

L-Carnitine supplementation for adults with end-stage kidney disease requiring maintenance hemodialysis: a systematic review and meta-analysis^{1–4}

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ABSTRACT

Background: A previous meta-analysis indicated that L-carnitine significantly increased hemoglobin and decreased the required erythropoietin dose in maintenance hemodialysis patients.

Objective: An updated systematic review and meta-analysis of randomized controlled trials (RCTs) was performed to reevaluate effects of L-carnitine.

Design: The Cochrane Library, PubMed, and EMBASE databases (31 December 2012) were searched to identify RCTs that investigated effects of L-carnitine in adults with end-stage kidney disease that required maintenance hemodialysis.

Results: Forty-nine RCTs (1734 participants) were included. L-Carnitine significantly decreased serum low-density lipoprotein (LDL) (mean difference: -5.82 mg/dL; 95% CI: -11.61 , -0.04 mg/dL) and C-reactive protein (CRP) (-3.65 mg/L; -6.19 , -1.12 mg/L). There were no significant differences in triglycerides (-0.89 mg/dL; -29.32 , 27.53 mg/dL), cholesterol (0.14 mg/dL; -6.15 , 6.42 mg/dL), high-density lipoprotein (1.13 mg/dL; -2.44 , 4.70 mg/dL), hemoglobin (0.68 g/dL; 0.14 , 1.50 g/dL), hematocrit (2.04% ; -1.39 , 5.48%), albumin (1.65 g/L; -0.22 , 3.51 g/L), or the required erythropoietin dose (-0.76 KU/wk; -1.75 , 0.23 KU/wk). No adverse effects were reported.

Conclusions: This meta-analysis failed to confirm the previous findings regarding the effects of L-carnitine on hemoglobin and the erythropoietin dose but showed that L-carnitine significantly decreased serum LDL and CRP. The extent of the decrease in LDL was not clinically relevant, whereas the significant decrease in CRP was both statistically and clinically relevant. However, the relevance of decrease in CRP with hard endpoints such as all-cause mortality and cardiovascular complications still remains to be clarified. *Am J Clin Nutr* 2014;99:408–22.

INTRODUCTION

L-Carnitine is critical for the transportation of long-chain fatty acids across the inner mitochondrial membrane for subsequent β oxidation and energy production (1–3). Patients with end-stage kidney disease (ESKD)⁵ who are undergoing maintenance hemodialysis usually suffer from progressive L-carnitine deficiency; loss via dialysis is the main cause (4, 5). Abnormalities in carnitine homeostasis may have profound biochemical effects on serum lipid, red blood cells, cardiac muscle, and skeletal muscle (6). Dialysis-related carnitine deficiency can be corrected with exogenous supplementation (6, 7).

In 2003, the National Kidney Foundation developed a practice recommendation for the use of L-carnitine in dialysis-related carnitine disorders, most notably erythropoietin-resistant anemia, intradialytic hypotension, cardiomyopathy, and fatigability (6). However, in 2006, the updated National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Recommendations stated that “there was insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with hemodialysis and chronic kidney disease” (8). After the US Food and Drug Administration approved the use of L-carnitine in hemodialysis in 1999, the US Centers for Medicare & Medicaid Services approved national reimbursement for the intravenous and oral administration of L-carnitine for ESKD patients in 2004 and 2012, respectively (6, 9).

A large number of mostly observational studies have shown the efficacy of L-carnitine supplementation in treating hemodialysis-related clinical disorders in ESKD patients (10–19); however,

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⁵ Abbreviations used: AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CRP, C-reactive protein; ESKD, end-stage kidney disease; FDR, false discovery rate; MD, mean difference; RCT, randomized controlled trial; SMD, standardized mean difference; 4D, German Diabetes and Dialysis.

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numerous randomized controlled trials (RCTs) have also been published with negative results (2, 20–41). A meta-analysis published in 2002 summarized the effect of L-carnitine in maintenance hemodialysis patients (42). A total of 18 RCTs enrolling 482 patients were identified from 1978 to 1999. L-Carnitine treatment significantly increased hemoglobin and decreased the required erythropoietin dose. However, no favorable effect of L-carnitine was observed on serum triglycerides, cholesterol, HDL, or LDL (42). In 2008, another meta-analysis (7 RCTs that enrolled 193 patients) failed to show any beneficial effect of L-carnitine supplementation on dialysis-related muscle cramping or intradialytic hypotension (1). A total of 21 new RCTs, which were not included in the 2 previous meta-analyses, continued to report inconsistent results regarding the benefit of L-carnitine treatment on previously reported and some new clinical markers (12, 13, 15, 17, 18, 24–27, 29, 30, 43–56). Inflammation is highly prevalent, and serum C-reactive protein (CRP) is a potent risk marker of all-cause and cardiovascular mortality in hemodialysis patients (57–61). It has been reported that L-carnitine could suppress chronic inflammation through a reduction of serum CRP in hemodialysis patients (12, 17, 43, 45). Therefore, it was important to review the accumulated evidence with the aim of providing an up-to-date assessment of the effect of L-carnitine supplementation in adults with ESKD who were undergoing maintenance hemodialysis.

METHODS

Data sources and search strategy

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and Cochrane guideline (62, 63). We searched the Cochrane Central Register of Controlled Trials (issue 12; 31 December 2012; <http://onlinelibrary.wiley.com/cochranelibrary/search>), PubMed (1966 to 31 December 2012; <http://www.ncbi.nlm.nih.gov/pubmed>), and EMBASE databases (1988 to 31 December 2012; <http://www.embase.com/home>) to identify RCTs that evaluated effects of L-carnitine supplementation for adult patients with ESKD requiring maintenance hemodialysis (see Supplementary Table 1 under “Supplemental data” in the online issue). Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Articles were not restricted according to language. Both parallel and crossover RCTs were included in this systematic review; however, because the carryover could have caused a problem or bias, only parallel RCTs and the first period of crossover RCTs were quantitatively summarized in the meta-analysis to eliminate a potential carryover effect in crossover RCTs (63). RCTs that compared L-carnitine supplementation (including acetyl-L-carnitine and propionyl-L-carnitine) with placebo or no treatment were included, whereas RCTs that compared different doses, routes, or durations of L-carnitine supplementation were excluded. RCTs were excluded if the duration of L-carnitine supplementation was <2 wk.

Prespecified outcomes

Primary outcomes were serum lipid profiles (triglycerides, cholesterol, HDL, and LDL), anemia-related markers (hemoglobin, hematocrit, and the required erythropoietin dose), and

inflammation and nutrition status markers (serum CRP and albumin). Secondary outcomes were myocardial and vascular function, skin and skeletal muscle function, platelet and coagulation function, quality of life, and adverse effects of L-carnitine supplementation.

Study selection and data extraction

Titles and abstracts, and full texts if necessary, were screened by 2 authors (YC and ZG). Study selection, data extraction, quality assessment, and data synthesis were independently performed by the same 2 authors by using a standardized approach. Disagreements were resolved by consulting a third author (XC). Publication reports were obtained for each trial, and standard information was separately extracted into a spreadsheet. Extracted data included patient baseline characteristics (country, age, sex, duration of dialysis, and plasma free carnitine concentration), treatment routes, doses, and durations, prespecified outcomes, the study design, and methodologic characteristics.

Quality assessment

The Cochrane-recommended method was used to assess the quality of studies. Six different domains, including a random sequence generation (selection bias), allocation concealment (selection bias), blinding of patients (performance bias), clinicians, and outcome assessors (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and any other potential bias, were judged as low risk of bias, high risk of bias, or unclear risk of bias (63).

