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A meta-analysis of the role of statins on renal outcomes in patients with chronic kidney disease. Is the duration of therapy important?

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ABSTRACT

Introduction: The efficacy of statin treatment in chronic kidney disease (CKD) patients remains controversial. Therefore, we performed a meta-analysis to investigate whether statins modulate renal function in patients with CKD.

Methods: Data from Scopus, PubMed, Web of Science, and the Cochrane Central Register of randomized controlled trials for years 1966–December 2012 were searched for appropriate studies.

Results: Twenty trials with 6452 CKD subjects randomized to receive either statin or placebo were included. Statin therapy significantly influenced high sensitivity C-reactive protein levels in patients on or off dialysis [−0.28 mg/dl, 95%CI: −0.93 to −0.37; $p < 0.05$ and −0.46 mg/dl, 95%CI: −0.87 to −0.05; $p = 0.03$], respectively], urinary protein (−0.77 g/24 h, 95%CI: −1.24 to −0.29, $p < 0.02$; this effect persisted for treatment ≤12 months), and serum creatinine but only for long-term therapy (3 years) (−0.65 mg/dl, 95%CI: −1.00 to −0.30; $p = 0.0003$). The summary for standardized effect size of mean differences of glomerular filtration rate was 0.29 ml/min/1.73 m^2 (95%CI: 0.01 to 0.58; $p = 0.04$), and depended on treatment duration — a significant increase was observed for between 1 and 3 years of statin therapy (0.50 ml/min/1.73 m^2, 95%CI: 0.40 to 0.60; $p < 0.0001$), with no significant increase for both ≤1 and >3 years of the therapy.

Conclusion: Statins might exert significant renoprotective effects in CKD patients; however, benefit may depend on the duration of treatment. This is an issue that warrants more definitive investigation. More studies are necessary in dialysis patients to credibly evaluate the renal effects of statin therapy.

1. Introduction

Chronic kidney disease (CKD) is associated with cardiovascular disease (CVD). Beyond established risk factors these patients have additional predictors of CVD such as proteinuria, electrolyte imbalances, inflammation, increased oxidative stress, and endothelial dysfunction that greatly amplify vascular risk [1,2]. Dyslipidemia is an independent risk factor for the progression of CKD [3,4].

Current recommendations to slow the progression of CKD include hypertension control using angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as well as lowering protein intake [5]. Statins can improve the lipid profile and cardiovascular (CV) outcomes in patients with CKD [6–8]. Evidence is accruing that the statins may also exert renoprotective effects that are partly attributed to their lipid-lowering activity, but it is conceivable that pleiotropic effects — anti-inflammatory activity, influence on renal hemodynamics, endothelial function, monocyte recruitment, mesangial cell proliferation, and matrix accumulation and immunomodulation — also play a role

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[9–14]. However, the effect of statins on renal outcome remains controversial, despite evidence that they may prevent the deterioration of kidney function [14–18] or improve glomerular filtration rate (GFR) [19,20]. The preservation or improvement of renal function by statins has been seen in subjects with renal disease [21,22].

Taking into account the divergent data and the enormous importance of this issue, we performed a meta-analysis to evaluate whether statins modulate renal function in CKD patients, and if this effect may depend on the duration of therapy.

2. Patients and methods

2.1. Search strategy

We searched PubMed, Web of Science (WoS), Cochrane Library, and SCOPUS for the years 1966–December 2012, using the keywords statins, chronic kidney disease, chronic renal failure, hemodialysis, dialysis, atorvastatin, lovastatin, simvastatin, rosuvastatin, pitavastatin, fluvastatin and pravastatin. The reference lists of retrieved articles were additionally reviewed for relevant studies. Meeting abstracts were searched in WoS.

2.2. Study selection

We limited our search only to randomized clinical trials (RCTs), written in English, with statin monotherapy for at least 3 months without any limitation on the group size. Studies including renal transplant patients, with incomplete (e.g. in some papers there were baseline data but the final data were lacking, some reported only amount of change at the end of follow up, others reported the data as median and interquartile range or percent of change which was not suitable for inclusion in analysis, finally the measured outcome of some papers was different from our outcomes) or unavailable data were excluded.

Studies were chosen if they met the inclusion criteria including: CKD, chronic renal failure, hemodialysis, peritoneal dialysis, and renal outcomes. When the literature search was done, after evaluation of included trials, we prespecified the studies according to the therapy duration on 3 groups: below 1 year; between 1 and 3 years, and above 3 years.

