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Original article

Effects of statins on lipid profile in chronic kidney disease patients: a meta-analysis of randomized controlled trials

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Abstract

Objective:
The available data on statin effects in chronic kidney disease (CKD) patients are still conflicting. We investigated the impact of short- and long-term statin therapy on lipid profiles in CKD patients requiring or not requiring dialysis.

Research design and methods:
Data from Scopus, PubMed, Web of Science, and the Cochrane Library from 1966 to May 2012 were searched for studies that investigated this effect. We included all randomized controlled clinical trials that investigated the impact of statin therapy on lipids and lipoproteins.

Results:
The final analysis included 16 trials with 3594 subjects. In CKD patients, statin therapy significantly reduced total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) ($p < 0.003$ for all comparisons), and the effect insignificantly intensified with duration of statin therapy (56.3 vs 66.8, 22.5 vs 24.1, and 53 vs 56.1 mg/dl, respectively). Comparing statin therapy for ≤ 3 and >3 months in CKD patients on dialysis, the magnitude of TC and LDL-C decreased (26.3 vs 25.9, and 42.2 vs 29.8 mg/dl, respectively, $p > 0.05$ for both), while TG increased modestly (4.5 vs 13.4 mg/dl). Short-term statin therapy increased high density lipoprotein cholesterol by a mean 0.7 mg/dl ($p = 0.04$), and long-term therapy was associated with a mean reduction of 2.4 mg/dL.

Conclusions:
Statin therapy significantly modifies the lipid profile in CKD patients not on dialysis therapy (with the trend to be more effective with longer therapy), and have less beneficial effect in patients on dialysis with the trend to be less effective with longer duration of therapy.

Introduction

Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. The incidence of CKD is rising worldwide, and CKD is associated with increased cardiovascular (CV) morbidity and mortality[1]. CKD with significant albuminuria/proteinuria is frequently associated with substantial alterations of serum lipid levels, most often with elevation in low-density lipoprotein (LDL) particle numbers and triglycerides (TG), and a reduction in high-density lipoprotein cholesterol (HDL-C)[2]. CKD increases the risk for end stage renal disease (ESRD), atherosclerotic disease, vascular calcification, as well as myocardial infarction, ischemic stroke and death[2,3]. Even patients in the early stages of CKD are at increased risk of cardiovascular disease (CVD)[3–6] and a large number of patients with CKD die before developing ESRD[1]. In fact, in patients with CKD, CV morbidity is a major concern[7,8] and accelerated atherosclerosis develops because of increased risk for heightened systemic inflammation, oxidative stress, endothelial dysfunction, hypertension, insulin resistance and diabetes mellitus (DM), and

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dyslipidemia[9]. Dyslipidemia and the generation of toxic lipid intermediates are major risk factors for the progression and amplification of nephropathy[10–14]. It has, therefore, been reasonable to assume that the treatment of dyslipidemia might be associated with reductions in CV cardiovascular morbidity and mortality and improvements in renal function in patients with CKD.

Hypercholesterolemia *per se* is present in around 50% of patients on dialysis[15]. Although dietary therapy is of benefit in some, the majority requires drug therapy[15] and inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) might be useful in hemodialysis (HD) patients to improve their lipid profiles. However, according to the update of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guideline for Diabetes and Chronic Kidney Disease, withholding statin treatment initiation in dialysis patients is suggested[16,17].

It has been shown that statins reduce the incidence of CV events in patients at high CV risk[15]. Statins have pleiotropic effects; thus, they not only reduce total cholesterol, low density lipoprotein cholesterol (LDL-C), and TG and slightly increase HDL-C but also attenuate oxidative stress and inflammation and improve endothelial function[6,17]. Considering the pleiotropic effects of statins, several investigations evaluated the effects of statins in CKD patients. The published data can be categorized into three groups: the lipid lowering effect of statins in CKD patients, the effect of statins on kidney function, and the effect of statins on primary and secondary outcomes. The benefits of statins in CKD patients, and especially in those undergoing hemodialysis have not been proven yet[18,19].

In this meta-analysis we evaluated the impact of short- and long-term therapy with statins on the lipid profiles of CKD patients requiring and not requiring dialysis therapy.

Patients and methods

Data sources

The PubMed, Web of Science (by Thomson Reuters Scientific), Cochrane Library, and Scopus were searched using the following keywords: statins, CKD, chronic renal failure (CRF), hemodialysis, rosuvastatin, atorvastatin, lovastatin, simvastatin, pitavastatin, pravastatin and fluvastatin. For PubMed, all relevant Medical Subject Heading (MeSH) terms were used. Data were collected for dates from 1966 to May 2012. The search was limited to randomized clinical trials written in English. Studies were chosen for inclusion in this meta-analysis if they studied patients with CKD, CRF, hemodialysis or peritoneal dialysis. Three reviewers (S.N., P.S., M.A.) assessed each article independently to diminish the probability of duplication, analyzing reviews, case studies and uncontrolled trials. Studies were excluded if they were uncontrolled or their results did not consider our outcomes of interest.

Assessment of trial quality

The Jadad score, which indicates the quality of the studies based on their description of randomization, blinding, and dropouts (withdrawals) was used to assess the methodological quality of trials[20]. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis

Data from selected studies were extracted in the form of 2×2 tables by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using StatsDirect software version 2.7.8 (Altrincham, UK). Standardized effect size and 95% confidence intervals (95% CI) were calculated using Hedges–Olkin (for fixed effects) or Der Simonian–Laird (for random effects) methods. The Cochran's Q test was used to test heterogeneity and $p < 0.05$ was considered significant. In case of heterogeneity, the random effects model was used. Funnel plots were used as indicator of publication bias. Comparisons of the effects of duration of statin treatment for mean differences of each parameter (TC, TG, LDL-C, and HDL-C) were evaluated by parametric unpaired t-test.

Results

The electronic search provided 667 articles: 293 from PubMed, 63 from Web of Sciences, 300 from Scopus, and 11 from Cochrane library. Of these, 28 studies were evaluated in full text, of which 12 trials were considered unsuitable while 16 studies with 3594 patients were finally included and analyzed (Table 1, Figure 1).

Effect of statins on total cholesterol in chronic kidney disease patients

The summary for effect size (weighted mean difference, WMD) on total cholesterol (TC) (ΔTC) in CKD patients with ≤3 months of statin therapy (short-term therapy) for five included trials (Table 2) compared to placebo[2,3,5,21,22] was −1.15 with 95% CI: −1.83 to −0.47 ($p = 0.0009$, Figure 2a). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTC in CKD patients receiving statin vs placebo therapy was −2.14 (95% CI: −20.8 to 16.52, $p = 0.74$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = 0.2, $p = 0.82$ (unbiased meta-analysis).

The summary for effect size (WMD) on TC (ΔTC) in CKD patients with >3 months of statin therapy (long-term therapy) for six included trials (Table 3) compared with placebo[2,5,21–24] was −1.54 with 95% CI: −2.53 to −0.54 ($p = 0.0025$, Figure 3a). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied.

Table 1. Characteristics of studies included in the meta-analysis.

