76 [-3.41 , 1.88]
Harmankaya 2002a	4.8	3.3	15	7.2	2.6	15	6.4%	-2.40 [-4.53 , -0.27]
Labonia 1995	3.5385	1.898	13	4.9091	2.9681	11	6.8%	-1.37 [-3.41 , 0.66]
Sorge-Haedicke 2001	6.0828	4.3956	43	5.661	4.2846	40	7.5%	0.42 [-1.45 , 2.29]
Maruyama 2017	4.078	2.467	30	5.995	3.96	30	8.5%	-1.92 [-3.59 , -0.25]
Cibulka 2005	4.5	3.557	46	4.5	3.5	39	9.5%	0.00 [-1.50 , 1.50]
Chazot 2003	1.934	2.728	23	1.029	2.073	22	10.0%	0.91 [-0.51 , 2.32]
Vaux 2004	-0.769	1.739	13	0.153	1.772	13	10.4%	-0.92 [-2.27 , 0.43]
Song 2013a	7.261	1.37	163	9.5685	1.5755	163	17.2%	-2.31 [-2.63 , -1.99]
Cui 2016	9.73385	0.85625	78	10.9737	0.84255	78	17.5%	-1.24 [-1.51 , -0.97]
Subtotal (95% CI)			**448**			**443**	**100.0%**	**-1.03 [-1.70 , -0.35]**
Heterogeneity: Tau² = 0.66; Chi² = 49.16, df = 10 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 2.99 (P = 0.003)								
2.27.2 Oral								
Mortazavi 2012	6.666	4.618	17	6.125	4.421	19	21.8%	0.54 [-2.42 , 3.50]
Garneata 2005	7.67173	2.43741	20	8.59205	2.60997	20	78.2%	-0.92 [-2.49 , 0.64]
Subtotal (95% CI)			**37**			**39**	**100.0%**	**-0.60 [-1.99 , 0.78]**
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 0.85 (P = 0.39)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.59), I² = 0%								



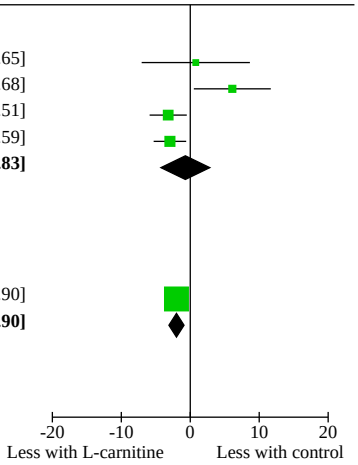
Analysis 2.28. Comparison 2: Subgroup analyses, Outcome 28: Anaemia-related markers (EPO resistance index): average of dose

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.28.1 Dose # 10 mg/kg/day								
Maruyama 2017	6.4	3.8	30	9.6	6.5	30	14.2%	-3.20 [-5.89 , -0.51]
Higuchi 2014	6.9	3.5	75	8.9	3.3	73	85.8%	-2.00 [-3.10 , -0.90]
Subtotal (95% CI)			**105**			**103**	**100.0%**	**-2.17 [-3.19 , -1.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%								
Test for overall effect: Z = 4.19 (P < 0.0001)								
2.28.2 Dose < 10 mg/kg/day								
CARNIDIAL 2012	15.6	15.9	35	9.5	5.8	38	45.9%	6.10 [0.52 , 11.68]
Steiber 2006	-1.62	3.52	15	1.33	3.44	19	54.1%	-2.95 [-5.31 , -0.59]
Subtotal (95% CI)			**50**			**57**	**100.0%**	**1.21 [-7.63 , 10.05]**
Heterogeneity: Tau² = 36.17; Chi² = 8.57, df = 1 (P = 0.003); I² = 88%								
Test for overall effect: Z = 0.27 (P = 0.79)								
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%								



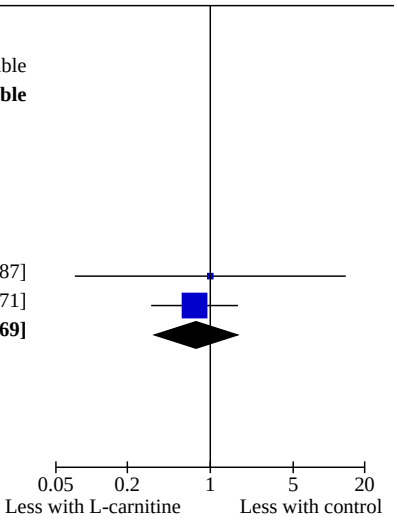
Analysis 2.29. Comparison 2: Subgroup analyses, Outcome 29: Anaemia-related markers (EPO resistance index): route of administration

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.29.1 Intravenous								
Kletzmayr 1999	17.2	10	12	16.4	11.1	16	13.5%	0.80 [-7.05 , 8.65]
CARNIDIAL 2012	15.6	15.9	35	9.5	5.8	38	20.1%	6.10 [0.52 , 11.68]
Maruyama 2017	6.4	3.8	30	9.6	6.5	30	32.5%	-3.20 [-5.89 , -0.51]
Steiber 2006	-1.62	3.52	15	1.33	3.44	19	34.0%	-2.95 [-5.31 , -0.59]
Subtotal (95% CI)			**92**			**103**	**100.0%**	**-0.71 [-4.25 , 2.83]**
Heterogeneity: Tau² = 8.15; Chi² = 9.96, df = 3 (P = 0.02); I² = 70%								
Test for overall effect: Z = 0.39 (P = 0.69)								
2.29.2 Oral								
Higuchi 2014	6.9	3.5	75	8.9	3.3	73	100.0%	-2.00 [-3.10 , -0.90]
Subtotal (95% CI)			**75**			**73**	**100.0%**	**-2.00 [-3.10 , -0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.58 (P = 0.0003)								
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.50), I² = 0%								