2.3. Data extraction

Three reviewers (SN, PS, MA) 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 were not consistent with our goals. Any disagreements were resolved by consensus.

2.4. Assessment of trial quality

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 [23]. 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 (Supplementary Table 1).

2.5. Outcomes assessed

The primary outcome was the difference in selected renal parameters concentrations among the treatment (monotherapy with statins) and control groups (placebo) compared with baseline levels. Additionally we analyzed the effect of the therapy duration on the renal parameters.

2.6. Statistical analysis

The meta-analysis was performed in line with recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. 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 2.7.9. 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 Q test was used to test heterogeneity and a $p < 0.05$ was considered significant. In case of heterogeneity or few included trials, the random effects model was used. The Eger and Begg–Mazumdar test was used to evaluate publication bias indicators in funnel plot.

3. Results

The electronic search provided 670 articles; 293 from PubMed, 66 from Web of Sciences, 300 from Scopus, and 11 from Cochrane Library. Of those, 39 studies were scrutinized in full text, of which 20 were finally analyzed (Table 1, Fig. 1).

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

Study	Sex (M/F) (n)		Age (years)		Disease	Type of statin	Dosage per day	Concomitant therapy	Duration of study
	Statin	Placebo	Statin	Placebo					
Atthobari et al. [21]	276/124[a]	242/146	52.1 ± 11.9[a]	50.9 ± 11.5[a]	CKD	Pravastatin	40 mg/d	AHTN, RASI, HG	4 years
	279/198[b]	1224/1739	57.9 ± 9.8[b]	49.3 ± 11.8[b]					
Ichihara et al. [27]	8/4	6/4	65.8 ± 3.0	64.3 ± 3.7	CKD, HD, DM	Fluvastatin	20 mg/d	–	6 months
Burmeister et al. [25]	16/12	21/10	53.7 ± 16.6	60.1 ± 13.8	CKD/HD	Rosuvastatin	10 mg/d	–	3 months
Arabul et al. [26]	12/10	10/8	48.7 ± 11.3	43.6 ± 14.4	ESRD, HD, PD	Fluvastatin	40 mg/d	–	8 weeks
Bianchi et al. [18]	19/9	19/9	56.5 ± 1.5	56.8 ± 1.5	CKD	Atorvastatin	40 mg/d	ACEI, ARB, AHTN	1 year
Nakamura et al. [29]	9/6	9/6	39.5 ± 10	40.5 ± 11	CKD	Pitavastatin	1 mg/d	APLT, ARB, ACEI, Steroid	6 months
Sawara et al. [24]	11/11	9/7	63.8 ± 9.1	67 ± 7.9	CKD	Rosuvastatin	2.5 mg/d	ARB, ACEI, CCB, BB	1 year
Athyros et al. [33]	292/73	278/69	59 ± 8.0	58 ± 7.0	CHD, MetS	Atorvastatin	10 mg/d	ASA, BB, ACEI, D, HG,	3 years
Nakamura et al. [31]	20	20	–	–	CGN, HL	Cerivastatin	0.15 mg/d	–	6 months
Fassett et al. [35]	12/17	17/13	53 ± 15.0	49 ± 12.0	ADPKD	Pravastatin	20 mg/d	ARB, ACEI	2 years
Goicoechea et al. [37]	27/17	13/6	66.2 ± 13.6	70 ± 14.3	CKD	Atorvastatin	20 mg/d	RASI	6 months
Fassett et al. [30]	36/22	44/21	60 ± 15.0	60.3 ± 15.2	CKD	Atorvastatin	10 mg/d	Erythropoietic therapy, ACEI, ARB	2.5 years
Verma et al. [34]	19/29	13/30	73 ± 10.0	74 ± 19.0	CKD	Rosuvastatin	10 mg/d	–	20 weeks
Panichi et al. [12]	23/5	21/6	60 ± 10.0	55 ± 13.0	CKD	Simvastatin	40 mg/d	BB, CCB, ACEI	6 months
Fassett et al. [38]	9/7	12/6	62.3 ± 16.3	64.8 ± 15.0	CKD	Atorvastatin	10 mg/d	ACEI, ARB, CCB, BB, erythropoietic therapy	3 years
Fassett et al. [39]	29/19	25/15	58.6 ± 15.9	58.7 ± 14.5	CKD	Atorvastatin	10 mg/d	Erythropoietic therapy, ACEI, ARB,	2.9 ears
Koren et al. [15]	217/69	228/65	65.6 ± 7.4	64.8 ± 7.0	CHD, CKD	Atorvastatin	80 mg/d	–	54.3 months
Imai et al. [32]	19/13	13/12	58.8 ± 9.2	49.5 ± 11.4	HTN, CKD, HL,	Pravastatin	5–10 mg/d	CCB	6 months
Geith et al. [36]	9/12	9/13	23 ± 13.3	22.2 ± 9.5	NS, HL, CKD,	Fluvastatin	20 mg/d	–	12 months
Joy et al. [28]	6/13	11/15	63 ± 15.0	61 ± 14.0	DM, ESRD, HTN, CHD, PAD	Atorvastatin	10–80 mg/d	–	36 weeks