Study	Sex (M/F)		Age		Disease	Type of statin	Dosage per day	Concomitant therapy	Duration of study
	Statin	Placebo	Statin	placebo					
Ichihara *et al.*,[25]	8/4	6/4	65.8 ± 3	64.3 ± 3.7	CKD (HD), DM	Fluvastatin	20 mg	–	(3) 6 m
Burmeister *et al.*,[26]	16/12	21/10	53.7 ± 16.6	60.1 ± 13.8	CKD (HD)	Rosuvastatin	10 mg	–	3 m
Bianchi *et al.*,[2]	19/9	19/9	56.5 ± 1.5	56.8 ± 1.5	CKD	Atorvastatin	40 mg	ACEIs, ARBs, AHTN	(3) 12 m
Nakamura *et al.*,[21]	9/6	9/6	39.5 ± 10	40.5 ± 11	CKD	Pitavastatin	1 mg	APLTs, ARBs, ACEIs, steroid	(3) 6 m
Goicoechea *et al.*,[23]	27/17	13/6	66.2 ± 13.6	70 ± 14.3	CKD	Atorvastatin	20 mg	RASBs	6 m
Verma *et al.*,[24]	19/29	13/30	73 ± 10	74 ± 19	CKD	Rosuvastatin	10 mg	–	20 wks
Panichi *et al.*,[6]	23/5	21/6	60 ± 10	55 ± 13	CKD	Simvastatin	40 mg	BBS, CCBs, ACEIs	6 m
Holmberg *et al.*,[22]	70	73	–	–	CKD	Atorvastatin	10 mg	–	(3) 36 m
Di Lullo *et al.*,[5]	80	50	59.4	58.7	CKD	Fluvastatin	80 mg	–	(3) 6 m
Dogra *et al.*,[3]	19/11	20/12	65 ± 14	62 ± 11	CKD	Atorvastatin	40 mg	AHTN, erythropoietic therapy	6 wks
Nannayakkara *et al.*,[4]	24/23	29/17	54 ± 11	52 ± 13	CKD	Pravastatin	40 mg	AHTN, ACEIs, D, BBs, α-Bs, CCBs	6 m
Chang *et al.*,[16]	8/23	10/21	63 ± 11	60 ± 12	HD	Simvastatin	20 mg	–	8 wks
Fellström *et al.*,[18]	806/583	872/512	64.1 ± 8.6	64.3 ± 8.7	HD	Rosuvastatin	10 mg	ACEIs, ARBs, CCBs, BBs, D, APLT, Ca, Vit D, sevelamer, erythropoietin	(3 m) 3.8 yrs
Saltissi *et al.*,[15]	10/28	6/13	–	–	ESRD	Simvastatin	5 mg	–	24 wks
Walker *et al.*,[27]	24	29	–	–	HD	Simvastatin	10 mg	–	6 m
Mastalerz-Migas *et al.*,[28]	16/14	11/2	54.2 ± 13.4	57.5 ± 12.2	CKD	Lovastatin	20 mg	–	6 m

CKD: chronic kidney disease; HD: hemodialysis; DM: diabetes mellitus; AHTN: anti-hypertension drugs; ESRD: end-stage renal disease; ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; APLTs: anti-platelets; CCBs: calcium channel blockers; BBs: beta-blockers; α-Bs: alpha-blockers; D: diuretics; RASBs: renin angiotensin system blockers; Ca: calcium; Vit D: vitamin D.
The numbers in the brackets in duration of study column signify that the groups were evaluated after 3 months (3) and 6 months (as an example from the first study).

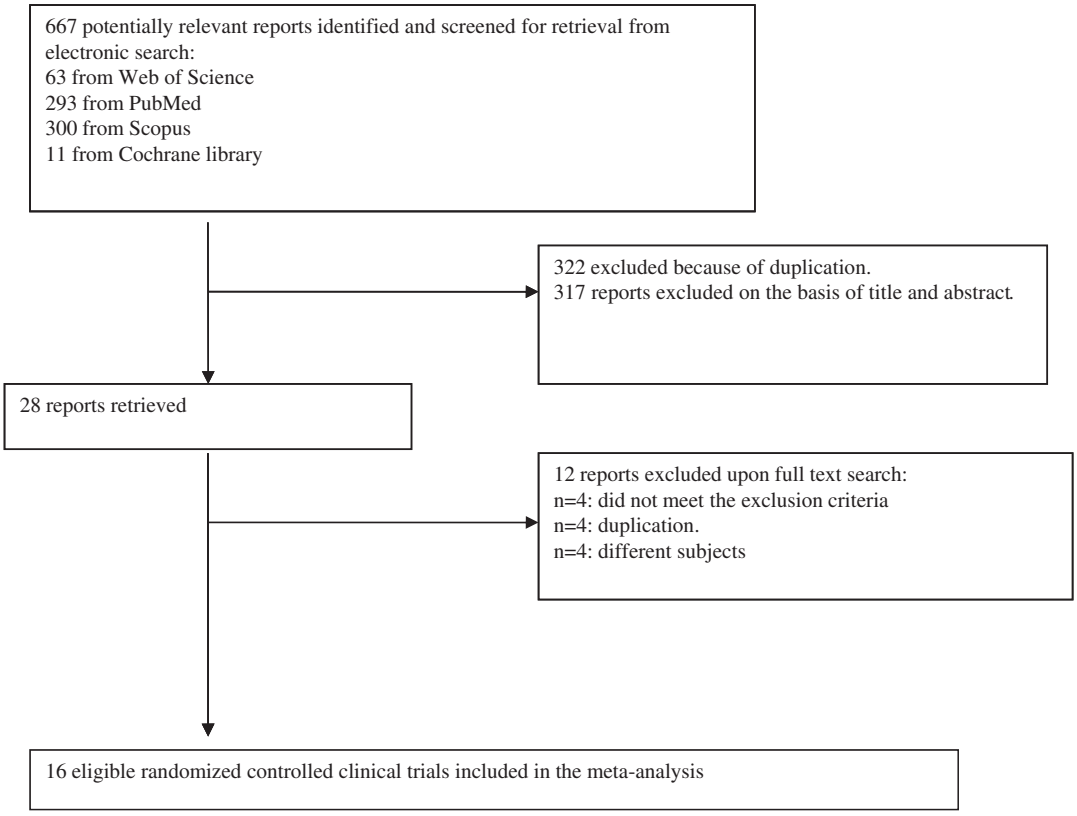

Figure 1. Flow diagram for study selection process.

For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTC in CKD patients receiving statin vs placebo therapy was −8.62 (95% CI: −27.28 to 10.05, $p = 0.27$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.33, $p = 0.27$ (unbiased meta-analysis).

Comparing the effect of statins on TC analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of long-term statin treatment ($p = 0.28$, Figure 4a).

Effect of statins on triglycerides in chronic kidney disease patients

The summary for effect size (WMD) on TG (ΔTG) in CKD patients with ≤3 months of statin therapy (short-term therapy) for five included trials (Table 2) compared with placebo[2,3,5,21,22] was −0.37 with 95% CI: −0.56 to −0.17 ($p = 0.0002$, Figure 2b). The Cochran's Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.18$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTG in CKD patients receiving statin vs placebo therapy was −0.03 (95% CI: −7.89 to 7.84, $p = 0.99$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = 0.2, $p = 0.82$ (unbiased meta-analysis).

The summary for effect size (WMD) on TG (ΔTG) in CKD patients with >3 months of statin therapy (long-term therapy) for eight included trials (Table 3) compared to placebo[2,4–6,21–24] was −0.35 with 95% CI: −0.5 to −0.19 ($p = 0.0002$, Figure 3b). The Cochran's Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.25$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTG in CKD patients among statins vs placebo therapy was −0.97 (95% CI: −5.6 to 3.66, $p = 0.6$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.43, $p = 0.11$ (unbiased meta-analysis).

Comparing the effect of statins on TG analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of long-term statin treatment ($p = 0.47$, Figure 4a).

Table 2. Mean changes after no more than 3 months of treatment in total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein for statin therapy in chronic kidney disease patients.