Data synthesis and analysis

Continuous outcomes were expressed as the mean difference (MD) and 95% CI or the standardized mean difference (SMD) and 95% CI if different scales were used. Dichotomous outcomes were expressed as the RR and 95% CI. Heterogeneity was explored by using Cochran's Q test and the I^2 statistic (63). The I^2 statistic was generated by using the formula

$$[(Q - df) \div Q] \times 100\% \quad (1)$$

where Q is Cochran's Q, which has a chi-square distribution with $k-1$ df where k is the number of studies included in the meta-analysis (63). I^2 statistics <25%, 25–49%, 50–75%, and >75% were interpreted to indicate low, medium, high, and very high levels of heterogeneity, respectively. If I^2 was <25%, the fixed-effect model was used, and the estimate of the common treatment effect was provided. Otherwise, the random-effects model was used, and the estimate of the average treatment effect was provided (64, 65). A fixed-effect meta-analysis model assumes that all studies estimate the same (common) treatment effect, and there is no between-study heterogeneity in the true treatment effect (65). In contrast, a random-effects meta-analysis model assumes that the observed estimates can vary across studies because of sampling variability (chance) as well as real differences in the treatment effect (heterogeneity). Heterogeneity might be caused by differences in study populations (such as the ethnicity of the patients), interventions (such as the duration, route, and dose of a drug), and other factors (65). To explore potential sources of heterogeneity, preplanned subgroup analyses were

performed to evaluate whether results were different by the ethnicity of the patients (whites or nonwhites), duration of L-carnitine treatment (<6 or ≥ 6 mo), and route of L-carnitine treatment (intravenous or oral). The preplanned sensitivity analysis, with the exclusion of trials that had high risk of bias in the random sequence generation and concealment, used a crossover design, or only existed in abstract form, was performed to evaluate whether results were different by the quality of trials. Small-study effects were explored by using the Harbord's modified tests and corresponding Galbraith modified plots (66). Review Manager (version 5.1; The Cochrane Collaboration) and STATA (version 11.2; StataCorp LP) software were used.

RESULTS

Literature search results and trial characteristics

We identified 1164 publications, of which 1010 publications were excluded after we screened titles and abstracts (31 December 2012). An additional full-text assessment excluded 105 publications because they were unrelated publications, reviews, basic studies, observational studies, or clinical trials that failed to fulfill the inclusion criteria. A total of 49 trials that enrolled 1734 patients were included in the systematic review. Thirty-one of the identified 49 trials (29 parallel RCTs and 2 crossover RCTs) that enrolled 1255 patients were included in the meta-analysis, whereas the remaining 18 trials (9

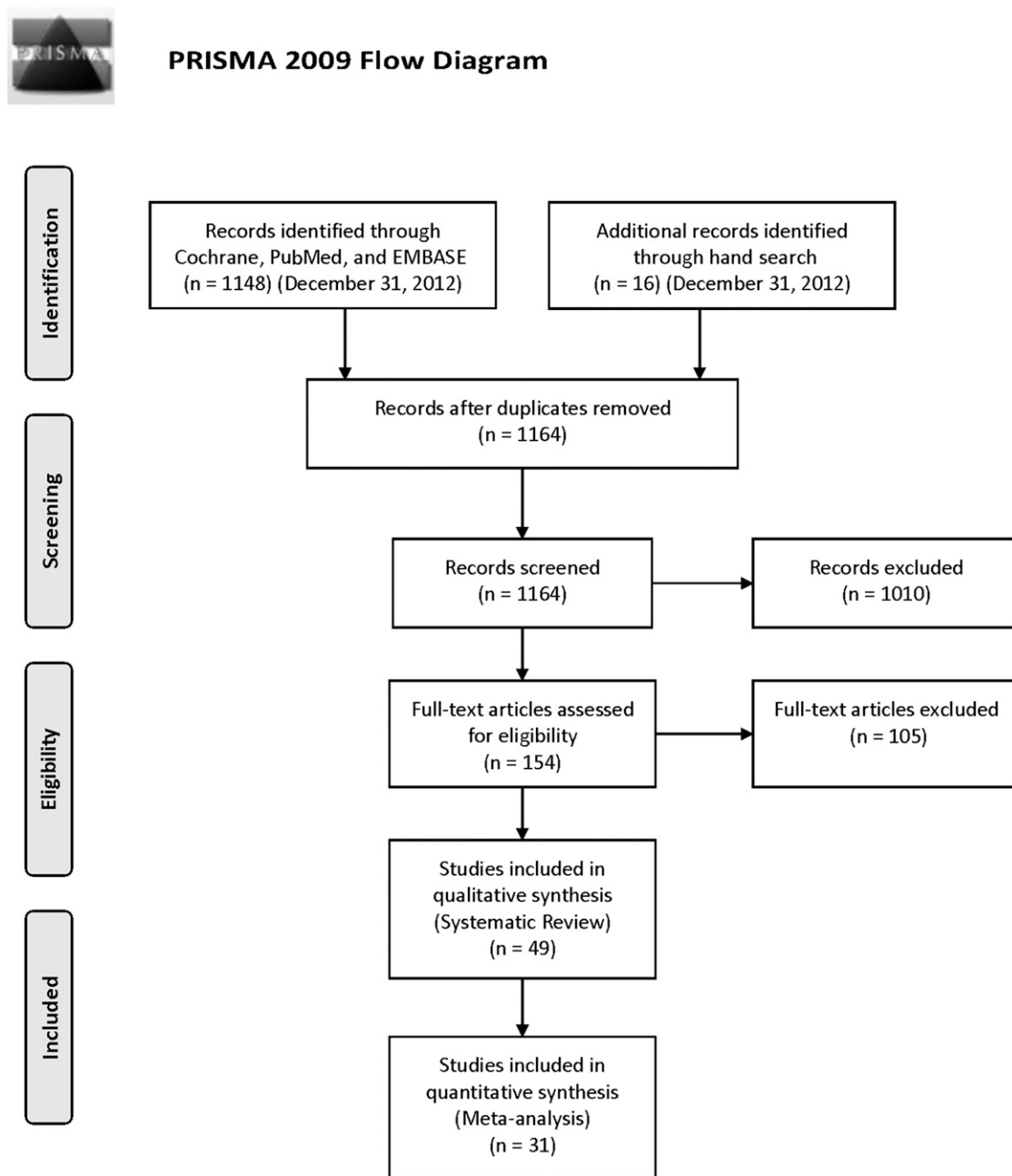


FIGURE 1. PRISMA study selection flowchart. Cochrane: <http://onlinelibrary.wiley.com/cochranelibrary/search>; PubMed: <http://www.ncbi.nlm.nih.gov/pubmed>; EMBASE: <http://www.embase.com/home>. Cochrane, Cochrane Central Register of Controlled Trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

parallel RCTs and 9 crossover RCTs) that enrolled 479 patients were excluded from the meta-analysis because of a lack of quantitatively combinable data (**Figure 1**). Whites were investigated in 35 trials, and other ethnicities were investigated in 14 trials (*see* Supplementary Table 2 under “Supplemental data” in the online issue). The duration of L-carnitine supplementation was <6 mo in 32 trials and ≥6 mo in 17 trials. L-Carnitine was intravenously administered in 37 trials and orally administered in 12 trials. A parallel design was used in 38 trials, and a crossover design was used in 11 trials. Forty-two trials were published in English, and 7 trials were published in a non-English language, including 4 trials in Italian (10, 67–69), one trial in Spanish (27), one trial in Arabic (15), and one trial in Korean (70). Full texts were retrieved for 46 trials, and abstracts were retrieved for 3 trials (56, 71–73). All 3 abstracts fulfilled the inclusion and exclusion criteria for the study selection and reported at least one prespecified primary or secondary outcome (56, 71–73). Because of the insufficient information of study characteristics, these 3 studies were judged to have a potential bias. The potential bias was explored by the preplanned sensitivity analysis.

The quality of studies was variable (**Figures 2 and 3**). Fourteen trials (29%) specified appropriate methods of random sequence generation. Only 3 trials (6%) reported appropriate allocation concealment methods. Forty-one trials (84%) declared the use of double blinding. Thirty-four trials (69%) were considered to have low risk of bias on the issue of incomplete outcome data. Data on serum lipid profiles, anemia-related markers, and inflammation and nutrition markers were available for a quantitative meta-analysis in 20 trials (41%), 18 trials (37%), and 13 trials (27%), respectively. Data on skin and skeletal muscle function, myocardial and vascular function, platelet and coagulation function, and quality of life were only available for qualitative description in 21 trials (43%), 12 trials (24%), 4 trials (8%), and 10 trials (20%), respectively. Twenty-two trials (45%) reported that there were no adverse effects of L-carnitine supplementation.