Abbreviations: M, male: F, female; CKD, chronic kidney disease; HD, hemodialysis; DM, diabetes mellitus; ESRD, end stage renal disease; PD, peritoneal dialysis; CHD, coronary heart disease; MetS, metabolic syndrome; CGN, chronic glomerulonephritis; HL, hyperlipidemia; Autosomal dominant polycystic kidney disease; HTN, arterial hypertension; NS, nephrotic syndrome; PAD, peripheral arterial disease; AHTN, antihypertensives; RASI, renin–angiotensin system inhibitor; HG, hypoglycemic drug; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; APLT, antiplatelet drug, CCB, Calcium channel blocker; BB, beta-blocker; D, diuretics; ASA, acetylsalicylic acid.

[a] Data from randomized controlled trial [21].

[b] Data from observational study [21].

3.1. Effect of statins on C-reactive protein (CRP) in CKD patients

The standardized effect size of mean differences of high sensitivity CRP (mg/dL) (ΔhsCRP) in CKD patients without dialysis therapy in 1 trial comparing statin therapy with placebo [24] was −0.28 mg/dL (95%CI: −0.93 to −0.37; $p < 0.05$). The standardized effect size of ΔhsCRP in CKD patients on dialysis for 2 included trials comparing statin therapy with placebo [25,26] was −0.46 mg/dL (95%CI: −0.87 to −0.05; $p = 0.03$) (Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.61$) and could be combined. Because of few included studies the random effects for individual and summary of effect size for standardized mean were applied. Eger regression of normalized effect vs. precision for all included studies for ΔhsCRP in CKD patients on dialysis among statin vs. placebo therapy for evaluation of publication bias could not be calculated because of too few strata.

The summary for standardized effect size of mean differences of CRP (mg/dL) (ΔCRP) in CKD patients on dialysis for 3 included trials comparing statin therapy with placebo (2 groups in the Ichihara et al. study) [27,28] was −1.13 mg/dL (95%CI: −2.53 to 0.26; $p = 0.11$, Fig. 2b). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.001$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. Eger regression of normalized effect vs. precision for all included studies for ΔCRP in CKD patients on dialysis among statins vs. placebo therapy for evaluation of publication bias could not be calculated because of too few strata.

3.2. Effect of statins on urinary albumin in CKD patients

The summary for standardized effect size of mean differences of urinary albumin (g/24 h) (ΔUAlb) in CKD patients without dialysis therapy for 1 trial (2 groups) [21] was 0.003 g/24 h (95%CI: −0.08 to 0.09; $p = 0.95$). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.97$) and could be combined. Because of few included studies the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test (for evaluation of publication bias) of normalized effect vs. precision for all included studies for ΔUAlb in CKD patients among statin vs. placebo therapy for evaluation of publication bias could not be calculated because of too few strata.

3.3. Effect of statins on urinary protein in CKD patients

The summary for standardized effect size of mean differences of urinary protein (g/24 h) (ΔUPr) in CKD patients without dialysis therapy for 5 included trials comparing statin therapy with placebo in 4 studies (2 groups in Nakamura et al. study) [18,24,29,30] was −0.77 g/24 h (95%CI: −1.24 to −0.29; $p < 0.02$) (Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p = 0.01$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔUPr in CKD patients among statin vs. placebo therapy was −3.61 (95%CI: −10.3–3.07, $p = 0.18$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated that tau = −0.6, $p = 0.08$.