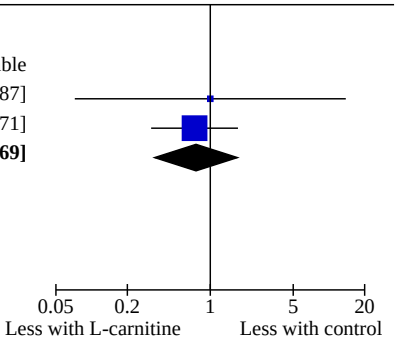
Analysis 2.30. Comparison 2: Subgroup analyses, Outcome 30: Myocardial function (intradialytic hypotension): average dose

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.30.1 Dose ≥ 10 mg/kg/day						
Vaux 2004	0	13	0	13		Not estimable
Subtotal (95% CI)		**13**		**13**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.30.2 Dose < 10 mg/kg/day						
Rathod 2006	1	10	1	10	9.3%	1.00 [0.07 , 13.87]
Ahmad 1990	7	38	11	44	90.7%	0.74 [0.32 , 1.71]
Subtotal (95% CI)		**48**		**54**	**100.0%**	**0.76 [0.34 , 1.69]**
Total events:	8		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



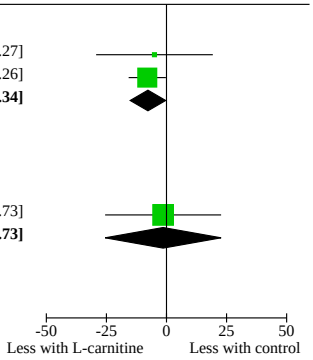
Analysis 2.31. Comparison 2: Subgroup analyses, Outcome 31: Myocardial function (intradialytic hypotension): route of administration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.31.1 Intravenous						
Vaux 2004	0	13	0	13		Not estimable
Rathod 2006	1	10	1	10	9.3%	1.00 [0.07 , 13.87]
Ahmad 1990	7	38	11	44	90.7%	0.74 [0.32 , 1.71]
Subtotal (95% CI)		**61**		**67**	**100.0%**	**0.76 [0.34 , 1.69]**
Total events:	8		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



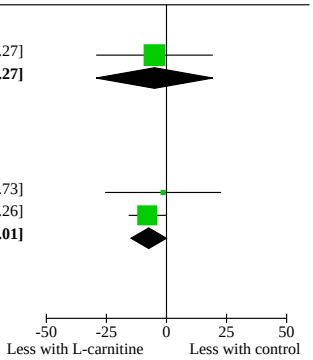
Analysis 2.32. Comparison 2: Subgroup analyses, Outcome 32: Myocardial function (LVM): average dose

Study or Subgroup	L-carnitine Mean [g/m²]	L-carnitine SD [g/m²]	L-carnitine Total	Control Mean [g/m²]	Control SD [g/m²]	Control Total	Weight	Mean Difference IV, Random, 95% CI [g/m²]
2.32.1 Dose ≥ 10 mg/kg/day								
Kudoh 2013	97.1	30.2	10	102.1	22.3	8	9.2%	-5.00 [-29.27 , 19.27]
Higuchi 2014	104	23	75	112	25	73	90.8%	-8.00 [-15.74 , -0.26]
Subtotal (95% CI)			**85**			**81**	**100.0%**	**-7.72 [-15.10 , -0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 2.05 (P = 0.04)								
2.32.2 Dose < 10 mg/kg/day								
Sugiyama 2021	118.6	35.8	34	120	44	17	100.0%	-1.40 [-25.53 , 22.73]
Subtotal (95% CI)			**34**			**17**	**100.0%**	**-1.40 [-25.53 , 22.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%								



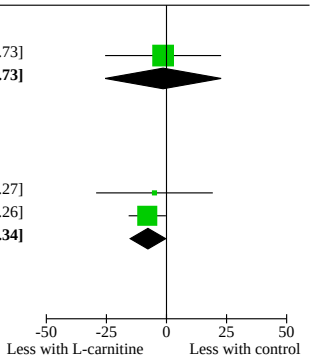
Analysis 2.33. Comparison 2: Subgroup analyses, Outcome 33: Myocardial function (LVM): intervention duration

Study or Subgroup	L-carnitine Mean [g/m²]	L-carnitine SD [g/m²]	L-carnitine Total	Control Mean [g/m²]	Control SD [g/m²]	Control Total	Weight	Mean Difference IV, Random, 95% CI [g/m²]
2.33.1 ≤ 6 months								
Kudoh 2013	97.1	30.2	10	102.1	22.3	8	100.0%	-5.00 [-29.27 , 19.27]
Subtotal (95% CI)			**10**			**8**	**100.0%**	**-5.00 [-29.27 , 19.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
2.33.2 > 6 months								
Sugiyama 2021	118.6	35.8	34	120	44	17	9.3%	-1.40 [-25.53 , 22.73]
Higuchi 2014	104	23	75	112	25	73	90.7%	-8.00 [-15.74 , -0.26]
Subtotal (95% CI)			**109**			**90**	**100.0%**	**-7.38 [-14.76 , -0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%								
Test for overall effect: Z = 1.96 (P = 0.05)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%								



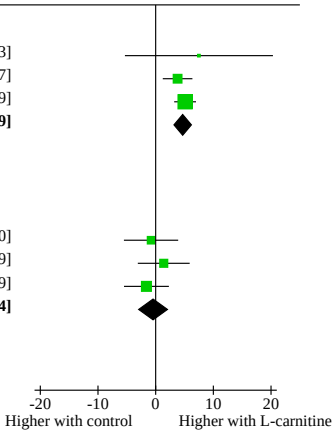
Analysis 2.34. Comparison 2: Subgroup analyses, Outcome 34: Myocardial function (LVM): route of administration