Effects of L-carnitine on serum lipid profiles

Overall, there were no significant differences in serum triglycerides (19 trials with 601 patients; MD: -0.89 mg/dL; 95% CI: $-29.32, 27.53$ mg/dL; $P = 0.95$, $I^2 = 90\%$, P -heterogeneity < 0.00001) (**Figure 4A**), cholesterol (19 trials with 603 patients; MD: 0.14 mg/dL; 95% CI: $-6.15, 6.42$ mg/dL; $P = 0.97$, $I^2 = 31\%$, P -heterogeneity $= 0.09$) (**Figure 4B**), or HDL (14 trials with 460 patients; MD: 1.13 mg/dL; 95% CI: $-2.44, 4.70$ mg/dL; $P = 0.53$, $I^2 = 89\%$, P -heterogeneity < 0.00001) (**Figure 5A**). However, L-carnitine significantly decreased serum LDL (11 trials with 402 patients; MD: -5.82 mg/dL; 95% CI: $-11.61, -0.04$ mg/dL; $P = 0.05$, $I^2 = 44\%$, P -heterogeneity $= 0.05$) (**Figure 5B**). Sensitivity analyses suggested that low-quality or unpublished results could not substantially modify estimates for serum lipid profiles (**Figures 4 and 5**). Subgroup analyses indicated significantly different magnitudes for effects on decreasing cholesterol according to the ethnicity of the patients. The effect was greater in nonwhites than whites [MD: -7.07 mg/dL (95% CI: $-15.90, 1.77$ mg/dL) compared with 8.07 mg/dL (95% CI: $1.61, 14.53$ mg/dL); subgroup difference: $I^2 = 86.4\%$, $P = 0.007$] (**Table 1**).

Effects of L-carnitine on anemia-related markers

Overall, there were no significant differences in hemoglobin (14 trials with 693 patients; MD: 0.68 g/dL; 95% CI: $-0.14, 1.50$ g/dL; $P = 0.11$, $I^2 = 95\%$, P -heterogeneity < 0.00001) (**Figure 6A**), hematocrit (9 trials with 406 patients; MD: 2.04% ; 95% CI: $-1.39, 5.48\%$; $P = 0.24$, $I^2 = 95\%$, P -heterogeneity < 0.00001) (**Figure 6B**), or the required erythropoietin dose (8 trials with 319 patients; MD: -0.76 KU/wk; 95% CI: $-1.75, 0.23$ KU/wk; $P = 0.13$, $I^2 = 44\%$, P -heterogeneity $= 0.09$) (**Figure 6C**). Sensitivity analyses suggested that low-quality or unpublished results could not substantially modify estimates for anemia-related markers (**Figure 6**). Subgroup analyses showed significantly different effects with higher hematocrit via oral

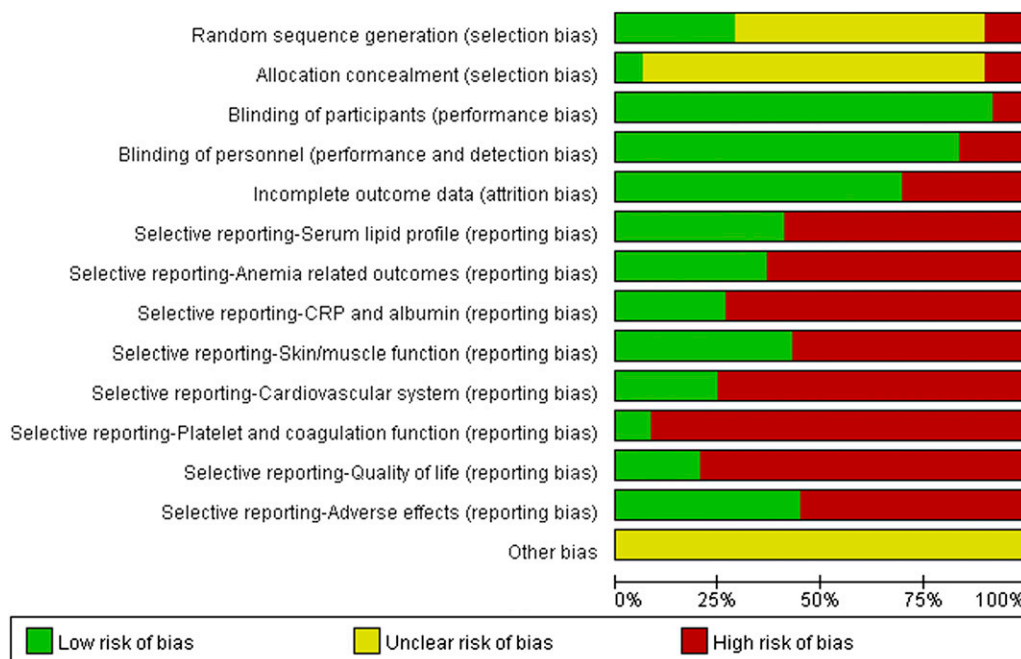


FIGURE 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

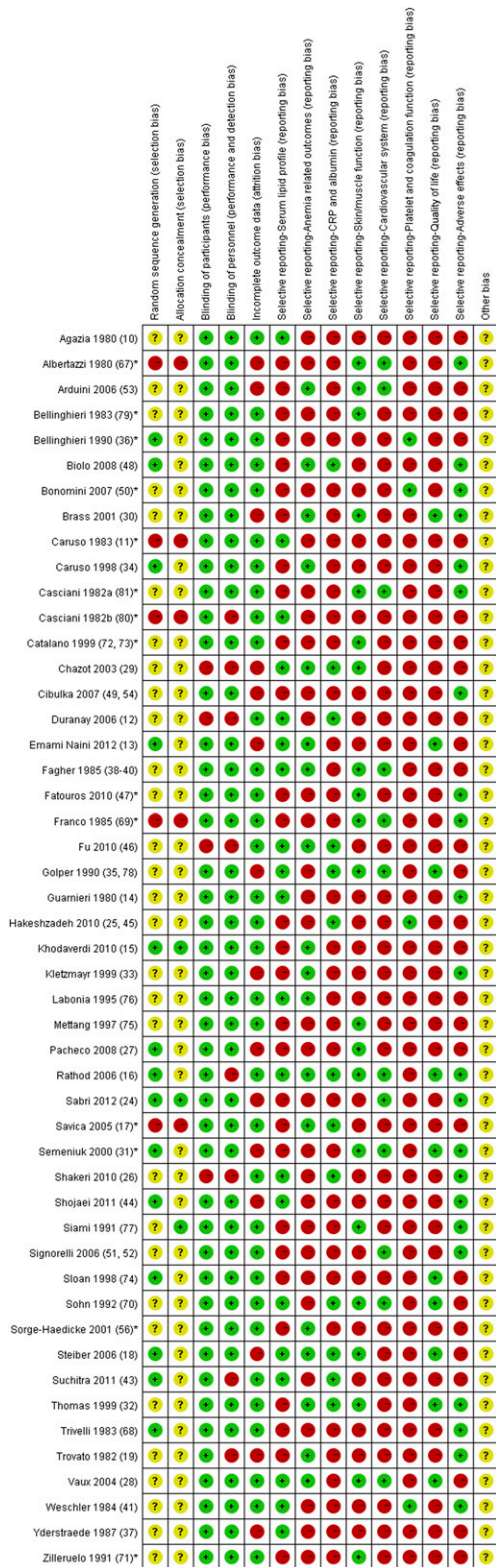


FIGURE 3. Risk of bias summary: review authors’ judgments about each risk of bias item for each included study. *Trials that had high risk of bias in the random sequence generation and concealment, used a crossover design, or only existed in abstract form.

than via intravenous administration [MD: 15.54% (95 % CI: 13.31, 17.77%) compared with 0.85% (−1.62, 3.32%); subgroup difference: $I^2 = 98.7\%$, $P < 0.00001$) (Table 1). It should be noted

that only one trial evaluated the effect of the oral administration of L-carnitine on hematocrit (19).

Effects of L-carnitine on inflammation and nutrition markers

Overall, L-carnitine significantly decreased serum CRP (8 trials with 366 patients; MD: −3.65 mg/L; 95% CI: −6.19, −1.12 mg/L; $P = 0.005$, $I^2 = 82\%$, P -heterogeneity < 0.00001) (Figure 7A). In contrast, there was no significant difference in serum albumin (11 trials with 466 patients; MD: 1.65 g/L; 95 % CI: −0.22, 3.51 g/L; $P = 0.08$, $I^2 = 80\%$, P -heterogeneity < 0.00001) (Figure 7B). Sensitivity analyses suggested that low-quality or unpublished results could not substantially modify estimates for serum CRP and albumin (Figure 7). Subgroup analyses failed to show significantly different magnitudes for effects on CRP and albumin according to the ethnicity of the patients and duration and route of L-carnitine treatment (Table 1).