The summary for standardized effect size of mean differences of UPr in CKD patients for 4 included trials comparing statin therapy with placebo with short-term follow up studies (≤1 year) (2 groups in Nakamura et al. study) [18,24,29] was −0.89 g/24 h (95%CI: −1.23 to −0.56; $p < 0.001$, Figs. 3b, 4). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.06$) and could be combined, thus the fixed effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔUPr in CKD patients among statin vs. placebo therapy was −3.45 (95%CI: −2.94 to 2.25, $p = 0.63$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated that tau = −0.33, $p = 0.33$.

3.4. Effect of statins on blood urea nitrogen (BUN) in CKD patients

The summary for standardized effect size of mean differences of BUN (mg/dl) (ΔBUN) in CKD patients without dialysis therapy comparing statin therapy to placebo for 3 included trials in 2 studies (2 groups in Nakamura et al. study) [31,32] was −0.77 mg/dl (95%CI −2.08 to 0.54; $p = 0.25$, Fig. 5). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects for individual and summary of effect

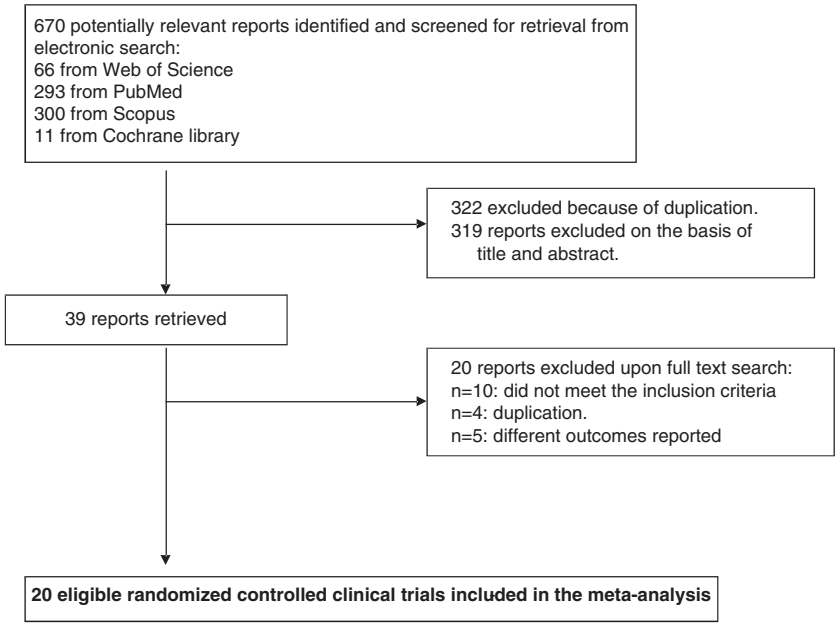

Fig. 1. Flow diagram for study selection.