Study or Subgroup	L-carnitine Mean [g/m²]	L-carnitine SD [g/m²]	L-carnitine Total	Control Mean [g/m²]	Control SD [g/m²]	Control Total	Weight	Mean Difference IV, Random, 95% CI [g/m²]
2.34.1 Intravenous								
Sugiyama 2021	118.6	35.8	34	120	44	17	100.0%	-1.40 [-25.53 , 22.73]
Subtotal (95% CI)			**34**			**17**	**100.0%**	**-1.40 [-25.53 , 22.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								
2.34.2 Oral								
Kudoh 2013	97.1	30.2	10	102.1	22.3	8	9.2%	-5.00 [-29.27 , 19.27]
Higuchi 2014	104	23	75	112	25	73	90.8%	-8.00 [-15.74 , -0.26]
Subtotal (95% CI)			**85**			**81**	**100.0%**	**-7.72 [-15.10 , -0.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 2.05 (P = 0.04)								
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%								



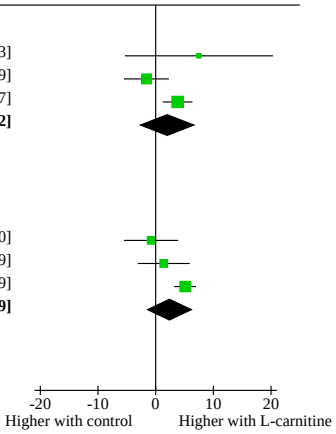
Analysis 2.35. Comparison 2: Subgroup analyses, Outcome 35: Myocardial function (ejection fraction): average dose

Study or Subgroup	L-carnitine Mean [%]	L-carnitine SD [%]	L-carnitine Total	Control Mean [%]	Control SD [%]	Control Total	Weight	Mean Difference IV, Random, 95% CI [%]
2.35.1 Dose # 10 mg/kg/day								
Kudoh 2013	64.4	13.8	10	56.9	13.8	8	1.4%	7.50 [-5.33 , 20.33]
Abdul-Hassan Mahdi 2021	52.3	5.91	70	48.5	6.53	35	34.6%	3.80 [1.23 , 6.37]
Higuchi 2014	58.6	5.5	75	53.5	6.2	73	64.0%	5.10 [3.21 , 6.99]
Subtotal (95% CI)			**155**			**116**	**100.0%**	**4.68 [3.17 , 6.19]**
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%								
Test for overall effect: Z = 6.07 (P < 0.00001)								
2.35.2 Dose < 10 mg/kg/day								
Sugiyama 2021	64.5	9.29	34	65.3	7.4	17	28.1%	-0.80 [-5.50 , 3.90]
Maruyama 2017	58.7	8.1	30	57.3	9.6	30	30.8%	1.40 [-3.09 , 5.89]
Fagher 1985	-0.6	5.2	14	1	5.3	14	41.1%	-1.60 [-5.49 , 2.29]
Subtotal (95% CI)			**78**			**61**	**100.0%**	**-0.45 [-2.95 , 2.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.72)								
Test for subgroup differences: Chi² = 11.91, df = 1 (P = 0.0006), I² = 91.6%								



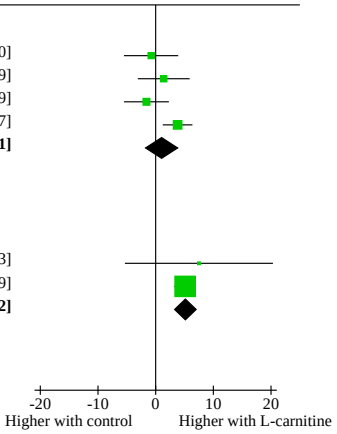
Analysis 2.36. Comparison 2: Subgroup analyses, Outcome 36: Myocardial function (ejection fraction): intervention duration

Study or Subgroup	L-carnitine Mean [%]	L-carnitine SD [%]	L-carnitine Total	Control Mean [%]	Control SD [%]	Control Total	Weight	Mean Difference IV, Random, 95% CI [%]
2.36.1 ≤ 6 months								
Kudoh 2013	64.4	13.8	10	56.9	13.8	8	10.6%	7.50 [-5.33 , 20.33]
Fagher 1985	-0.6	5.2	14	1	5.3	14	40.8%	-1.60 [-5.49 , 2.29]
Abdul-Hassan Mahdi 2021	52.3	5.91	70	48.5	6.53	35	48.6%	3.80 [1.23 , 6.37]
Subtotal (95% CI)			**94**			**57**	**100.0%**	**1.99 [-2.64 , 6.62]**
Heterogeneity: Tau² = 9.77; Chi² = 5.80, df = 2 (P = 0.05); I² = 66%								
Test for overall effect: Z = 0.84 (P = 0.40)								
2.36.2 > 6 months								
Sugiyama 2021	64.5	9.29	34	65.3	7.4	17	27.8%	-0.80 [-5.50 , 3.90]
Maruyama 2017	58.7	8.1	30	57.3	9.6	30	28.9%	1.40 [-3.09 , 5.89]
Higuchi 2014	58.6	5.5	75	53.5	6.2	73	43.3%	5.10 [3.21 , 6.99]
Subtotal (95% CI)			**139**			**120**	**100.0%**	**2.39 [-1.41 , 6.19]**
Heterogeneity: Tau² = 7.76; Chi² = 6.57, df = 2 (P = 0.04); I² = 70%								
Test for overall effect: Z = 1.23 (P = 0.22)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%								



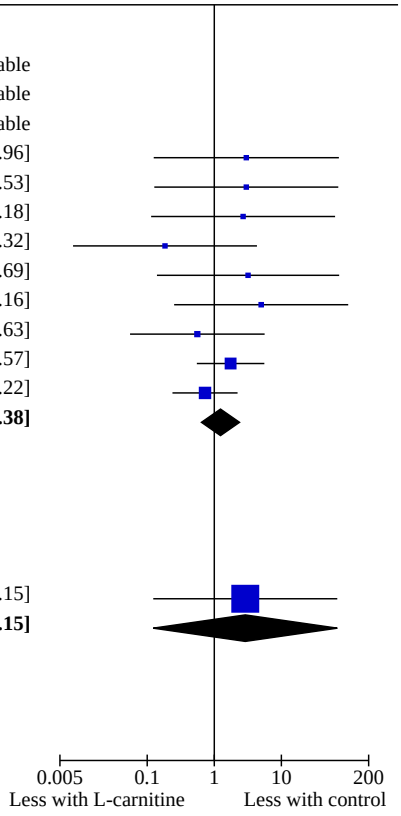
Analysis 2.37. Comparison 2: Subgroup analyses, Outcome 37: Myocardial function (ejection fraction): route of administration