Effects of L-carnitine on secondary outcomes

Secondary outcomes, including myocardial and vascular function, skin and skeletal muscle function, platelet and coagulation function, and quality of life, were qualitatively summarized because most of these trials used heterogeneous outcome measurements (*see* Supplementary Table 3 under “Supplemental data” in the online issue). Some outcomes were also quantitatively summarized. Three of 7 trials that reported combinable categorical data showed that L-carnitine could not significantly decrease the percentage of patients who experienced intradialytic hypotension symptoms at the end of treatment (3 trials with 128 patients; RR: 0.76; 95% CI: 0.34, 1.69; $P = 0.50$, $I^2 = 0\%$, P -heterogeneity = 0.83) (*see* Supplementary Figure 1 under “Supplemental data” in the online issue). Two of 7 trials that reported combinable categorical data showed that L-carnitine significantly decreased the percentage of patients who experienced dialysis-related muscle cramping symptoms at the end of treatment (2 trials with 102 patients; RR: 0.45; 95% CI: 0.20, 0.99; $P = 0.05$, $I^2 = 23\%$, P -heterogeneity = 0.25) (*see* Supplementary Figure 2 under “Supplemental data” in the online issue). Six of 10 trials that reported combinable continuous data showed that L-carnitine significantly improved the quality of life at the end of treatment (6 trials with 319 patients; SMD: 0.47; 95% CI: 0.04, 0.91; $P = 0.03$, $I^2 = 60\%$, P -heterogeneity = 0.03) (*see* Supplementary Figure 3 under “Supplemental data” in the online issue). However, no definitive conclusion could be drawn from these outcomes because of the paucity of available data.

Adverse effects of L-carnitine supplementation

No adverse effects were reported.

Small-study effects

Harbord’s modified tests showed that there was no evidence of small-study effects on triglycerides ($P = 0.387$), cholesterol ($P = 0.568$), LDL ($P = 0.262$), hemoglobin ($P = 0.456$), hematocrit ($P = 0.727$), the required erythropoietin dose ($P = 0.397$), CRP ($P = 0.790$), or albumin ($P = 0.360$). However, Harbord’s modified

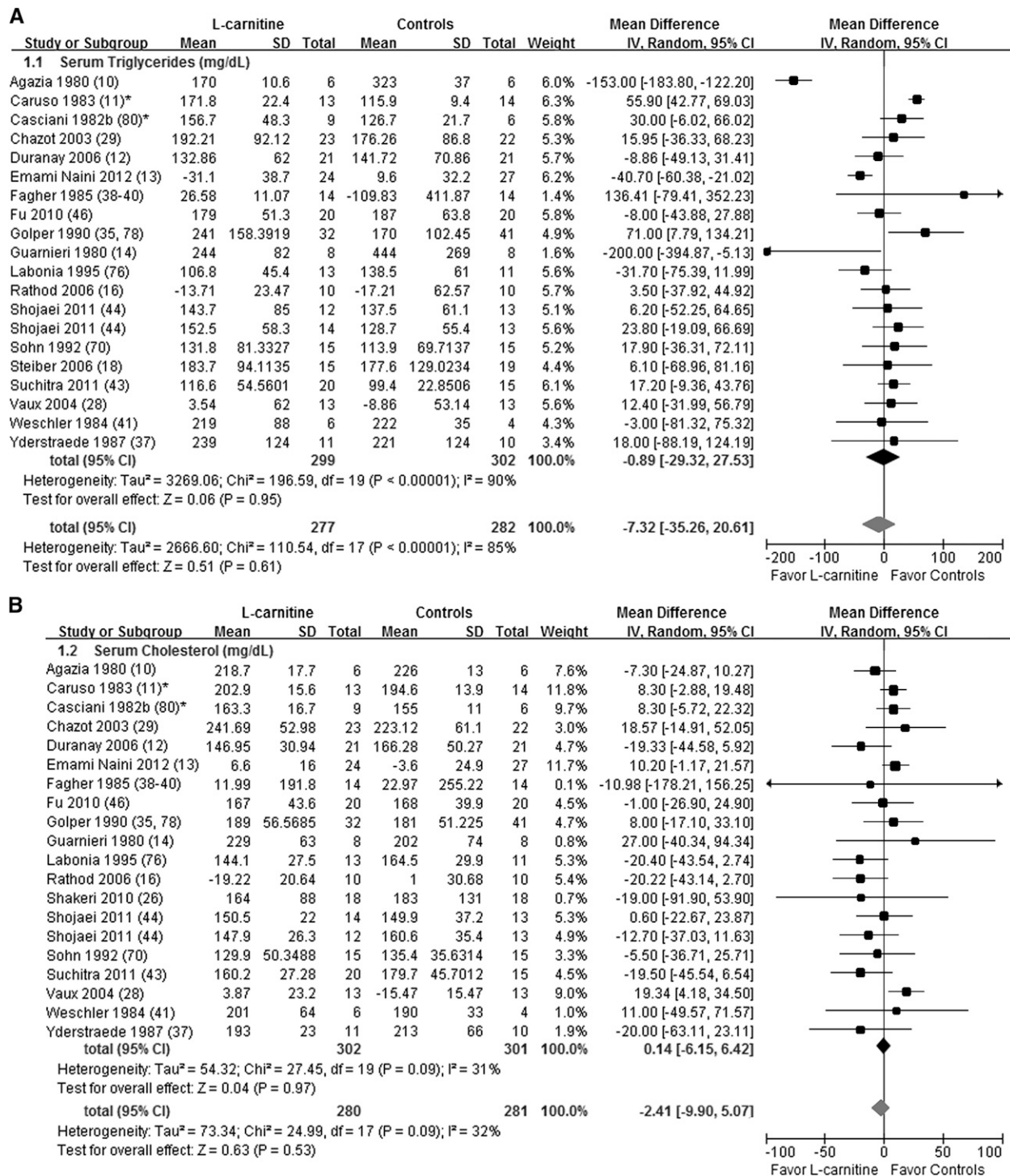


FIGURE 4. Forest plots from meta-analyses of effects of L-carnitine on serum triglycerides (A) and cholesterol (B). The area of each square is proportional to the inverse of the variance of the mean difference. Horizontal lines represent 95% CIs. Pooled estimates were obtained by using IV-weighted random-effects models. Black diamonds represent pooled estimates from all eligible trials, whereas gray diamonds represent pooled estimates from sensitivity analyses. Prespecified sensitivity analyses excluded trials (*) that had high risk of bias in the random sequence generation and concealment, used a crossover design, or existed only in abstract form. IV, inverse variance.

tests identified the presence of significant small-study effects for HDL ($P = 0.001$). The corresponding Galbraith modified plots were presented in **Figure 8**. Harbord's modified tests and corresponding Galbraith modified plots were not used to evaluate the existence of small-study effects for secondary outcomes because there were no adequate numbers of identified trials.

DISCUSSION

This updated systematic review provided an up-to-date analysis of the evidence regarding the effects of L-carnitine on a series of clinical markers with 172% more trials and 260% more patients compared with in the previous meta-analysis of Huot et al (42) (49 trials with 1734 patients compared with 18