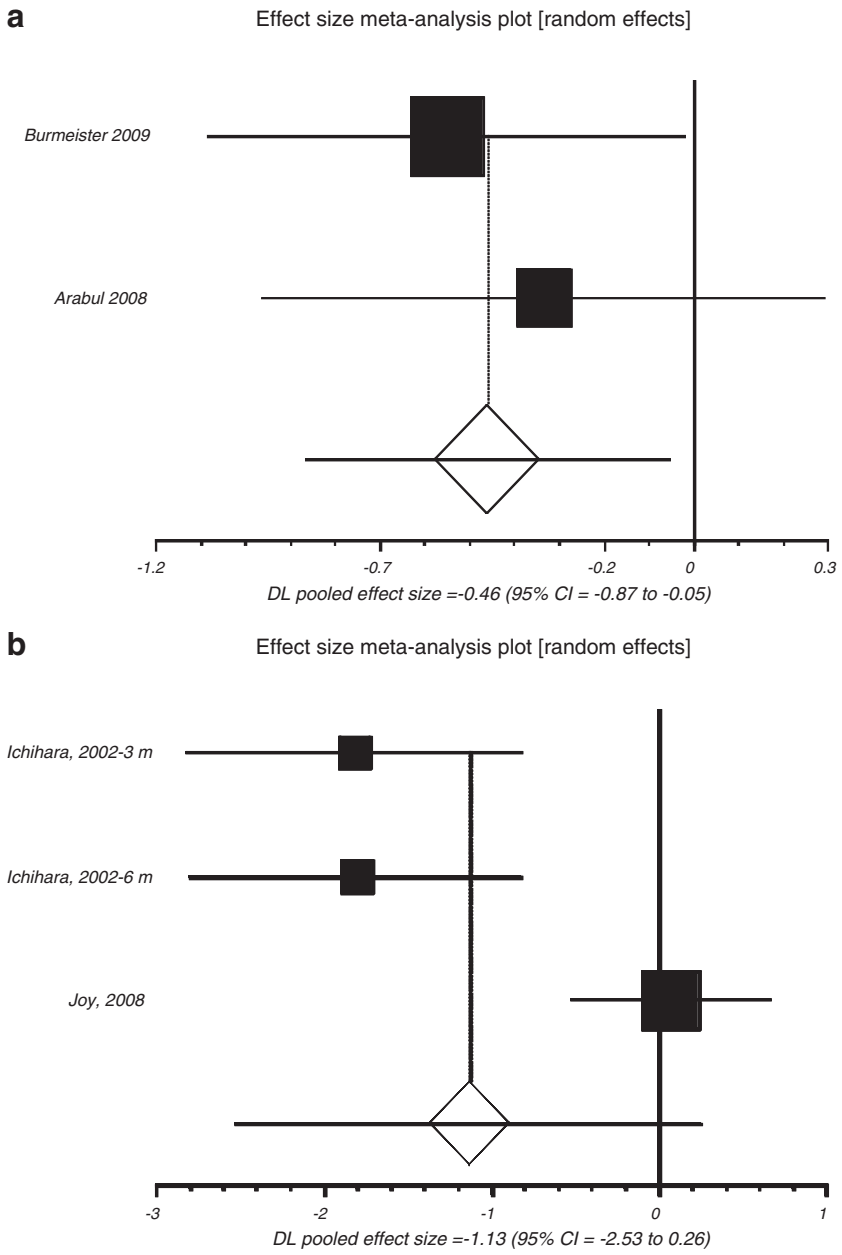

Fig. 2. Individual and pooled effect size for standardized mean for the outcome of ΔhsCRP (a) and ΔCRP (b) in the studies considering statins compared to placebo therapy in CKD patients on dialysis.

size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔBUN in CKD patients among statins vs. placebo therapy for evaluation of publication bias could not be calculated because of too few strata.

3.5. Effect of statins on serum creatinine in CKD patients

The summary for standardized effect size of mean differences of serum creatinine (mg/dl) (ΔSCr) in CKD patients without dialysis therapy for 5 included trials comparing statin therapy to placebo in 4 studies (2 groups in Athyros et al. study) [31–34] was −0.19 mg/dl (95%CI −0.39 to 0.77; $p = 0.52$) (Fig. 6a). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔSCr in CKD patients among statins vs. placebo therapy was 6.30 (95%CI −2.19–14.80, $p = 0.10$), and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated that tau = 0.80, $p = 0.08$.

The summary for standardized effect size of ΔSCr in CKD patients for 2 included trials with long term follow-up (=3 years) [33], and for 3 included trials with short term follow-up (<1 year) [31,32,34] comparing statin therapy to placebo was −0.65 mg/dl (95%CI −1.00 to −0.30; $p = 0.0003$; Figs. 4, 6b), and 0.95 mg/dl (95%CI −0.53 to 2.42; $p = 0.21$; Figs. 4, 6c), respectively. The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p = 0.0006$ and $p < 0.0001$, respectively) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔSCr in CKD patients among statins vs. placebo therapy for evaluation of publication bias could not be calculated because of too few strata.