Study	ΔTC (no. of patients)		ΔTG (no. of patients)		ΔLDL-C (no. of patients)		ΔHDL-C (no. of patients)	
	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
Bianchi *et al.*,[2]	−57 ± 52.91 (28)	3 ± 30.85 (28)	−19 ± 60.3 (28)	−11 ± 29.94 (28)	−5 ± 5.38 (28)	9 ± 30.85 (28)	0.7 ± 7.48 (28)	2.5 ± 7.48 (28)
Nakamura *et al.*,[21]	−10 ± 34.06 (15)	6 ± 43.86 (15)	−4 ± 15.62 (15)	2 ± 17.2 (15)	–	–	–	–
Holmberg *et al.*,[22]	−50.2 ± 74.05 (70)	−10.81 ± 84.63 (73)	−46.02 ± 145.3 (70)	−21.24 ± 230.12 (73)	−45.18 ± 59.27 (70)	−6.95 ± 67.15 (73)	2.32 ± 22.39 (70)	−0.38 ± 22.64 (73)
Di Lullo *et al.*,[5]	−74.19 ± 36.18 (80)	2.24 ± 36.94 (50)	−42.65 ± 62.15 (80)	1.68 ± 60.84 (50)	−48 ± 29.94 (80)	5.04 ± 33.28 (50)	0.28 ± 14.6 (80)	−8.15 ± 13.04 (50)
Dogra *et al.*,[3]	−89 ± 54.56 (31)	−3 ± 70 (32)	−53 ± 111.77 (31)	−3 ± 100.01 (32)	−75 ± 46.82 (31)	0 ± 59.41 (32)	−1.7 ± 20.6 (31)	−1.4 ± 20.81 (32)

Values are presented as mean difference ± standard deviation.
ΔTC: mean difference of total cholesterol; ΔTG: mean difference of total triglycerides; ΔLDL-C: mean difference of low-density lipoprotein cholesterol; ΔHDL-C: mean difference of high-density lipoprotein cholesterol.

Effect of statins on low-density lipoprotein cholesterol in chronic kidney disease patients

The summary for effect size (WMD) on LDL-C (ΔLDL-C) in CKD patients with ≤3 months of statin therapy for four included trials (table 2) compared to placebo[2,3,5,22] was −1.21 with 95% CI: −1.76 to −0.66 ($p<0.0001$, Figure 2c). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p=0.0005$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔLDL-C in CKD patients among statins vs placebo therapy was −5.36 (95% CI: −29.7 to 18.98, $p=0.44$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = 0, $p=0.75$ (unbiased meta-analysis).

The summary for effect size (WMD) on LDL-C (ΔLDL-C) in CKD patients with long-term statin therapy for seven included trials (Table 3) compared to placebo[2,4–6,22–24] was −1.31 with 95% CI: −1.82 to −0.79 ($p<0.0001$, Figure 3c). The Cochran's Q test for heterogeneity indicated that the studies are heterogeneous ($p<0.0001$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔLDL-C in CKD patients receiving statin vs placebo therapy was −6.18 (95% CI = −20.41 to 8.05, $p=0.31$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.52, $p=0.07$ (unbiased meta-analysis).

Comparing the effect of statins on LDL-C analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of long-term statin treatment ($p=0.41$, Figure 4a).

Effect of statins on high-density lipoprotein cholesterol in chronic kidney disease patients

The summary for effect size (WMD) on HDL-C (ΔHDL-C) in CKD patients with ≤3 months of statin therapy for four included trials (table 2) compared to placebo[2,3,5,22] was 0.15 with 95% CI: −0.2 to 0.5 ($p=0.4$, Figure 2d). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p=0.04$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔHDL-C

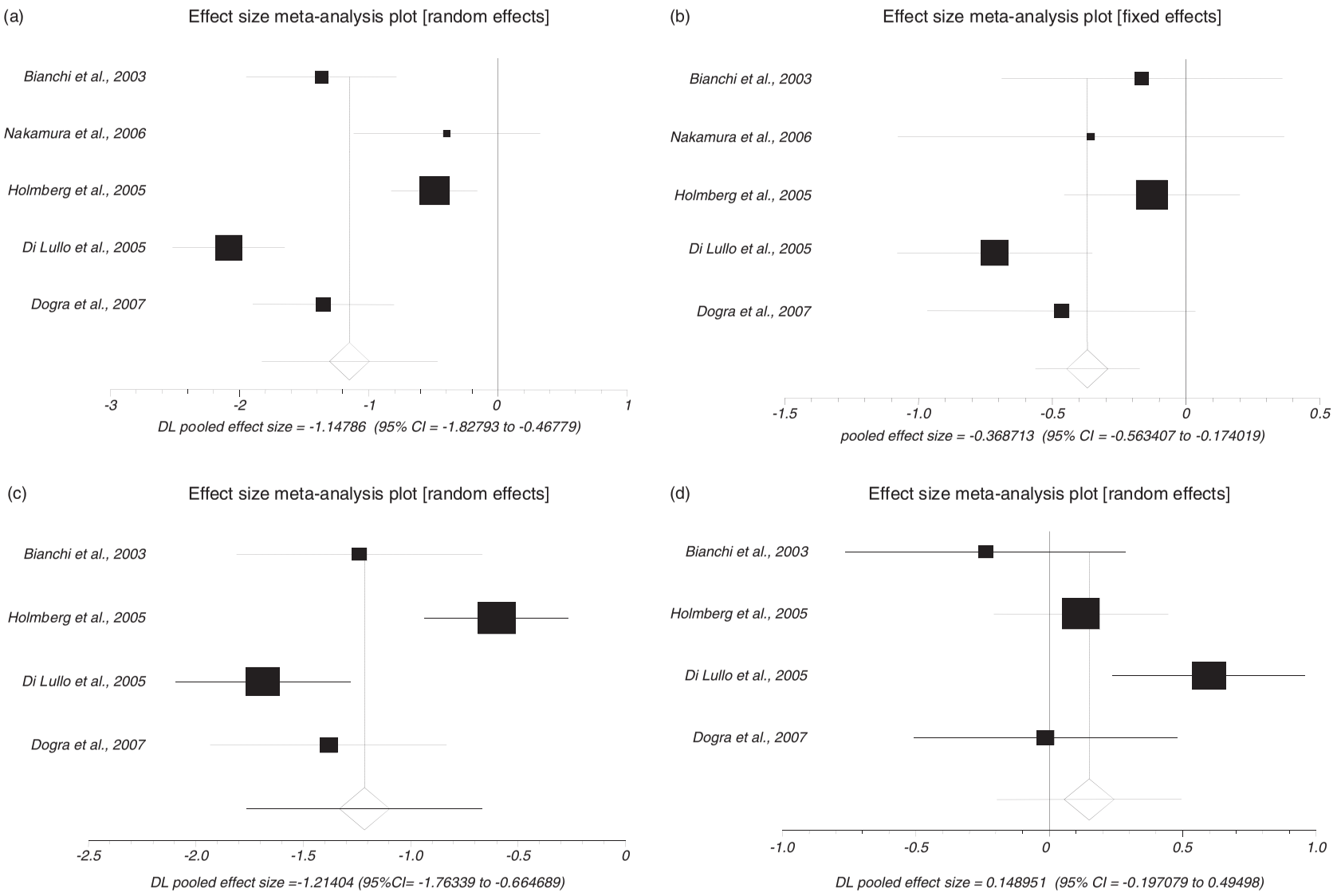

Figure 2. (a) Individual and pooled effect size for standardized mean for the outcome of ΔTC in the studies considering statins comparing with placebo therapy for ≤3 months in CKD patients. In patients treated ≤3 months TC was reduced by mean 56.3 mg/dl. (b) Individual and pooled effect size for standardized mean for the outcome of ΔTG in the studies considering statins comparing with placebo therapy for ≤3 months in CKD patients. In patients treated ≤3 months TG was reduced by mean 22.5 mg/dl. (c) Individual and pooled effect size for standardized mean for the outcome of ΔLDL-C in the studies considering statins comparing to placebo therapy for ≤3 months in CKD patients. In patients treated ≤3 months LDL-C was reduced by mean 53 mg/dl. (d) Individual and pooled effect size for standardized mean for the outcome of ΔHDL in the studies considering statins comparing to placebo therapy for ≤3 months in CKD patients. In patients treated ≤3 months HDL-C was increased by mean 2.5 mg/dl.

Table 3. Mean changes for more than 3 months of treatment in total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein for statin therapy in chronic kidney disease patients.