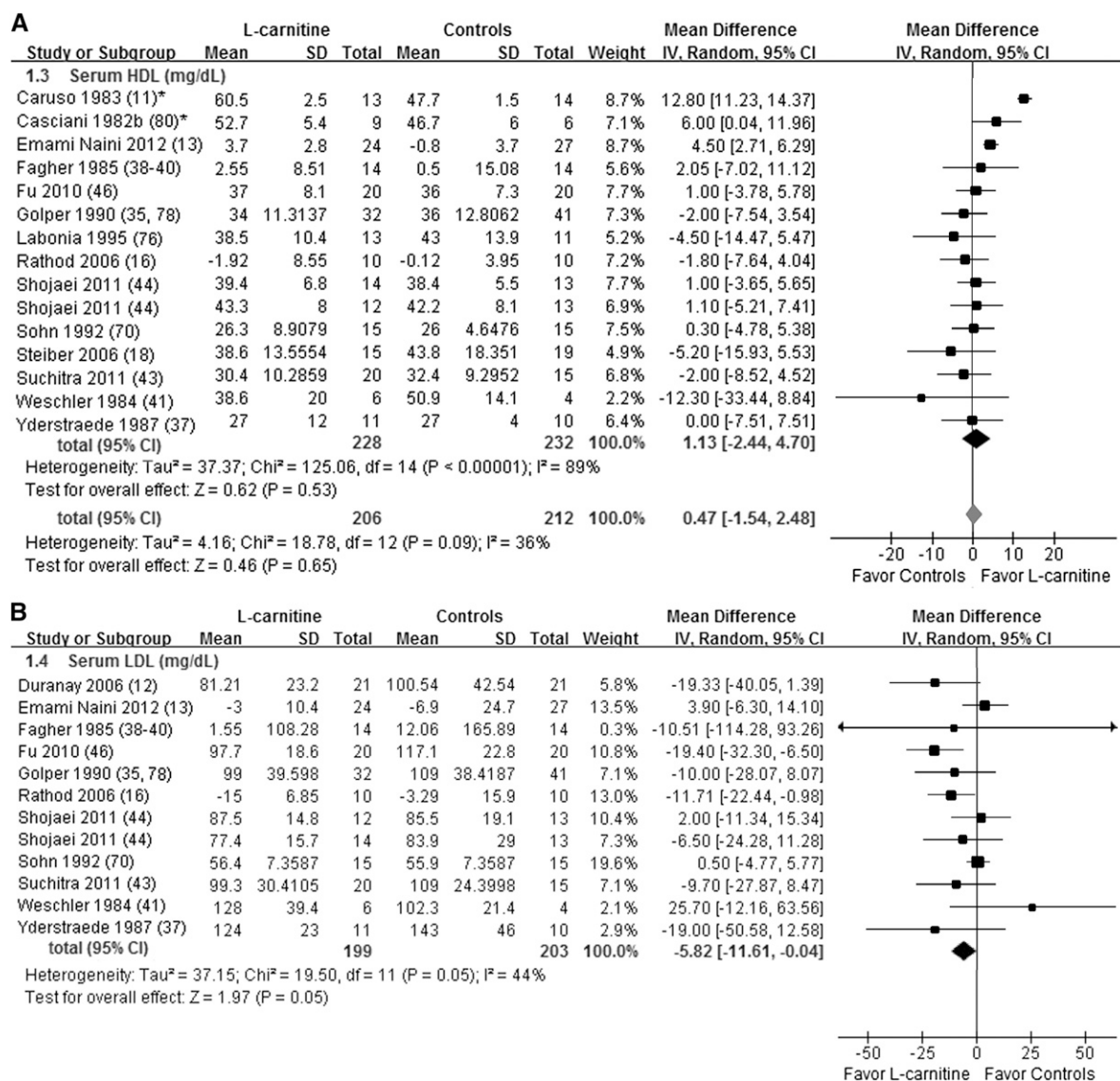


FIGURE 5. Forest plots from meta-analyses of effects of L-carnitine on serum HDL (A) and LDL (B). L-Carnitine could not significantly change serum HDL (A), whereas L-carnitine could significantly decrease serum LDL (B). The area of each square is proportional to the inverse of the variance of the mean difference. Horizontal lines represent 95% CIs. Pooled estimates were obtained by using IV-weighted random-effects models. Black diamonds represent pooled estimates from all eligible trials, whereas gray diamonds represent pooled estimates from sensitivity analyses. Prespecified sensitivity analyses excluded trials (*) that had high risk of bias in the random sequence generation and concealment, used a crossover design, or only existed in abstract form. The prespecified sensitivity analysis was not performed for the effect of L-carnitine on LDL because there was no trial that had high risk of bias in the random sequence generation and concealment, used a crossover design, or existed only in abstract form. IV, inverse variance.

trials with 482 patients, respectively). Indeed, there were more studies in this meta-analysis, but these studies did not have data on all questions under consideration. For example, serum triglycerides was reported in 19 of 49 studies, and the erythropoietin dose was reported in 8 of 49 studies. It should be alerted that not all studies and data that can be used for all questions. Although we used 49 studies in this meta-analysis, for any one question the number of studies with available data ranged from 8 to 19. In the current meta-analysis, there was no evidence that L-carnitine could significantly decrease serum triglycerides and cholesterol and increase HDL, which was consistent with the findings of a previous meta-analysis (Table 2). The previous meta-analysis indicated that L-carnitine might be associated with significantly decreased LDL (5 trials; $P = 0.06$). The current

meta-analysis showed that the beneficial effect of L-carnitine on decreasing LDL could be considered statistically significant (11 trials; $P = 0.05$). The identification of the benefit on LDL might have been, at least in part, attributable to the doubled number of trials included in the current meta-analysis.

In the previous meta-analysis, there was evidence that supported the use of L-carnitine to increase hemoglobin (3 trials; $P < 0.01$) and decrease the required erythropoietin dose (6 trials; $P < 0.01$) (Table 2). However, the current meta-analysis did not confirm the beneficial effects of L-carnitine on hemoglobin (14 trials; $P = 0.11$) and the required erythropoietin dose (8 trials; $P = 0.13$). It should be noted that there was an overlap of included studies between this meta-analysis and the previous meta-analysis. The previous meta-analysis might be

TABLE 1

Subgroup analyses of effects of L-carnitine on a series of clinical markers according to the ethnicity of patients and duration and route of L-carnitine supplementation¹

Markers and subgroups	No. of trials	Mean difference (95% CI)	P-each stratum	P-subgroup difference
Triglycerides (mg/dL)				
Ethnicity				
Whites	10	1.06 (−59.30, 61.41)	0.97	0.85
Nonwhites	9	−5.05 (−22.82, 12.71)	0.58	
Duration of treatment				
<6 mo	13	−6.27 (−45.44, 32.89)	0.75	0.54
≥6 mo	6	8.02 (−15.96, 32.00)	0.95	
Route of treatment				
Intravenous	16	0.04 (−33.06, 33.13)	1.00	0.84
Oral	3	−6.47 (−60.39, 47.46)	0.81	
Cholesterol (mg/dL)				
Ethnicity				
Whites	9	8.07 (1.61, 14.53)	0.01	0.007
Nonwhites	10	−7.07 (−15.90, 1.77)	0.12	
Duration of treatment				
<6 mo	14	3.74 (−2.22, 9.70)	0.22	0.14
≥6 mo	5	−8.35 (−23.38, 6.68)	0.28	
Route of treatment				
Intravenous	15	−2.77 (−10.48, 4.94)	0.48	0.05
Oral	4	9.08 (0.40, 17.75)	0.04	
HDL (mg/dL)				
Ethnicity				
Whites	6	2.82 (−4.28, 9.91)	0.44	0.60
Nonwhites	8	0.83 (−1.52, 3.18)	0.49	
Duration of treatment				
<6 mo	10	2.57 (−1.38, 6.51)	0.20	0.05
≥6 mo	4	−2.71 (−6.36, 0.95)	0.15	
Route of treatment				
Intravenous	11	0.55 (−4.28, 5.38)	0.82	0.19
Oral	3	4.44 (1.09, 7.79)	0.009	
LDL (mg/dL)				
Ethnicity				
Whites	3	−12.18 (−27.69, 3.33)	0.12	0.41
Nonwhites	8	−5.16 (−11.71, 1.38)	0.12	
Duration of treatment				
<6 mo	8	−3.32 (−9.90, 3.26)	0.32	0.09
≥6 mo	3	−12.54 (−20.98, −4.10)	0.004	
Route of treatment				
Intravenous	9	−8.00 (−14.04, −1.96)	0.009	0.07
Oral	2	6.86 (−7.78, 21.50)	0.36	
Hemoglobin (g/dL)				
Ethnicity				
Whites	10	0.40 (−0.60, 1.41)	0.43	0.13
Nonwhites	4	1.55 (0.46, 2.64)	0.005	
Duration of treatment				
<6 mo	7	0.90 (−0.03, 1.84)	0.06	0.68
≥6 mo	7	0.58 (−0.64, 1.79)	0.35	
Route of treatment				
Intravenous	12	0.39 (−0.13, 0.91)	0.14	0.32
Oral	2	3.10 (−2.18, 8.39)	0.25	
Hematocrit (%)				
Ethnicity				
Whites	7	1.18 (−2.72, 5.08)	0.55	0.36
Nonwhites	2	6.07 (−3.53, 15.67)	0.22	
Duration of treatment				
<6 mo	2	4.11 (−10.54, 18.76)	0.58	0.74
≥6 mo	7	1.54 (−1.87, 4.95)	0.38	
Route of treatment				
Intravenous	8	0.85 (−1.62, 3.32)	0.50	<0.00001
Oral	1	15.54 (13.31, 17.77)	<0.0001	

(Continued)

TABLE 1 (Continued)