Study or Subgroup	L-carnitine Mean [%]	L-carnitine SD [%]	L-carnitine Total	Control Mean [%]	Control SD [%]	Control Total	Weight	Mean Difference IV, Random, 95% CI [%]
2.37.1 Intravenous								
Sugiyama 2021	64.5	9.29	34	65.3	7.4	17	20.2%	-0.80 [-5.50 , 3.90]
Maruyama 2017	58.7	8.1	30	57.3	9.6	30	21.2%	1.40 [-3.09 , 5.89]
Fagher 1985	-0.6	5.2	14	1	5.3	14	24.7%	-1.60 [-5.49 , 2.29]
Abdul-Hassan Mahdi 2021	52.3	5.91	70	48.5	6.53	35	33.9%	3.80 [1.23 , 6.37]
Subtotal (95% CI)			**148**			**96**	**100.0%**	**1.03 [-1.76 , 3.81]**
Heterogeneity: Tau² = 4.24; Chi² = 6.43, df = 3 (P = 0.09); I² = 53%								
Test for overall effect: Z = 0.72 (P = 0.47)								
2.37.2 Oral								
Kudoh 2013	64.4	13.8	10	56.9	13.8	8	2.1%	7.50 [-5.33 , 20.33]
Higuchi 2014	58.6	5.5	75	53.5	6.2	73	97.9%	5.10 [3.21 , 6.99]
Subtotal (95% CI)			**85**			**81**	**100.0%**	**5.15 [3.28 , 7.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 5.40 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.80, df = 1 (P = 0.02), I² = 82.8%								



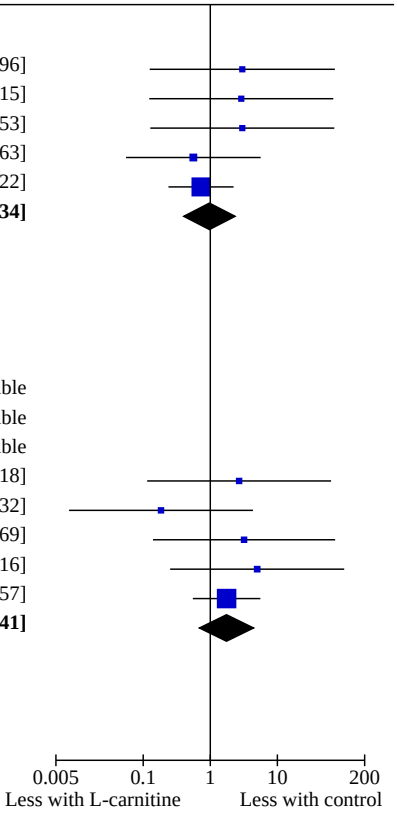
Analysis 2.38. Comparison 2: Subgroup analyses, Outcome 38: Death (any cause): dialysis modality

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.38.1 HD patients only						
Mettang 1997	0	8	0	7		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Vaux 2004	0	13	0	13		Not estimable
Fukami 2013	1	51	0	51	4.2%	3.00 [0.13 , 71.96]
Naini 2011	1	27	0	27	4.3%	3.00 [0.13 , 70.53]
Chazot 2003	1	28	0	25	4.3%	2.69 [0.11 , 63.18]
Sugiyama 2021	0	37	1	20	4.3%	0.18 [0.01 , 4.32]
Caruso 1998	1	15	0	16	4.4%	3.19 [0.14 , 72.69]
Ahmadi 2016	2	25	0	25	4.8%	5.00 [0.25 , 99.16]
Mortazavi 2012	1	17	2	19	8.0%	0.56 [0.06 , 5.63]
CARNIDIAL 2012	7	46	4	46	31.7%	1.75 [0.55 , 5.57]
Higuchi 2014	5	110	7	112	34.1%	0.73 [0.24 , 2.22]
Subtotal (95% CI)		**409**		**393**	**100.0%**	**1.24 [0.64 , 2.38]**
Total events:	19		14			
Heterogeneity: Tau² = 0.00; Chi² = 5.10, df = 8 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
2.38.2 PD patients only						
Mortazavi 2011a	1	28	0	27	100.0%	2.90 [0.12 , 68.15]
Subtotal (95% CI)		**28**		**27**	**100.0%**	**2.90 [0.12 , 68.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.61), I² = 0%						



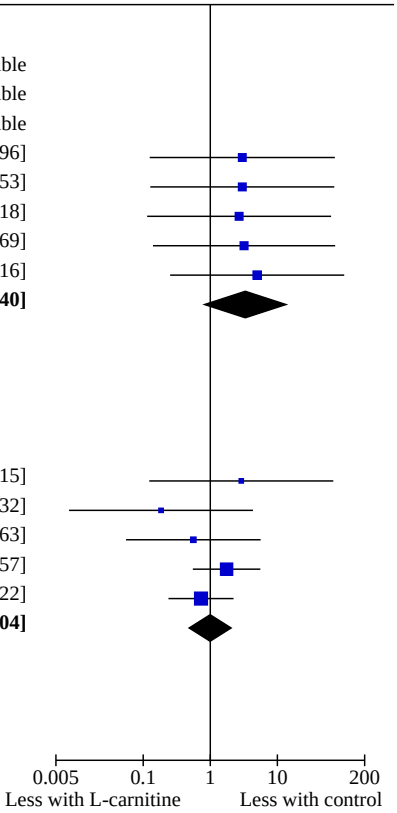
Analysis 2.39. Comparison 2: Subgroup analyses, Outcome 39: Death (any cause): average dose