Study	ΔTC mean ± SD (no. of patients)		ΔTG mean ± SD (no. of patients)		ΔLDL-C mean ± SD (no. of patients)		ΔHDL-C mean ± SD (no. of patients)	
	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
Bianchi *et al.*,[2]	−78 ± 41.32 (28)	−2 ± 35.49 (28)	−26 ± 60.33 (28)	−16 ± 26.46 (28)	−66 ± 48.78 (28)	9 ± 30.85 (28)	2.1 ± 7.12 (28)	−0.2 ± 6.46 (28)
Goicoechea *et al.*,[23]	−51 ± 38.94 (44)	−8.5 ± 48.81 (22)	−22 ± 88.62 (44)	6 ± 61.29 (22)	−46.5 ± 32.14 (44)	−11.6 ± 43.4 (22)	−0.8 ± 26.81 (44)	2.2 ± 15.91(22)
Nakamura *et al.*,[21]	−16 ± 30.53 (15)	8 ± 45.34 (15)	−6 ± 12.81 (15)	4 ± 15.62 (15)	–	–	–	–
Panichi *et al.*,[6]	–	–	−28 ± 49.04 (27)	0 ± 70.71 (27)	−39 ± 50.61 (27)	4 ± 38.27 (27)	3 ± 17.69 (27)	−8 ± 17.80 (27)
Holmberg *et al.*,[22]	−53.28 ± 71.1 (70)	−11.96 ± 80.18 (73)	−38.94 ± 149.11 (70)	−10.62 ± 235.94 (73)	−47.88 ± 55.14 (70)	−8.88 ± 62.48 (73)	1.16 ± 21.84 (70)	−1.93 ± 24.57 (73)
Verma *et al.*,[24]	−66 ± 71.87 (48)	4 ± 62.13 (43)	−37 ± 201.69 (48)	−9 ± 121.49 (43)	−60 ± 56.86 (48)	9 ± 52.15 (43)	−1 ± 24.76 (48)	3 ± 24.08 (43)
Di Lullo *et al.*,[5]	−134.87 ± 33.29 (80)	8.36 ± 35.67 (50)	−44.31 ± 67.09 (80)	6.66 ± 61.57 (50)	−69.99 ± 28.43 (80)	9.08 ± 32.88 (50)	6.87 ± 14.84 (80)	−7.4 ± 11.15 (50)
Nannayakkara *et al.*,[4]	–	–	−21.24 ± 127.8 (47)	10.62 ± 143.4 (46)	−44.02 ± 47.35 (47)	4.25 ± 49.99 (46)	4.65 ± 20.51 (47)	−1.55 ± 21.86 (46)

Values are presented as mean difference ± standard deviation.
ΔTC: mean difference of total cholesterol; ΔTG: mean difference of total triglycerides; ΔLDL-C: mean difference of low-density lipoprotein cholesterol; ΔHDL-C: mean difference of high-density lipoprotein cholesterol.

in CKD patients among statins vs placebo therapy was −4.48 (95% CI: −22.28 to 13.32, $p = 0.39$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.67, $p = 0.08$ (unbiased meta-analysis).

The summary for effect size (WMD) on HDL-C (ΔHDL-C) in CKD patients with long-term statin therapy for seven included trials (Table 3) comparing with placebo[2,4–6,22–24] was 0.31 with 95% CI: −0.03 to 0.64 ($p = 0.07$, Figure 3d). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p = 0.0004$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔHDL-C in CKD patients among statins vs placebo therapy was −0.66 (95% CI: −12.87 to 11.56, $p = 0.9$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = 0.14, $p = 0.77$ (unbiased meta-analysis).

Comparing the effect of statins on HDL-C analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of long-term statin treatment ($p = 0.24$, Figure 4a).

Effect of statins on total cholesterol in chronic kidney disease patients on dialysis

The summary for effect size (WMD) on TC (ΔTC) in CKD patients on dialysis with ≤3 months of statin therapy for four included trials (Table 4) compared with placebo[16,18,25,26] was −0.73 with 95% CI: −1.56 to 0.1 ($p = 0.085$, Figure 5a). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTC in CKD patients on dialysis among statins vs placebo therapy was −3.3 (95% CI: −10.82 to 4.22, $p = 0.2$) and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.67, $p = 0.08$ (unbiased meta-analysis).

The summary for effect size (WMD) on TC (ΔTC) in CKD patients on dialysis with more than 3 months of statin therapy for five included trials retrieved from four studies (there were two groups in the study by Saltissi *et al.*[15]) (Table 5) compared with placebo[15,25,27,28] was −0.62 with 95% CI: −0.94 to −0.3 ($p = 0.0001$, Figure 6a). The Cochran's Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.68$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized

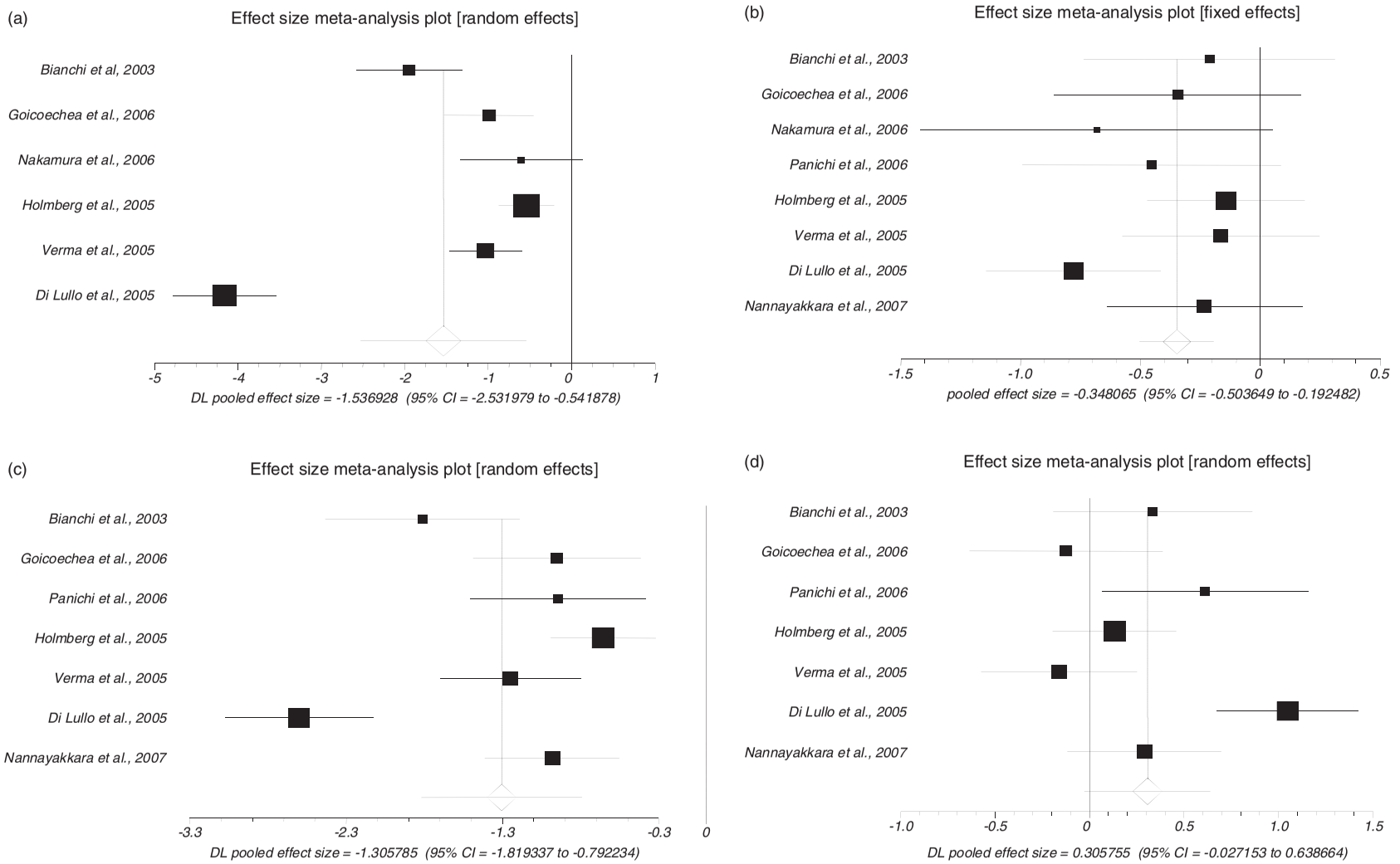

Figure 3. (a) Individual and pooled effect size for standardized mean for the outcome of ΔTC in the studies considering statins comparing with placebo therapy for >3 months in CKD patients. In patients treated >3 months TC was reduced by mean 66.8 mg/dl. (b) Individual and pooled effect size for standardized mean for the outcome of ΔTG in the studies considering statins comparing to placebo therapy for >3 months in CKD patients. In patients treated >3 months TG was reduced by mean 24.1 mg/dl. (c) Individual and pooled effect size for standardized mean for the outcome of ΔLDL-C in the studies considering statins comparing to placebo therapy for >3 months in CKD patients. In patients treated >3 months LDL-C was reduced by mean 56.1 mg/dl. (d) Individual and pooled effect size for standardized mean for the outcome of ΔHDL-C in the studies considering statins comparing to placebo therapy for >3 months in CKD patients. In patients treated >3 months HDL-C was increased by mean 4.8 mg/dl.

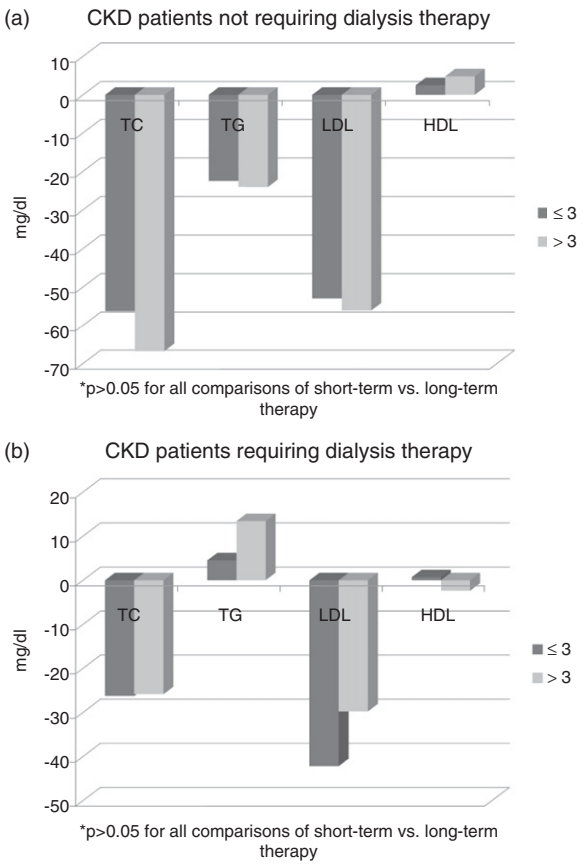

Figure 4. The effect of statins on TC, TG, LDL-C and HDL-C in CKD patients not requiring (a) and requiring (b) dialysis therapy. TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CKD: chronic kidney disease; CKD-D: chronic kidney disease with dialysis therapy.

mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTC in CKD patients on dialysis among statins vs placebo therapy was −3 (95% CI: −6.1 to 0.09, $p = 0.054$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.6, $p = 0.08$ (unbiased meta-analysis).

Comparing the effect of statins on TC analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of short-term statin treatment ($p = 0.43$, Figure 4b).

Effect of statins on triglycerides in chronic kidney disease patients on dialysis

The summary for effect size (WMD) on TG (ΔTG) in CKD patients on dialysis with ≤3 months of statin therapy for four included trials (Table 4) compared with placebo[16,18,25,26] was 0.042 with 95% CI: −0.32 to 0.41 ($p = 0.82$, Figure 5b). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous

Table 4. Mean changes after no more than 3 months of treatment in total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol for statin therapy in CKD patients on dialysis.

Study	ΔTC (no. of patients)		ΔTG (no. of patients)		ΔLDL-C (no. of patients)		ΔHDL-C (no. of patients)	
	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
Ichihara *et al.*[25]	−15 ± 17.03 (12)	9 ± 23.34 (10)	−8 ± 15.62 (12)	−3 ± 14.87 (10)	–	–	0 ± 6.4 (12)	4 ± 7.07 (10)
Chang *et al.*,[16]	−67 ± 46.32 (28)	4 ± 30.48 (30)	−31 ± 131.49 (28)	3 ± 140.03(30)	−67 ± 41 (28)	4 ± 38.9 (30)	1 ± 22.67 (28)	−1 ± 20.52 (30)
Burmeister *et al.*[26]	−21 ± 68.25 (27)	−11 ± 65.79 (29)	−18 ± 87.09 (27)	−18 ± 87.09 (29)	−21 ± 50.45 (27)	−9 ± 51.62 (29)	0 ± 22.67 (27)	1 ± 12.81 (29)
Fellström *et al.*,[18]	−1.2 ± 0.9 (1389)	−1 ± 27 (1384)	26 ± 71 (1389)	+1.8 ± 72 (1384)	−42 ± 30 (1389)	−1.9 ± 23 (1384)	1.2 ± 10 (1389)	0.4 ± 9.3 (1384)

Values are presented as mean difference ± standard deviation.
ΔTC: mean difference of total cholesterol; ΔTG: mean difference of total triglycerides; ΔLDL-C: mean difference of low-density lipoprotein cholesterol; ΔHDL-C: mean difference of high-density lipoprotein cholesterol.