Markers and subgroups	No. of trials	Mean difference (95% CI)	<i>P</i> -each stratum	<i>P</i> -subgroup difference
Erythropoietin dose (KU/wk)				
Ethnicity				
Whites	6	−0.43 (−1.55, 0.70)	0.46	0.16
Nonwhites	2	−1.84 (−3.49, −0.19)	0.03	
Duration of treatment				
<6 mo	2	−1.40 (−2.97, 0.17)	0.08	0.37
≥6 mo	6	−0.49 (−1.73, 0.75)	0.44	
Route of treatment				
Intravenous	7	−0.55 (−1.54, 0.43)	0.27	0.15
Oral	1	−2.75 (−5.57, 0.07)	0.06	
C-reactive protein (mg/L)				
Ethnicity				
Whites	3	−2.52 (−8.37, 3.33)	0.40	0.60
Nonwhites	5	−4.24 (−7.03, −1.45)	0.003	
Duration of treatment				
<6 mo	4	−2.70 (−5.79, 0.39)	0.09	0.11
≥6 mo	4	−6.41 (−9.75, −3.06)	0.0002	
Route of treatment				
Intravenous	6	−4.45 (−8.28, −0.62)	0.02	0.30
Oral	2	−2.27 (−3.73, −0.81)	0.0002	
Albumin (g/L)				
Ethnicity				
Whites	6	0.42 (−1.87, 2.70)	0.72	0.08
Nonwhites	5	3.80 (0.74, 6.87)	0.02	
Duration of treatment				
<6 mo	5	1.54 (−1.46, 4.54)	0.32	0.92
≥6 mo	6	1.75 (−0.96, 4.45)	0.21	
Route of treatment				
Intravenous	11	1.65 (−0.22, 3.51)	0.08	—
Oral	0	—	—	

[†] Pooled estimates were obtained by using inverse variance-weighted random-effects models in each stratum. *P* values indicate the intrastratum difference and the subgroup difference between strata (on the basis of an ANOVA-like partitioning of Cochran's *Q* statistic).

considered hypothesis generating, and recent studies might be considered hypothesis testing. Simply combining the previous and current studies may obscure the phenomenon of regression to the mean. It could be speculated that certain new trials might have a dominant influence on the overall estimate of the effects on anemia-related markers. Because the trial of Brass et al (30) was the largest RCT to date and recruited 183 patients, contributing ~26% of the total included patients in the meta-analysis of the effect on hemoglobin. The negative finding of this single trial largely influenced the result of our meta-analysis. If this trial, with ~24% weight on the overall effect, had been removed from the meta-analysis, there would have been a favorable effect of L-carnitine on hemoglobin (MD: 1.01 g/dL; 95% CI: 0.03, 2.00 g/dL; *P* = 0.04). Similarly, 2 of 8 trials, which contributed ~40% weight on the overall effect, had a dominant influence on the analysis of the required erythropoietin dose. The overall negative results regarding the required erythropoietin dose in the current meta-analysis might have been, at least in part, a result of the negative findings of these 2 trials of Chazot et al (29) and Vaux et al (28), which were only included in the current meta-analysis.

Another previous meta-analysis failed to show any favorable effect of L-carnitine on intradialytic hypotension or dialysis-related muscle cramping (1). The uncertainty of the effects of L-carnitine on these outcomes still continued because of the

paucity of available data. The current meta-analysis assessed the effects of L-carnitine on serum CRP, albumin, and quality of life, which was not performed in any previous meta-analysis. There was evidence that L-carnitine could significantly decrease serum CRP. No favorable effect on serum albumin was identified. L-Carnitine could significantly improve the quality of life (*P* = 0.03), but the number of available trials was limited, and methods used for the assessment of the quality of life varied. Furthermore, a mean change of 0.47 (95% CI: 0.04–0.91) could not be faithfully considered to be clinically relevant.

A recent meta-analysis of 11 RCTs with 1707 hemodialysis patients indicated that statin therapy could significantly decrease serum LDL (MD: −41.3 mg/dL; 95% CI: −54.4, −28.3 mg/dL) (82). In the German Diabetes and Dialysis (4D) study (which involved 2776 patients who were undergoing maintenance hemodialysis) (58, 59) and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) (which involved 1255 patients with type 2 diabetes who were receiving maintenance hemodialysis) (57), LDL decreased by 40–49 mg/dL in the statins groups at 1–3 mo. By contrast, our meta-analysis indicated that the MD in LDL between treatment and control groups was −5.8 mg/dL. The effect of L-carnitine on LDL appeared significant; however, the magnitude of improvement was very small compared with the usual decrease with statin

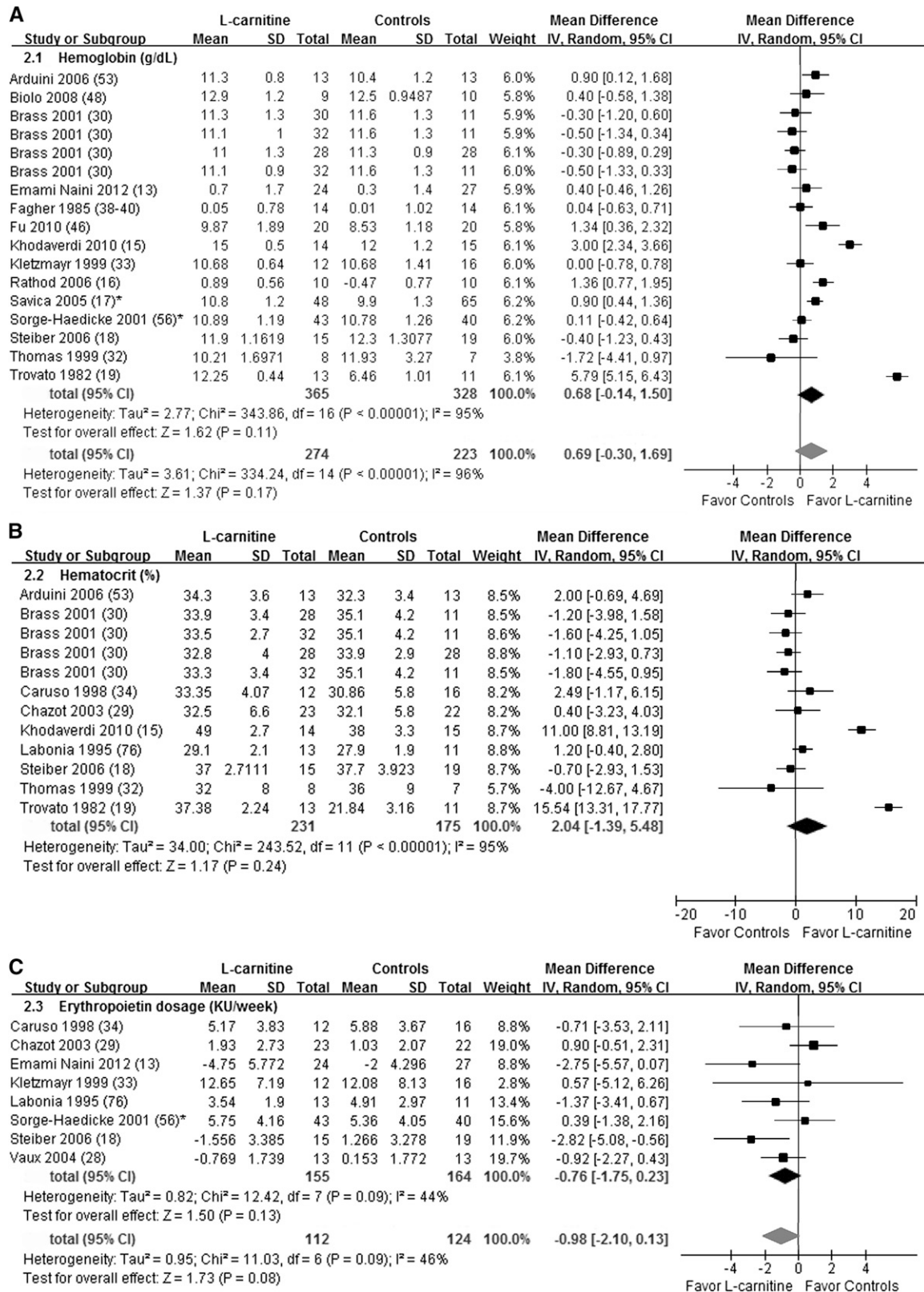


FIGURE 6. Forest plots from meta-analyses of effects of L-carnitine on hemoglobin (A), hematocrit (B), and the required erythropoietin dosage (C). L-Carnitine could not significantly change hemoglobin (A), hematocrit (B), and the required erythropoietin dosage (C). The area of each square is proportional to the inverse of the variance of the mean difference. Horizontal lines represent 95% CIs. Pooled estimates were obtained by using IV-weighted random-effects models. Black diamonds represent pooled estimates from all eligible trials, whereas gray diamonds represent pooled estimates from sensitivity analyses. Prespecified sensitivity analyses excluded trials (*) that had high risk of bias in the random sequence generation and concealment, used a crossover design, or only existed in abstract form. The prespecified sensitivity analysis was not performed for the effect of L-carnitine on hematocrit because there was no trial that had high risk of bias in the random sequence generation and concealment, used a crossover design, or existed only in abstract form. IV, inverse variance.