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.39.1 Dose # 10 mg/kg/day						
Fukami 2013	1	51	0	51	7.7%	3.00 [0.13 , 71.96]
Mortazavi 2011a	1	28	0	27	7.8%	2.90 [0.12 , 68.15]
Naini 2011	1	27	0	27	7.8%	3.00 [0.13 , 70.53]
Mortazavi 2012	1	17	2	19	14.6%	0.56 [0.06 , 5.63]
Higuchi 2014	5	110	7	112	62.2%	0.73 [0.24 , 2.22]
Subtotal (95% CI)		**233**		**236**	**100.0%**	**0.97 [0.40 , 2.34]**
Total events:	9		9			
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 4 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
2.39.2 Dose < 10 mg/kg/day						
Mettang 1997	0	8	0	7		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Vaux 2004	0	13	0	13		Not estimable
Chazot 2003	1	28	0	25	8.7%	2.69 [0.11 , 63.18]
Sugiyama 2021	0	37	1	20	8.7%	0.18 [0.01 , 4.32]
Caruso 1998	1	15	0	16	8.8%	3.19 [0.14 , 72.69]
Ahmadi 2016	2	25	0	25	9.7%	5.00 [0.25 , 99.16]
CARNIDIAL 2012	7	46	4	46	64.2%	1.75 [0.55 , 5.57]
Subtotal (95% CI)		**204**		**184**	**100.0%**	**1.74 [0.69 , 4.41]**
Total events:	11		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 4 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%						



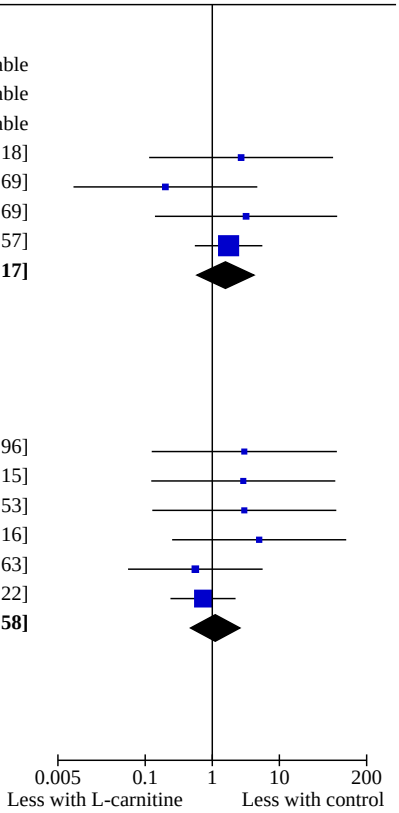
Analysis 2.40. Comparison 2: Subgroup analyses, Outcome 40: Death (any cause): intervention duration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.40.1 ≤ 6 months						
Vaux 2004	0	13	0	13		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Mettang 1997	0	8	0	7		Not estimable
Fukami 2013	1	51	0	51	19.3%	3.00 [0.13 , 71.96]
Naini 2011	1	27	0	27	19.5%	3.00 [0.13 , 70.53]
Chazot 2003	1	28	0	25	19.5%	2.69 [0.11 , 63.18]
Caruso 1998	1	15	0	16	19.9%	3.19 [0.14 , 72.69]
Ahmadi 2016	2	25	0	25	21.8%	5.00 [0.25 , 99.16]
Subtotal (95% CI)		**199**		**196**	**100.0%**	**3.32 [0.82 , 13.40]**
Total events:	6		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
2.40.2 > 6 months						
Mortazavi 2011a	1	28	0	27	5.2%	2.90 [0.12 , 68.15]
Sugiyama 2021	0	37	1	20	5.2%	0.18 [0.01 , 4.32]
Mortazavi 2012	1	17	2	19	9.7%	0.56 [0.06 , 5.63]
CARNIDIAL 2012	7	46	4	46	38.5%	1.75 [0.55 , 5.57]
Higuchi 2014	5	110	7	112	41.4%	0.73 [0.24 , 2.22]
Subtotal (95% CI)		**238**		**224**	**100.0%**	**0.99 [0.48 , 2.04]**
Total events:	14		14			
Heterogeneity: Tau² = 0.00; Chi² = 2.99, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 55.9%						



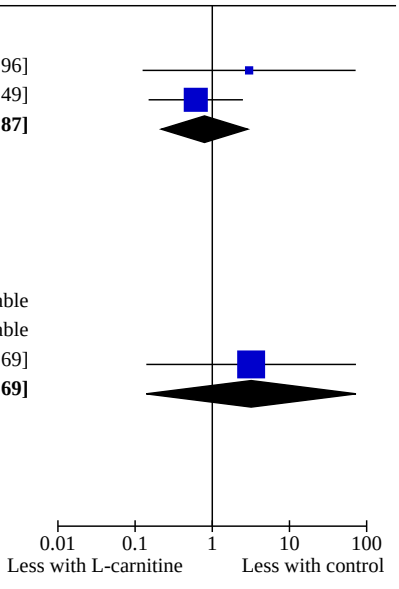
Analysis 2.41. Comparison 2: Subgroup analyses, Outcome 41: Death (any cause): route of administration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.41.1 Intravenous						
Mettang 1997	0	8	0	7		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Vaux 2004	0	13	0	13		Not estimable
Chazot 2003	1	28	0	25	9.6%	2.69 [0.11 , 63.18]
Sugiyama 2021	0	34	1	20	9.6%	0.20 [0.01 , 4.69]
Caruso 1998	1	15	0	16	9.8%	3.19 [0.14 , 72.69]
CARNIDIAL 2012	7	46	4	46	71.1%	1.75 [0.55 , 5.57]
Subtotal (95% CI)		**176**		**159**	**100.0%**	**1.57 [0.59 , 4.17]**
Total events:	9		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.37)						
2.41.2 Oral						
Fukami 2013	1	51	0	51	7.1%	3.00 [0.13 , 71.96]
Mortazavi 2011a	1	28	0	27	7.2%	2.90 [0.12 , 68.15]
Naini 2011	1	27	0	27	7.2%	3.00 [0.13 , 70.53]
Ahmadi 2016	2	25	0	25	8.0%	5.00 [0.25 , 99.16]
Mortazavi 2012	1	17	2	19	13.4%	0.56 [0.06 , 5.63]
Higuchi 2014	5	110	7	112	57.2%	0.73 [0.24 , 2.22]
Subtotal (95% CI)		**258**		**261**	**100.0%**	**1.11 [0.48 , 2.58]**
Total events:	11		9			
Heterogeneity: Tau² = 0.00; Chi² = 3.02, df = 5 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.81)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						