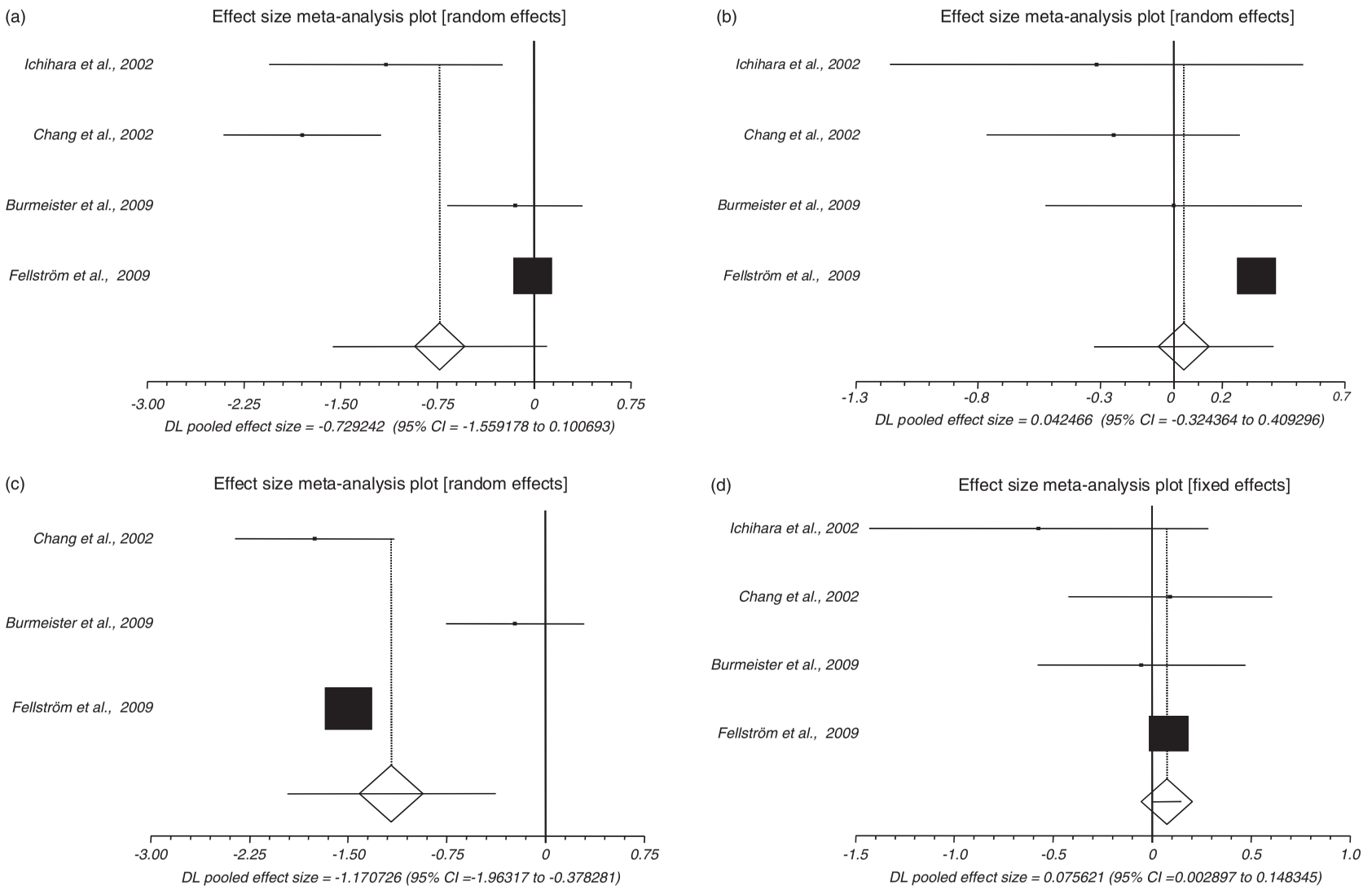

Figure 5. (a) Individual and pooled effect size for standardized mean for the outcome of ΔTC in the studies considering statins comparing with placebo therapy for ≤3 months in CKD patients on dialysis. In patients treated ≤3 months TC was reduced by mean 26.3 mg/dl. (b) Individual and pooled effect size for standardized mean for the outcome of ΔTG in the studies considering statins comparing with placebo therapy for ≤3 months in CKD patients on dialysis. In patients treated ≤3 months TG was increased by mean 4.5 mg/dl. (c) Individual and pooled effect size for standardized mean for the outcome of ΔLDL-C in the studies considering statins comparing with placebo therapy for ≤3 months in CKD patients on dialysis. In patients treated ≤3 months LDL-C was reduced by mean 42.2 mg/dl. (d) Individual and pooled effect size for standardized mean for the outcome of ΔHDL-C in the studies considering statins comparing with placebo therapy for ≤3 months in CKD patients on dialysis. In patients treated ≤3 months HDL-C was increased by mean 0.7 mg/dl.

($p = 0.0379$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTG in CKD patients on dialysis among statins vs placebo therapy was −1.9 (95% CI: −3.4 to −0.4, $p = 0.03$) and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.3, $p = 0.3$ (unbiased meta-analysis).

The summary for effect size (weighted mean difference) on TG (ΔTG) in CKD patients on dialysis with >3 months of statin therapy for five included trials retrieved from four studies (there were two groups in the study by Saltissi *et al.*[15]) (Table 5) compared with placebo[15,25,27,28] was −0.07 with 95% CI: −0.38 to 0.25 ($p = 0.673$, Figure 6b). The Cochran's Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.07$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔTG in CKD patients on dialysis among statins vs placebo therapy was 4.43 (95% CI: −5.2 to 14.1, $p = 0.24$) and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = 0.8, $p = 0.08$ (unbiased meta-analysis).

Comparing the effect of statins on TG analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of short-term statin treatment ($p = 0.37$, Figure 4b).

Effect of statins on low-density lipoprotein cholesterol in chronic kidney disease patients on dialysis

The summary for effect size (WMD) on LDL-C (ΔLDL-C) in CKD patients on dialysis with ≤3 months of statin therapy for three included trials (Table 4) compared with placebo[16,18,26] was −1.17 with 95% CI: −1.96 to −0.38 ($p = 0.0038$, Figure 5c). The Cochran's Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔLDL-C in CKD patients on dialysis among statins vs placebo therapy could not be calculated because of too few strata.

The summary for effect size (weighted mean difference) on LDL-C (ΔLDL-C) in CKD patients on dialysis with long-term statin therapy for four included trials retrieved

Table 5. Mean changes for more than 3 months of treatment in total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol for statin therapy in CKD patients on dialysis.

Study	ΔTC (no. of patients)		ΔTG (no. of patients)		ΔLDL-C (no. of patients)		ΔHDL-C (no. of patients)	
	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
Ichihara *et al.*, 2002[25]	−8 ± 15.81 (12)	4 ± 23.34 (10)	−7 ± 14 (12)	−24 ± 13.04 (10)	–	–	−1 ± 7.07 (12)	5 ± 7.07 (10)
Saltissi *et al.*, 2002 (ESRD)[15]	−47 ± 33.97 (22)	−25 ± 60.83 (11)	−38 ± 114.4 (22)	−16 ± 98 (11)	−38 ± 29.21 (22)	−19 ± 53.07 (11)	0 ± 17.69 (22)	−2 ± 15.62 (11)
Saltissi *et al.*, 2002 (CAPD)[15]	−53 ± 50.33 (16)	11 ± 102.41 (7)	−11 ± 193.76 (16)	5 ± 145.8 (7)	−59 ± 30.48 (16)	6 ± 92.65 (7)	0 ± 19.1 (16)	4 ± 19.1 (7)
Walker *et al.*, 1997[27]	−48.65 ± 81.02 (24)	−20.85 ± 64.11 (29)	−22.12 ± 123.3 (24)	3.54 ± 114.13 (29)	−50.2 ± 64.42 (24)	−19.31 ± 56.58 (29)	−0.39 ± 21.97 (24)	-0.77 ± 16.1 (29)
Mastalerz-Migas *et al.*, 2007[28]	−71 ± 51.88 (30)	−32 ± 60.6 (13)	−51 ± 178.89 (30)	14 ± 99.73 (13)	−43 ± 37.21 (30)	−12 ± 48.92 (13)	1 ± 17.69 (30)	−1 ± 12.21 (13)

Values are presented as mean difference ± standard deviation.
ΔTC: mean difference of total cholesterol; ΔTG: mean difference of total triglycerides; ΔLDL-C: mean difference of low-density lipoprotein cholesterol; ΔHDL-C: mean difference of high-density lipoprotein cholesterol; ESRD: end-stage renal disease, CAPD: continuous ambulatory peritoneal dialysis.