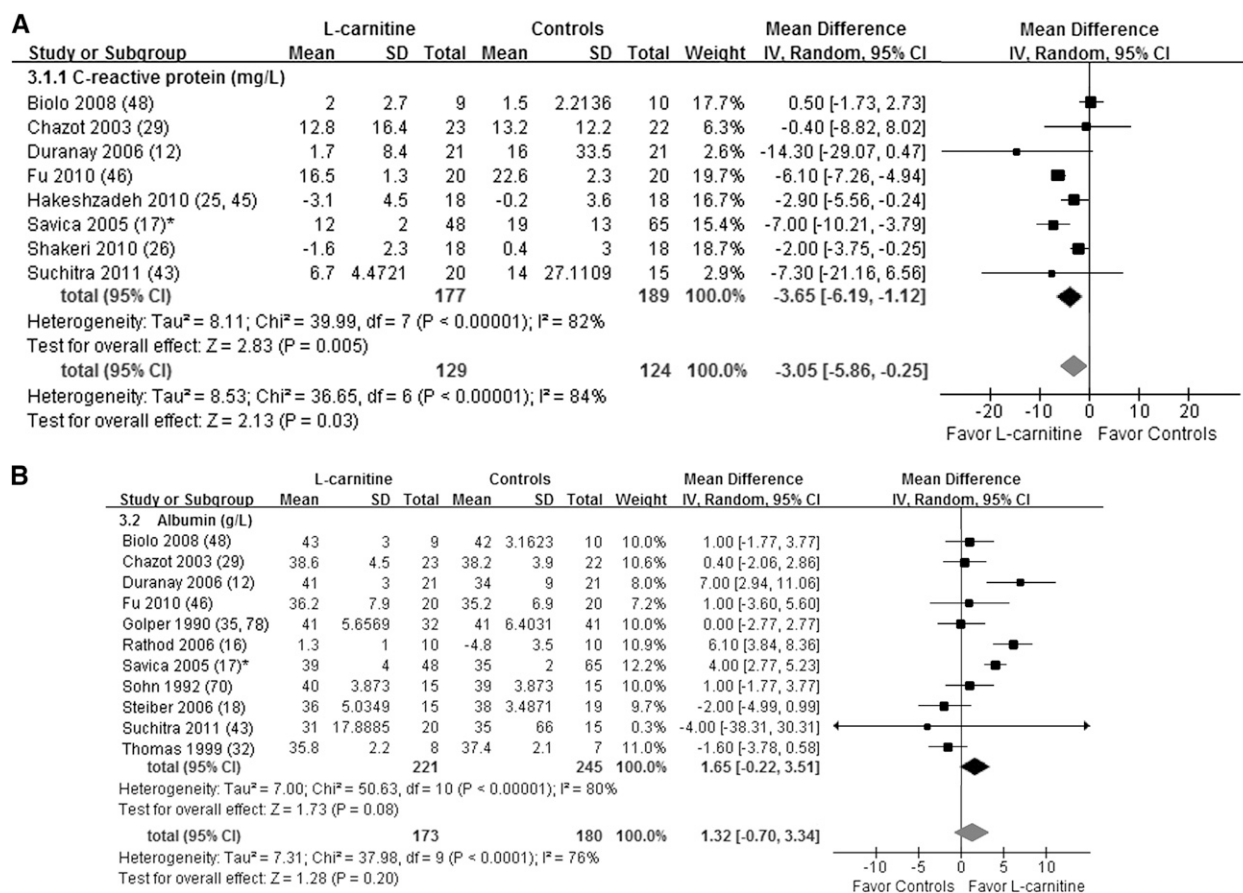


FIGURE 7. Forest plots from meta-analyses of effects of L-carnitine on serum C-reactive protein (A) and albumin (B). L-Carnitine could significantly decrease serum C-reactive protein (A), whereas L-carnitine could not significantly change serum albumin (B). The area of each square is proportional to the inverse of the variance of the mean difference. Horizontal lines represent 95% CIs. Pooled estimates were obtained by using IV-weighted random-effects models. Black diamonds represent pooled estimates from all eligible trials, whereas gray diamonds represent pooled estimates from sensitivity analyses. Prespecified sensitivity analyses excluded trials (*) that had high risk of bias in the random sequence generation and concealment, used a crossover design, or existed only in abstract form. IV, inverse variance.

treatment. Thus, the lipid-lowering effect of L-carnitine was very limited for hemodialysis patients, particularly compared with the effect with other currently approved medications such as statins.

Inflammation is highly prevalent in ESKD patients requiring maintenance hemodialysis, with a CRP concentration >12.4 mg/L reported in $>25\%$ of patients (57–59). Elevated CRP is a predictor of all-cause and cardiovascular mortality in hemodialysis patients (60, 61). The identification of strategies that reduce CRP and suppress chronic inflammation may translate into improved outcomes (61). A recent meta-analysis showed that statins could significantly decrease CRP (SMD: -0.54 ; 95% CI: -1.04 , -0.05 ; $P = 0.03$) in hemodialysis patients (83). In AURORA and 4D studies, the CRP concentrations decreased by 0.65 and 0.20 mg/L, respectively, at 3–6 mo after statin therapy, whereas the CRP concentrations increased by 0.21 and 0.50 mg/L, respectively, during placebo treatment. In hemodialysis patients, an increase in CRP over time might indicate an ongoing inflammatory state (57, 61). Statins did exert antiinflammatory effects. However, the potent antiinflammatory effects did not translate to a significant reduction in the composite primary endpoint of cardiovascular death, nonfatal myocardial infarction, or stroke in patients who were undergoing hemodialysis in 4D and AURORA studies (57, 59). A recent meta-analysis further confirmed that statins had no effect on all-cause mortality (13

RCTs with 4705 patients; RR: 0.96; 95% CI: 0.88, 1.04), cardiovascular mortality (13 RCTs with 4623 patients; RR: 0.94; 95% CI: 0.82, 1.07), or cardiovascular events (4 RCTs with 7084 patients; RR: 0.95; 95% CI: 0.87, 1.03) in patients who were receiving dialysis (82). It could be speculated that statins could not sufficiently decrease CRP and achieve a significant antiinflammatory effect or that a different, more potent antiinflammatory strategy needs to be applied to control CRP in this patient population (61). Our meta-analysis indicated that the overall MD in CRP between patients with and without L-carnitine treatment was -3.65 mg/L, which was in contrast to the decrease of 0.20–0.65 mg/L with statin treatment (57–59). Thus, L-carnitine might possess a more potent antiinflammatory effect than statins. However, it is still unclear whether L-carnitine could significantly reduce cardiovascular morbidity and mortality.

Recently, hepcidin has emerged as the master regulator of iron metabolism (84). Hepcidin can bind to the cell surface iron exporter ferroportin and induce its internalization, thereby inhibiting iron enteral absorption and iron release from liver and reticuloendothelial system (85). Inflammation could induce hepcidin overproduction and, thus, cause or aggravate absolute iron-deficiency by inhibiting iron enteral absorption and functional iron deficiency by decreasing the release of stored iron from the liver and reticuloendothelial system (86). Our meta-