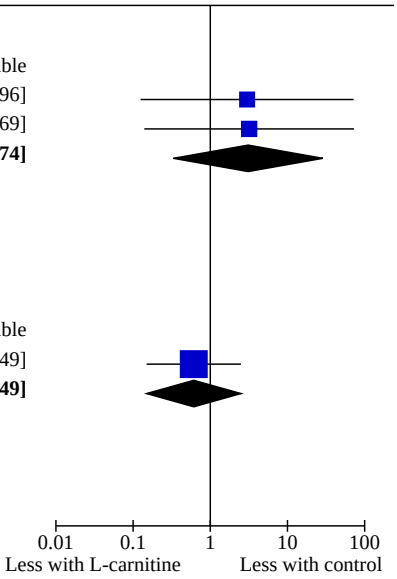
Analysis 2.42. Comparison 2: Subgroup analyses, Outcome 42: Death (cardiovascular): average dose

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.42.1 Dose ≥ 10 mg/kg/day						
Fukami 2013	1	51	0	51	16.4%	3.00 [0.13 , 71.96]
Higuchi 2014	3	110	5	112	83.6%	0.61 [0.15 , 2.49]
Subtotal (95% CI)		**161**		**163**	**100.0%**	**0.79 [0.22 , 2.87]**
Total events:	4		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
2.42.2 Dose < 10 mg/kg/day						
Vaux 2004	0	13	0	13		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Caruso 1998	1	15	0	16	100.0%	3.19 [0.14 , 72.69]
Subtotal (95% CI)		**60**		**61**	**100.0%**	**3.19 [0.14 , 72.69]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%						



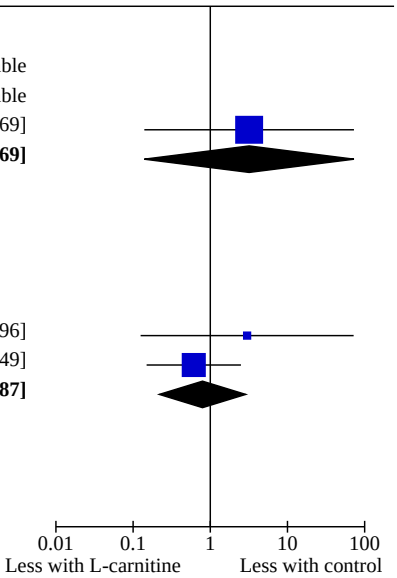
Analysis 2.43. Comparison 2: Subgroup analyses, Outcome 43: Death (cardiovascular): intervention duration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.43.1 ≤ 6 months						
Vaux 2004	0	13	0	13		Not estimable
Fukami 2013	1	51	0	51	49.2%	3.00 [0.13 , 71.96]
Caruso 1998	1	15	0	16	50.8%	3.19 [0.14 , 72.69]
Subtotal (95% CI)		**79**		**80**	**100.0%**	**3.09 [0.33 , 28.74]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
2.43.2 > 6 months						
Signorelli 2006	0	32	0	32		Not estimable
Higuchi 2014	3	110	5	112	100.0%	0.61 [0.15 , 2.49]
Subtotal (95% CI)		**142**		**144**	**100.0%**	**0.61 [0.15 , 2.49]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Chi² = 1.46, df = 1 (P = 0.23), I² = 31.3%						



Analysis 2.44. Comparison 2: Subgroup analyses, Outcome 44: Death (cardiovascular): route of administration

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.44.1 Intravenous						
Vaux 2004	0	13	0	13		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Caruso 1998	1	15	0	16	100.0%	3.19 [0.14 , 72.69]
Subtotal (95% CI)		**60**		**61**	**100.0%**	**3.19 [0.14 , 72.69]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
2.44.2 Oral						
Fukami 2013	1	51	0	51	16.4%	3.00 [0.13 , 71.96]
Higuchi 2014	3	110	5	112	83.6%	0.61 [0.15 , 2.49]
Subtotal (95% CI)		**161**		**163**	**100.0%**	**0.79 [0.22 , 2.87]**
Total events:	4		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%						

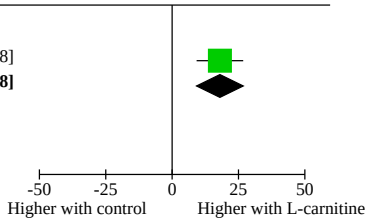


Comparison 3. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 QoL (SF-36 PCS): source of funding	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 NGO/not for profit funding	1	51	Mean Difference (IV, Random, 95% CI)	18.00 [9.22, 26.78]
3.2 QoL (SF-36 MCS): source of funding	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2.1 NGO/not for profit funding	1	51	Mean Difference (IV, Random, 95% CI)	20.60 [9.90, 31.30]
3.3 QoL (total): overall risk of bias	1	24	Mean Difference (IV, Random, 95% CI)	0.66 [-5.36, 6.68]
3.4 Fatigue score: overall risk of bias	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.4.1 Low risk of bias	1	173	Mean Difference (IV, Random, 95% CI)	0.28 [-1.07, 1.63]
3.5 Adverse events: source of funding	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.5.1 NGO/not for profit funding	4	243	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.53, 1.63]
3.6 Adverse events: overall risk of bias	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.6.1 Low risk of bias	3	353	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.88, 1.80]
3.7 Adverse events: language of publication	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.7.1 published in English	11	986	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.86, 1.52]
3.8 Anaemia-related markers (EPO dose): not imputed	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.8.1 Not imputed	7	287	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.78, -0.29]