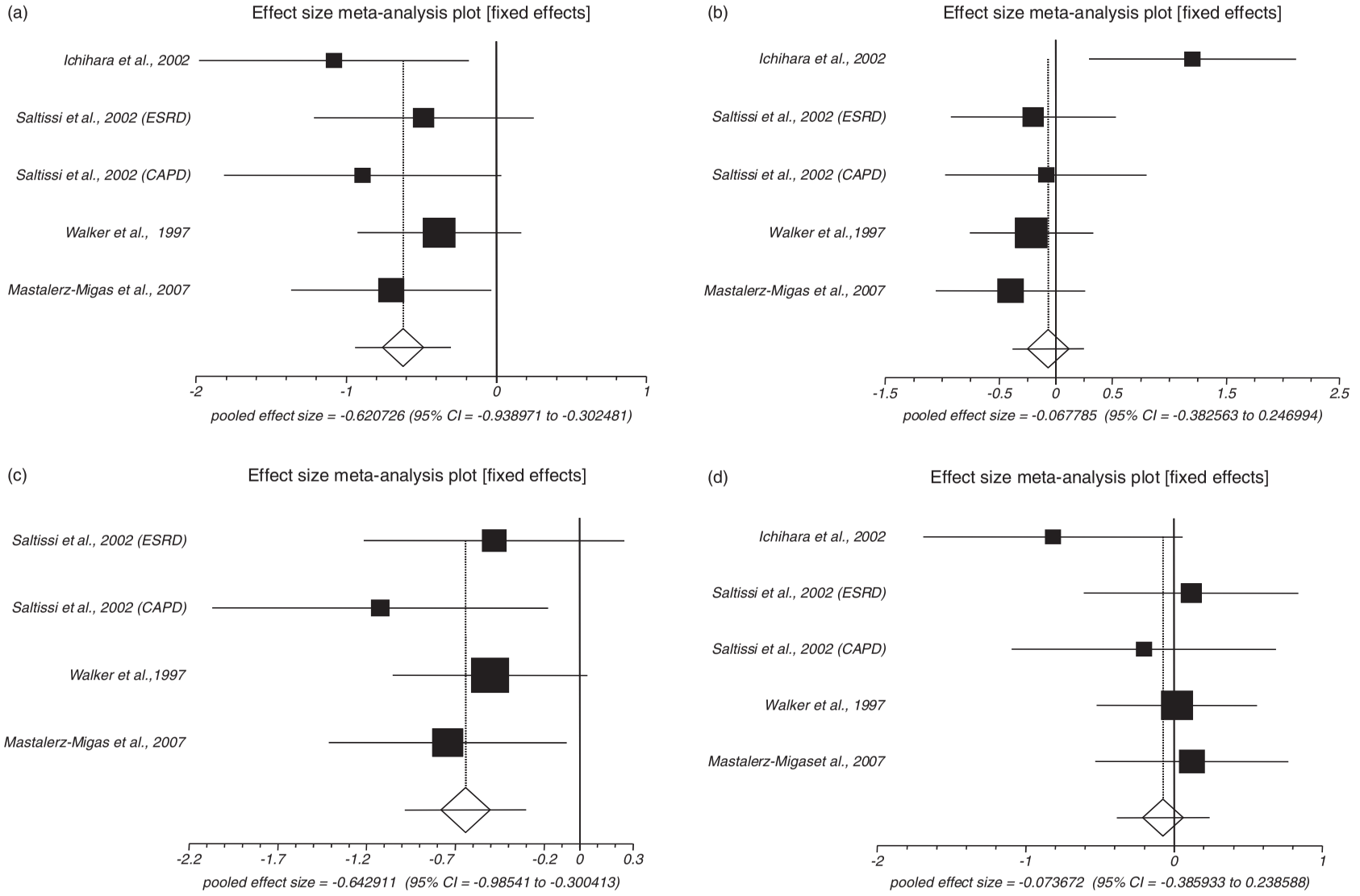

Figure 6. (a) Individual and pooled effect size for standardized mean for the outcome of ΔTC in the studies considering statins comparing with placebo therapy for >3 months in CKD patients on dialysis. In patients treated >3 months TC was reduced by mean 25.9 mg/dl. (b) Individual and pooled effect size for standardized mean for the outcome of ΔTG in the studies considering statins comparing with placebo therapy for >3 months in CKD patients on dialysis. In patients treated >3 months TG was increased by mean 13.4 mg/dl. (c) Individual and pooled effect size for standardized mean for the outcome of ΔLDL-C in the studies considering statins comparing with placebo therapy for >3 months in CKD patients on dialysis. In patients treated >3 months LDL-C was reduced by mean 29.8 mg/dl. (d) Individual and pooled effect size for standardized mean for the outcome of ΔHDL-C in the studies considering statins comparing with placebo therapy for >3 months in CKD patients on dialysis. In patients treated >3 months HDL-C was reduced by mean 2.4 mg/dl.

from three studies (there were two groups in the study by Saltissi *et al.*[15]) (Table 5) compared with placebo[15,27,28] was −0.64 with 95% CI: −0.99 to −0.3 ($p = 0.0002$, Figure 6c). The Cochran's Q test for heterogeneity indicated that the studies are not heterogeneous ($p = 0.68$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔLDL-C in CKD patients on dialysis among statins vs placebo therapy was −2.56 (95% CI: −8.74 to 3.62, $p = 0.22$), and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.67, $p = 0.08$ (unbiased meta-analysis).

Comparing the effect of statins on LDL-C analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of short-term statin treatment ($p = 0.17$, Figure 4b).

Effect of statins on high-density lipoprotein cholesterol in chronic kidney disease patients on dialysis

The summary for effect size (WMD) on HDL-C (ΔHDL-C) in CKD patients on dialysis with ≤3 months of statin therapy for four included trials (Table 4) compared with placebo[16,18,25,26] was 0.08 with 95% CI: 0.003 to 0.15 ($p = 0.042$, Figure 5d). The Cochran's Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.48$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔHDL-C in CKD patients on dialysis among statins vs placebo therapy was −0.78 (95% CI: −2.97 to 1.4, $p = 0.26$) and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −1, $p < 0.0001$ (unbiased meta-analysis).

The summary for effect size (WMD) on HDL-C (ΔHDL-C) in CKD patients on dialysis with >3 months of statin therapy for five included trials retrieved from four studies (there were two groups in the study by Saltissi *et al.*[15]) (Table 5) compared with placebo[15,25,27,28] was −0.07 with 95% CI: −0.39 to 0.24 ($p = 0.6438$, Figure 6d). The Cochran's Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.47$) and could be combined, thus the fixed effects model for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias Egger's regression test was used, and regression of normalized effect vs precision for all included studies for ΔHDL-C in CKD patients on dialysis among statins vs placebo therapy was −2.94 (95% CI: −9.21 to 3.34, $p = 0.23$) and Begg–Mazumdar Kendall's test on standardized effect vs variance indicated tau = −0.4, $p = 0.23$ (unbiased meta-analysis).

Comparing the effect of statins on HDL-C analyzing on the basis of therapy duration (short-time vs long-time) we showed an advantage (but not significant) of short-term statin treatment ($p = 0.44$, Figure 4b).

Discussion

The effectiveness of statins in CKD patients, especially those requiring dialysis, is still debated[29,30]. It has been suggested that the pathogenesis of vascular disease is different and the effectiveness of CV interventions is underpowered in dialysis patients[31]. Other potential reasons for treatment failure might be initiating statin therapy at advanced stages of CKD or if the wrong CV risk factors are targeted. We provide information on the specific effect of statins on lipid profile in 3594 patients with CKD treated with statins ($n = 1938$) (short- and long-term). Statin therapy was highly effective in patients with CKD not requiring dialysis (with the trend to be more effective with longer therapy). In individuals receiving dialysis, it was effective only with short-term (≤3 months) therapy and with reference only to TC and LDL-C (with the trend to be less effective with longer therapy).

Lipid abnormalities in patients with CKD may include increased LDL-C, increased very-low-density lipoprotein (VLDL), TG and lipoprotein(a) [Lp(a)], as well as decreased HDL-C[32–35]. The mechanisms responsible for these lipid abnormalities are complex, but proteinuria seems to play a major role[2]. In addition, in the setting of CKD, there can be increased hepatic VLDL secretion and impaired clearance of VLDL and its remnants from serum. This results in hypertriglyceridemia as well as increased HDL catabolism. It is known that LDL-C can bind to specific receptors in mesangial cells and stimulate cell hypertrophy and potentiate glomerulosclerosis[36]. In a pro-inflammatory state LDL can undergo enzymatic oxidation. The oxidized LDL is toxic mesangial cells[37] and stimulates macrophage scavenging and foam cell formation. Foam cells amplify local inflammation by increasing the production of interleukins and cytokines and propagate tissue injury[38]. Oxidized LDL (oxLDL) may attract monocytes directly[39] or indirectly, via activation of monocyte chemoattractant protein-1 (MCP-1). It is also known that oxLDL down-regulates endothelial nitric oxide (NO) activity[40]. Therefore, a reduction in oxLDL may have contributed to the improvement in endothelial function in the glomeruli contributing to less vasoconstriction[2].