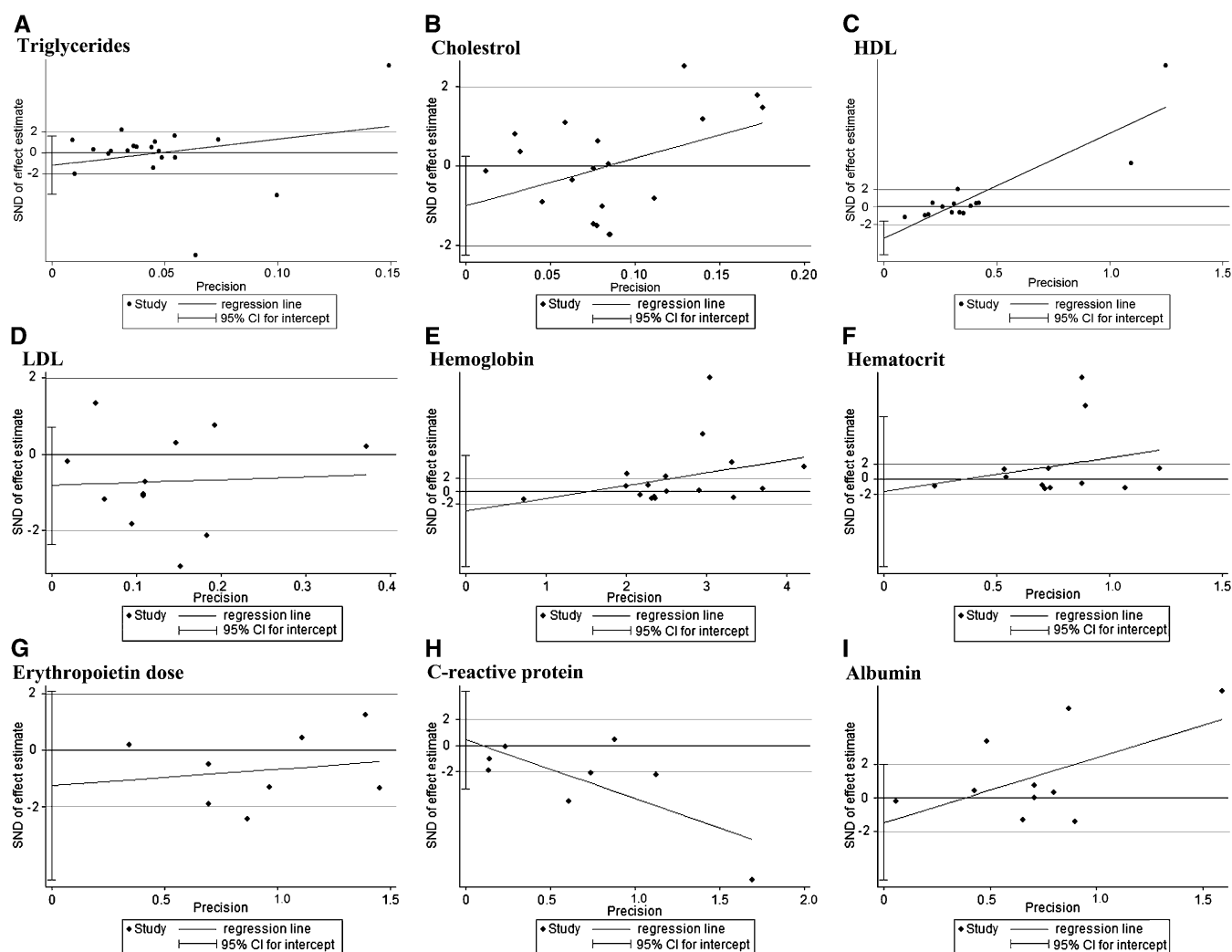


FIGURE 8. Galbraith modified plots from meta-analyses of effects of L-carnitine on serum triglycerides (A), cholesterol (B), HDL (C), LDL (D), hemoglobin (E), hematocrit (F), the required erythropoietin dose (G), C-reactive protein (H), and albumin (I). SND, standard normal deviate.

analysis indicated no beneficial effect of L-carnitine on hemoglobin, hematocrit, and the required erythropoietin dose. However, it could be speculated that L-carnitine, with a potent anti-inflammatory effect, could inhibit inflammation-induced hepcidin overexpression and help maintain the iron homeostasis.

This meta-analysis had several limitations. First, most of the included RCTs were short term, generally lasting <1 y. Treatment regimens and patient populations varied. Sensitivity analyses and subgroup analyses failed to show the prespecified covariates (a low- or high-quality study design, published or not, the ethnicity of patients, and the duration and route of L-carnitine treatment) as potential sources of heterogeneity, which reflected unmeasured factors that influenced findings and many imbalances in baseline characteristics of patients included in trials. Second, the quality of trials also varied. Only 14 of 49 trials explained how the random sequence was generated, and details of allocation were noted in only 3 of 49 trials, which suggested that a selection bias may have been introduced. The number of trials that contributed substantial data to the meta-analysis was small because most included trials only reported some outcomes. The presence of small-study effects was also identified in HDL reporting. A selective outcome re-

porting bias and small-study effects could have reduced the strength of our findings. Third, there were 62 *P* values for overall effects (9) and subgroups (54) (one test was not performed because of the lack of data; $9 + 54 - 1 = 62$) (Table 1). There was no prespecified overall plan on how to deal with the multiple testing at the design stage of this meta-analysis. All statistical testing in this meta-analysis was unadjusted for multiple testing. With the use of a raw *P* value, the effect of L-carnitine on CRP was significant ($P = 0.005$). The effect remained significant by using a post hoc multiple-testing method, such as the false discovery rate (FDR) (FDR $P = 0.045$). However, had the FDR been applied, the effect on LDL would not have been significant (raw $P = 0.05$ compared with FDR $P = 0.225$). A number of relatively small raw *P* values indicated that there might have been effects on albumin ($P = 0.08$), hemoglobin ($P = 0.11$), and the erythropoietin dose ($P = 0.13$). As regards the 53 subgroup analyses, results of 6 subgroup analyses were considered significant (all raw *P* values ≤ 0.005 and FDR *P* values ≤ 0.05). Three of 6 analyses were related to the effect on CRP (Table 1). With the aim to overcome the weakness that multiple testing of subgroup analyses might have increased the chance to detect false-positive results, no

TABLE 2

Comparison of the results from the current meta-analysis and 2 previous meta-analyses

Markers and meta-analysis	No. of trials	<i>P</i>
Triglycerides		
Current	19	0.95
Hurot et al (42)	9	0.80
Cholesterol		
Current	19	0.97
Hurot et al (42)	9	0.09
HDL		
Current	14	0.53
Hurot et al (42)	8	0.66
LDL		
Current	11	0.05
Hurot et al (42)	5	0.06
Hemoglobin		
Current	14	0.11
Hurot et al (42)	3	<0.01
Hematocrit		
Current	9	0.24
—	—	—
Erythropoietin dose		
Current	8	0.13
Hurot et al (42)	6	<0.01
C-reactive protein		
Current	8	0.005
—	—	—
Albumin		
Current	11	0.08
—	—	—
Dialysis-related muscle cramp		
Current	7	0.05
Lynch et al (1)	6	0.05
Intradialytic hypotension		
Current	7	0.50
Lynch et al (1)	5	0.20
Quality of life		
Current	6	0.03
—	—	—

definitive conclusion was drawn on the basis of any *P* values in the 53 intrastatum subgroup differences and 26 pairwise subgroup differences regardless of positive or negative findings. Even positive findings with small *P* values or large MDs of subgroup analyses should be interpreted with cautions and need to be validated as the primary concern in future RCTs. Thus, it is important that this systematic review be updated when results from more RCTs become available.

These limitations notwithstanding, this systematic review had several important strengths. First, we used Cochrane- and Preferred Reporting Items for Systematic Reviews and Meta-Analyses—recommended methods for the quality assessment and data synthesis of included RCTs. Second, we included more trials than in 2 previous meta-analyses and focused on more clinical markers, such as CRP, albumin, and quality of life. Furthermore, we qualitatively summarized data from 18 RCTs with 479 patients and provided descriptive information on effects of L-carnitine on the cardiovascular system, skeletal muscle function, platelet and coagulation function, and quality of life. In addition, the language bias may have been reduced by the inclusion of trials published in a non-English language.

In conclusion, previous meta-analyses indicated that L-carnitine significantly increased hemoglobin and decreased the required

erythropoietin dose. This meta-analysis failed to confirm previous findings but indicated that L-carnitine significantly decreased serum LDL and CRP. The extent of decrease of LDL was not clinically relevant, whereas the significant decrease of CRP was suggested to be both statistically and clinically relevant. However, the association of the decrease of CRP and hard endpoints such as all-cause mortality and cardiovascular complications remains unclear. Therefore, high-quality RCTs with an adequate sample size and hard endpoints are needed to reliably define the efficacy and safety of L-carnitine supplementation in ESKD patients requiring maintenance hemodialysis.

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Update

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Erratum

Li S, Na L, Li Y, Gong L, Yuan F, Niu Y, Zhao Y, Sun C. Long-term calcium supplementation may have adverse effects on serum cholesterol and carotid intima-media thickness in postmenopausal women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2013;98:1353–9.

Two errors appear in the article. In Table 1 (page 1356), the word *esterol* should be *estradiol*. In the Results section on page 1355, the second sentence under “Descriptive and biochemical characteristics and dietary intakes” should read as follows: “Serum estradiol concentrations in premenopausal women were significantly higher than those in postmenopausal women (147.44 ± 28.29 compared with 33.08 ± 8.41 ng/L; $P < 0.01$).”

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Erratum

Chen Y, Abbate M, Tang L, Cai G, Gong Z, Wei R, Zhou J, Chen X. L-Carnitine supplementation for adults with end-stage kidney disease requiring maintenance hemodialysis: a systematic review and meta-analysis. *Am J Clin Nutr* 2014;99:408–22.

The references in the original online supplemental data were incorrect. A corrected version of the online supplemental data has been posted.

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