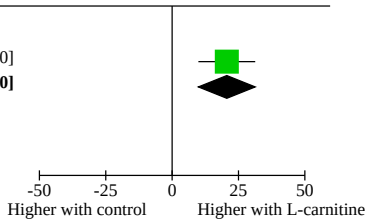
Analysis 3.1. Comparison 3: Sensitivity analyses, Outcome 1: QoL (SF-36 PCS): source of funding

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 NGO/not for profit funding								
Naini 2011	52.5	18	24	34.5	13.3	27	100.0%	18.00 [9.22 , 26.78]
Subtotal (95% CI)			**24**			**27**	**100.0%**	**18.00 [9.22 , 26.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.02 (P < 0.0001)								
Test for subgroup differences: Not applicable								



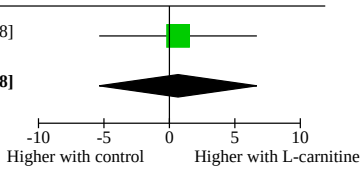
Analysis 3.2. Comparison 3: Sensitivity analyses, Outcome 2: QoL (SF-36 MCS): source of funding

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 NGO/not for profit funding								
Naini 2011	58.2	21.2	24	37.6	17.3	27	100.0%	20.60 [9.90 , 31.30]
Subtotal (95% CI)			**24**			**27**	**100.0%**	**20.60 [9.90 , 31.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.77 (P = 0.0002)								
Test for subgroup differences: Not applicable								



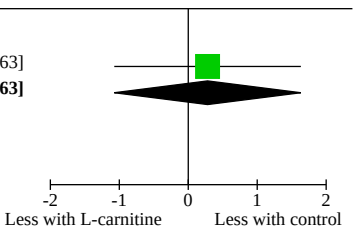
Analysis 3.3. Comparison 3: Sensitivity analyses, Outcome 3: QoL (total): overall risk of bias

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hamedi-Kalajahi 2021	67.33	8.12	12	66.67	6.88	12	100.0%	0.66 [-5.36 , 6.68]
Total (95% CI)			**12**			**12**	**100.0%**	**0.66 [-5.36 , 6.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								
Test for subgroup differences: Not applicable								



Analysis 3.4. Comparison 3: Sensitivity analyses, Outcome 4: Fatigue score: overall risk of bias

Study or Subgroup	L-carnitine Mean	L-carnitine SD	L-carnitine Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 Low risk of bias								
Fukuda 2015	5.59	4.56	87	5.31	4.52	86	100.0%	0.28 [-1.07 , 1.63]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**0.28 [-1.07 , 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.69)								
Test for subgroup differences: Not applicable								



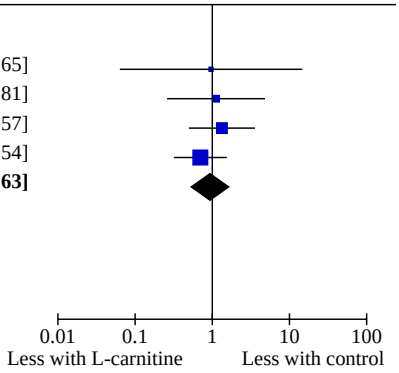
Analysis 3.5. Comparison 3: Sensitivity analyses, Outcome 5: Adverse events: source of funding

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 NGO/not for profit funding						
Mortazavi 2011a	1	28	1	27	4.2%	0.96 [0.06 , 14.65]
Mortazavi 2012	3	17	3	19	14.5%	1.12 [0.26 , 4.81]
Fukami 2013	8	51	6	51	31.9%	1.33 [0.50 , 3.57]
Chi 2021	7	25	10	25	49.4%	0.70 [0.32 , 1.54]
Subtotal (95% CI)		**121**		**122**	**100.0%**	**0.93 [0.53 , 1.63]**
Total events:	19		20			

Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 3 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.25 (P = 0.81)

Test for subgroup differences: Not applicable



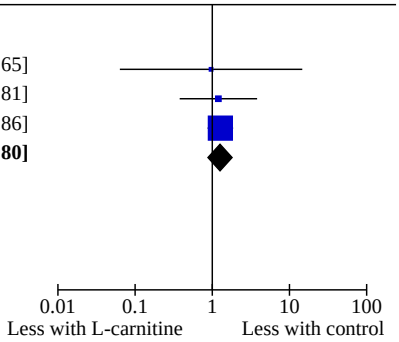
Analysis 3.6. Comparison 3: Sensitivity analyses, Outcome 6: Adverse events: overall risk of bias

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Low risk of bias						
Mortazavi 2011a	1	28	1	27	1.7%	0.96 [0.06 , 14.65]
Fukuda 2015	6	103	5	103	9.6%	1.20 [0.38 , 3.81]
CARNIDIAL 2012	28	46	22	46	88.6%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**177**		**176**	**100.0%**	**1.26 [0.88 , 1.80]**
Total events:	35		28			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%

Test for overall effect: Z = 1.26 (P = 0.21)

Test for subgroup differences: Not applicable

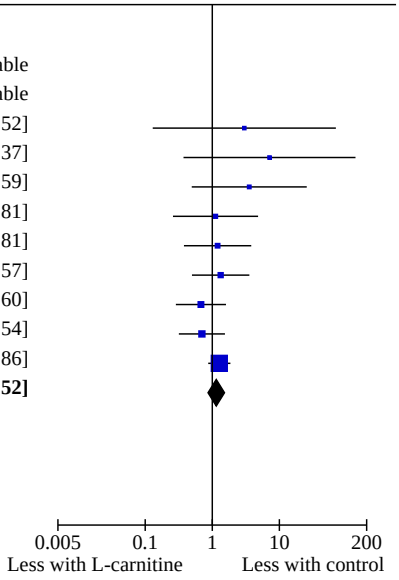


Analysis 3.7. Comparison 3: Sensitivity analyses, Outcome 7: Adverse events: language of publication