Experimental evidence suggests that lipid abnormalities may contribute to the progression of kidney disease[2]; yet, dyslipidemia may not be a primary contributor to arterial

dysfunction in patients with CKD, since in one study[3] there was no improvement in endothelial-dependent flow-mediated dilatation, despite a significant decrease in TC and LDL-C, TG and oxLDL levels and an increase in HDL-C concentrations[2,3]. Statins act as an antioxidant in lipoprotein particles in non-dialysis patients[41] and can reduce the basal level of adherent leukocytes with an improved leukocyte rolling velocity[16]. It is considered that pleiotropic effects of statins, such as alterations in inflammatory responses, plaque stabilization and improved endothelial function, can be partially responsible for the reduction of CV events in CKD patients[22,42–44]. Pleiotropic properties of statins may be prominent in their benefit beyond their lipid-lowering capacity because they may act as anti-inflammatory, antioxidant and also renoprotective (decreasing proliferation and promoting mesangial cell apoptosis) agents[45]. On the other hand, it has been suggested that in patients with end-stage renal disease (ESRD), statins might be less effective than in other patient groups[4,46].

Starting with statin therapy early in the course of CKD may be beneficial[47,48] given that in patients with advanced CKD (including patients requiring renal replacement therapy [RRT]), other nonconventional CVD risk factors (such as calcium-phosphate product, inflammation, oxidative stress, and insulin resistance) are likely to have a significant contributory role[3]. The effects of statins on the inhibiting of progression of vascular calcification may be caused both by their LDL-C-lowering effect[49], and pleiotropic effects[50], but in patients with intensified endothelial calcification the therapy might be ineffective or much less effective. There is evidence that statins decrease inflammation in chronic hemodialysis patients[51]; however, Fellström *et al.*[18] have suggested that despite a decrease in elevated levels of high-sensitivity C-reactive protein, there is no reduction in the rate of CV events in patients undergoing hemodialysis and the overall time on hemodialysis or on RRT does not influence the response to therapy. It has been suggested that CKD might represent a clinical model of atherogenesis and these conditions (inflammation, calcification, oxidative stress, small dense LDL) are emerging risk factors in the pathogenesis of atherosclerosis[52]. It may explain a beneficial effect of statins in the early stage of CKD (patients not receiving dialysis) decreasing mortality and major CV events[51,52]; while advanced stages of CKD could be compared with the state of coronary heart disease, and CV mortality continues but the underlying pathogenesis may be less related to atherosclerosis and less affected by lipid-lowering therapy in those patients (dialysis)[52,53]. But the latest meta-analysis reported that lipid-lowering therapy decreased cardiac mortality even in those on dialysis, which remains to be fully elucidated in the future[54]. At the same time the results of another meta-analysis showed that statins reduced mortality and cardiovascular events in subject with early stages of CKD, while in subjects undergoing dialysis the effect was uncertain[55]. Also, the results of German Diabetes and Dialysis Study (4D)[56] and the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[18], showed that statin therapy provided no benefit in reducing of all the individual components of the primary end point (except fatal stroke in the 4D trial) in patients with ESRD requiring RRT[18,56].

Our results confirm that statins have beneficial effects on the lipid profiles of CKD patients[57,58]. Of interest, statins seem to significantly decrease TC and LDL-C as well as TG levels depending on the duration of the treatment (the longer the more effective) in CKD patients without RRT. In contrast, the beneficial impact of statin therapy on lipid profiles appears to dampen as a function of time in patients on dialysis, perhaps reducing their capacity to impact cardiovascular events in these patients. What is even more interesting in CKD-RRT patients is that much less effect of statin therapy (in comparison to CKD patients) was seen only with short-term therapy ($\leq$3 months), with much worse effect for the longer lipid lowering therapy (even with the lipid paradox phenomenon for TG and HDL-C). These results confirm the previous data suggesting lack of effect of statin therapy in dialysis patients[29,34], but we also clearly indicated that there might be no further benefits of long-term therapy in these patients, and it might lead to reverse effects of the therapy (HDL-C reduction, TG increase). These results still raise the question of the cut-off point at which statin therapy may become ineffective or much less effective in CKD patients. It is also a matter of great interest why short-term statin intervention in dialysis patients seems to be beneficial, and if that might have any clinical relevance.

Recently, the negative results of statin therapy in CKD-RRT patients have been discussed, and authors highlighted that statins must be used with great caution in the late stages of CKD[59,60]. Our results confirm and even strengthen the current recommendation of NKF-KDOQI Clinical Practice Guideline for Diabetes and Chronic Kidney Disease, suggesting withholding of statin treatment initiation in dialysis patients[17].

There is currently high interest in the differential effects among various statins. It has been shown that fluvastatin improves the lipid profile and has good safety and tolerability in patients with chronic renal failure, but may also contribute to nephroprotection in such patients[61]. Atorvastatin reduces TC but has not consistently shown significant reductions in LDL-C, HDL-C or TG levels in patients undergoing long-term dialysis[62]; however, in hypercholesterolemic patients on HD, atorvastatin may favorably modulate the uremic lipid profile[63]. Simvastatin therapy may have a significant benefit on the lipid profile in HD patients, particularly on TG

levels[64]. Plasma lipids as well as remnant-like particle cholesterol were also beneficially modulated in CKD patients who received rosuvastatin[65].

In the present study, we have found a greater benefit of therapy in patients receiving statins for at least 3 months for CKD patients without dialysis therapy. In this view, it has been suggested that the greater benefit of statins may be related to the lack of delay in initiating lipid lowering[65]. This is the first analysis to date comparing short- and long-term statin therapy in CKD patients, which confirms the influence of statins on lipids, and indicating the significant importance of therapy duration in CKD patients with and without dialysis therapy, and the possible need for longer therapy only for CKD patients without RRT. The recent Study of Heart and Renal Protection (SHARP) trial also confirms the effectiveness of combination statin therapy and ezetimibe on LDL-C in CKD patients on lipid lowering therapy for almost 5 years. However, the authors did not evaluate the statin effect in different stages of CKD (only 33% patients included in the study required dialysis)[66–69].

Our meta-analysis has some inevitable limitations. Some included studies were heterogeneous. In addition, different statins, at various doses and therapy durations were included. Currently there are too few available studies to analyze the effect of a single statin in CKD patients. In some studies, patients also received concomitant therapy (not lipid lowering). Finally, duration of follow up was different (range: 6 weeks to 3.8 years) and some studies had small patient populations (range: 12–1389 in the statin groups).

Conclusions

Our findings support significant lipid-lowering effects of statins in CKD patients not requiring dialysis, with the possible effect depending on treatment duration. There was much lower effectiveness of statins in CKD patients on dialysis with an insignificant reduction of the effect with the treatment duration. Further studies are necessary to confirm these findings.

Transparency

Declaration of funding
This meta-analysis was written independently; no company or institution supported it financially. No professional writer was involved in the preparation of this meta-analysis.

Declaration of financial/other relationships
DG, SN, PS, JR, MA have no conflict of interest. MR has given talks and participated in conferences sponsored by Astra-Zeneca, Bracco, Bromatech, Chiesi Farmaceutici, Novartis, Novo-Nordisk, Rikrea and Servier. KKR has received honoraria for lectures or advisory boards from Pfizer, Astra-Zeneca, MSD, Roche, Novartis, Sanofi, Regeneron, Servier, Lilly, Daiichi Sankyo, Kowa, Novo-Nordisk, Abbott, Bayer. MJP is a member of DSMB for AbbVie. DPM has given talks, attended conferences and participated in trials and advisory boards sponsored by MSD, Genzyme and Abbott. PPT has given talks for AbbVie, Amarin, Astra-Zeneca, Genzyme, Kowa, Merck and is consultant for Amgen, Atherotech, Genzyme, Kowa, Liposcience, Merck. SJN has received research support from AstraZeneca, Eli Lilly, Novartis, Anthera, Resverlogix, Roche and Amgen, and is a consultant for AstraZeneca, Merck, Roche, Takeda, CSL Behring, Omthera, Amgen, Boehringer Ingelheim and Kowa. MB has given talks, attended conferences and has received research support from MSD, Abbott, AstraZeneca, Roche, Synageva, Polfarmex and Amgen.

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