Study or Subgroup	L-carnitine Events	L-carnitine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 published in English						
Maruyama 2017	0	30	0	30		Not estimable
Signorelli 2006	0	32	0	32		Not estimable
Kletzmayr 1999	1	20	0	20	0.8%	3.00 [0.13 , 69.52]
Higuchi 2014	3	110	0	112	0.9%	7.13 [0.37 , 136.37]
Mettang 1997	4	9	1	8	2.0%	3.56 [0.49 , 25.59]
Mortazavi 2012	3	17	3	19	3.7%	1.12 [0.26 , 4.81]
Fukuda 2015	6	103	5	103	6.0%	1.20 [0.38 , 3.81]
Fukami 2013	8	51	6	51	8.2%	1.33 [0.50 , 3.57]
Ahmad 1990	7	47	11	50	10.8%	0.68 [0.29 , 1.60]
Chi 2021	7	25	10	25	12.7%	0.70 [0.32 , 1.54]
CARNIDIAL 2012	28	46	22	46	54.9%	1.27 [0.87 , 1.86]
Subtotal (95% CI)		**490**		**496**	**100.0%**	**1.15 [0.86 , 1.52]**
Total events:	67		58			

Heterogeneity: Tau² = 0.00; Chi² = 6.43, df = 8 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable

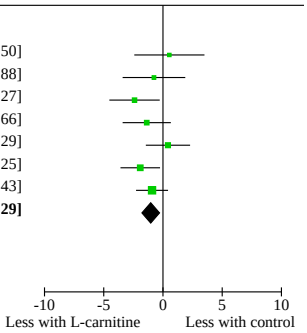


Analysis 3.8. Comparison 3: Sensitivity analyses, Outcome 8: Anaemia-related markers (EPO dose): not imputed

Study or Subgroup	L-carnitine Mean [1000]	L-carnitine SD [1000]	L-carnitine Total	Control Mean [1000]	Control SD [1000]	Control Total	Weight	Mean Difference IV, Random, 95% CI [1000]
3.8.1 Not imputed								
Mortazavi 2012	6.666	4.618	17	6.125	4.421	19	6.2%	0.54 [-2.42 , 3.50]
Caruso 1998	6.364	3.557	12	7.125	3.5	16	7.7%	-0.76 [-3.41 , 1.88]
Harmankaya 2002a	4.8	3.3	15	7.2	2.6	15	11.8%	-2.40 [-4.53 , -0.27]
Labonia 1995	3.5385	1.898	13	4.9091	2.9681	11	12.8%	-1.37 [-3.41 , 0.66]
Sorge-Haedicke 2001	6.0828	4.3956	43	5.661	4.2846	40	15.1%	0.42 [-1.45 , 2.29]
Maruyama 2017	4.078	2.467	30	5.995	3.96	30	18.7%	-1.92 [-3.59 , -0.25]
Vaux 2004	-0.769	1.739	13	0.153	1.772	13	27.8%	-0.92 [-2.27 , 0.43]
Subtotal (95% CI)			**143**			**144**	**100.0%**	**-1.03 [-1.78 , -0.29]**

Heterogeneity: Tau² = 0.04; Chi² = 6.25, df = 6 (P = 0.40); I² = 4%
Test for overall effect: Z = 2.73 (P = 0.006)

Test for subgroup differences: Not applicable



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 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)

(Continued)

	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. 15.(PD or CAPD or CCPD or APD).tw. 16.peritoneal dialysis fluid/ 17.peritoneal dialysis catheter/ 18.or/1-17

(Continued)

	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 Detection bias due to knowledge of the allocated interventions by outcome assessors.	*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.
	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.

(Continued)

	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

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: Norihiro Nishioka, Norio Watanabe
2. Study selection: Norihiro Nishioka, Yan Luo, Takuya Taniguchi
3. Extract data from studies: Norihiro Nishioka, Yan Luo, Takuya Taniguchi, Tsuyoshi Ohnishi
4. Enter data into RevMan: Norihiro Nishioka, Yan Luo, Takuya Taniguchi
5. Carry out the analysis: Norihiro Nishioka, Norio Watanabe, Yan Luo, Takuya Taniguchi

6. Interpret the analysis: Norihiro Nishioka, Tsuyoshi Ohnishi, Miho Kimachi, Roland Ng, Norio Watanabe
7. Draft the final review: Norihiro Nishioka, Yan Luo, Takuya Taniguchi, Tsuyoshi Ohnishi, Miho Kimachi, Roland Ng, Norio Watanabe
8. Disagreement resolution: Tsuyoshi Ohnishi, Miho Kimachi, Roland Ng
9. Update the review: Norihiro Nishioka, Yan Luo, Takuya Taniguchi, Tsuyoshi Ohnishi, Miho Kimachi, Roland Ng, Norio Watanabe

DECLARATIONS OF INTEREST

- Norihiro Nishioka: no relevant interests were disclosed
- Yan Luo: no relevant interests were disclosed
- Takuya Taniguchi: no relevant interests were disclosed
- Tsuyoshi Ohnish: Astellas Pharma (Independent Contractor - Other), Mitsubishi Tanabe Pharma Corporation (Independent Contractor - Other)
- Miho Kimachi: no relevant interests were disclosed
- Roland CK Ng: 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.
- Norio Watanabe: no relevant interests were disclosed

SOURCES OF SUPPORT

Internal sources

- No Source of support, Other

External sources

- No Source of support, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Information on EPO dose was of two patterns (unit/week or unit/body weight/week); most studies did not report body weight. We therefore imputed them using body weight from RCTs of similar patients in the same country.

We could not carry out prespecified subgroup analyses including participants (age (< 18 years versus ≥ 18 years), ethnicity of patients, iron store parameters (serum ferritin ≤ 200 µg/L versus > 200 µg/L and transferrin saturation ≤ 20% versus > 20%) and co-prescribing treatments (iron, renin-angiotensin-aldosterone system inhibitors) due to the small number of eligible included studies and the lack of reported information.