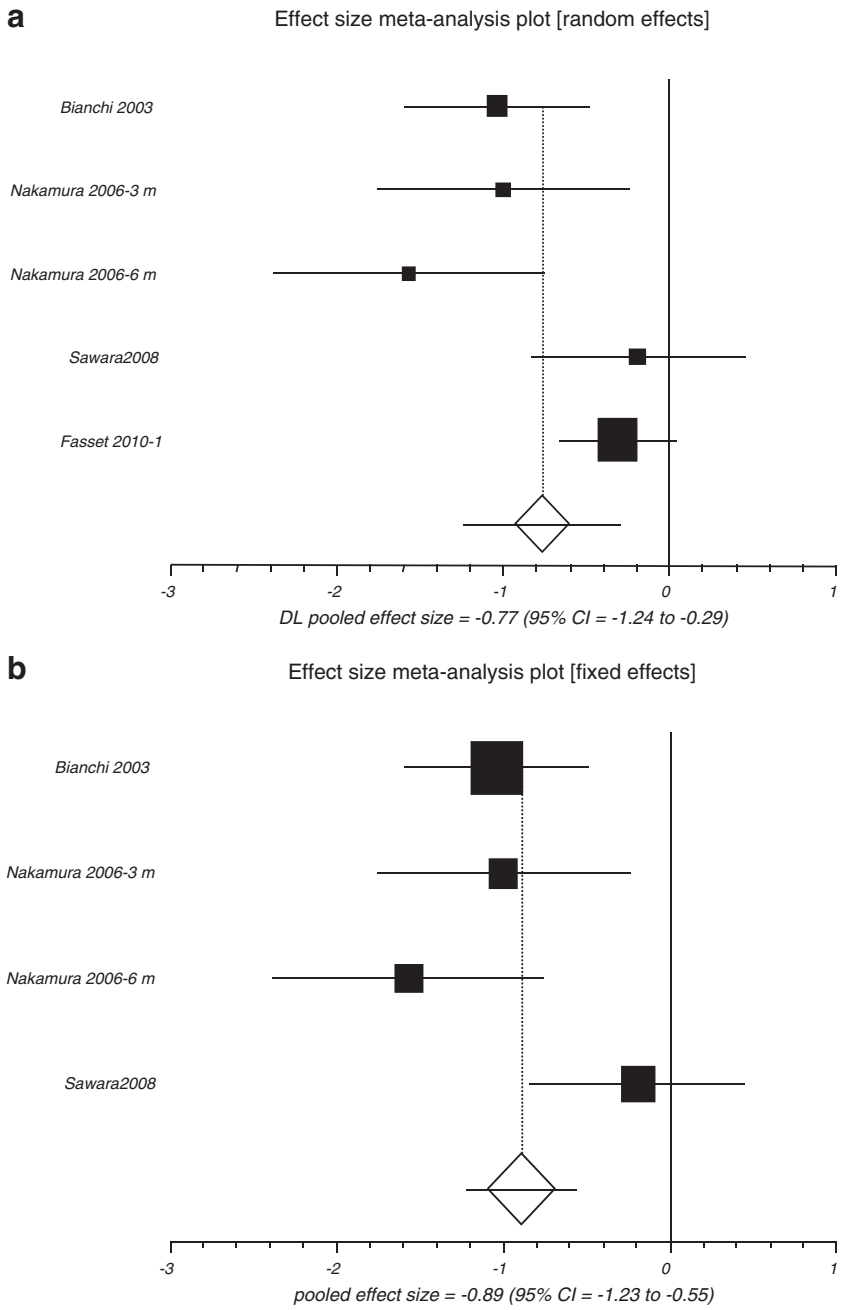

Fig. 3. Individual and pooled effect size for standardized mean for the outcome of ΔUPr (a), and ΔUPr with short-term therapy (b) in the studies considering statins compared to placebo therapy in CKD patients.

3.6. Effect of statins on creatinine clearance in CKD patients

The summary for standardized effect size of mean differences of creatinine clearance (CrCl) (ml/min) (ΔCrCl) in CKD patients without dialysis therapy for 7 included trials comparing statin therapy to placebo in 5 studies (2 groups in Nakamura et al. and Geith et al. studies) [18,31,32,35,36] was 0.37 ml/min (95%CI −0.17 to 0.91; $p = 0.18$) (Fig. 7a). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for "ΔCrCl" in CKD patients among statins vs. placebo therapy was 24.45 (95%CI −21.42–70.32, $p = 0.36$) and Begg–Mazumdar Kendall's tau = 0.33, $p = 0.38$.

The summary for standardized effect size of ΔCrCl in CKD patients for 3 included trials with long term follow-up (≥1 year) comparing statin therapy with placebo [18,35,36] was 0.69 ml/min (95%CI −0.59 to 1.97; $p = 0.29$) (Figs. 4, 7b). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔCrCl in CKD patients among statins vs. placebo in therapy long term follow up for evaluation of publication bias could not be calculated because of too few strata.

The summary for standardized effect size of ΔCrCl in CKD patients for 4 included trials with in short term follow-up (<1 year) in 3 studies comparing statin therapy to placebo (2 groups in Nakamura et al. study)

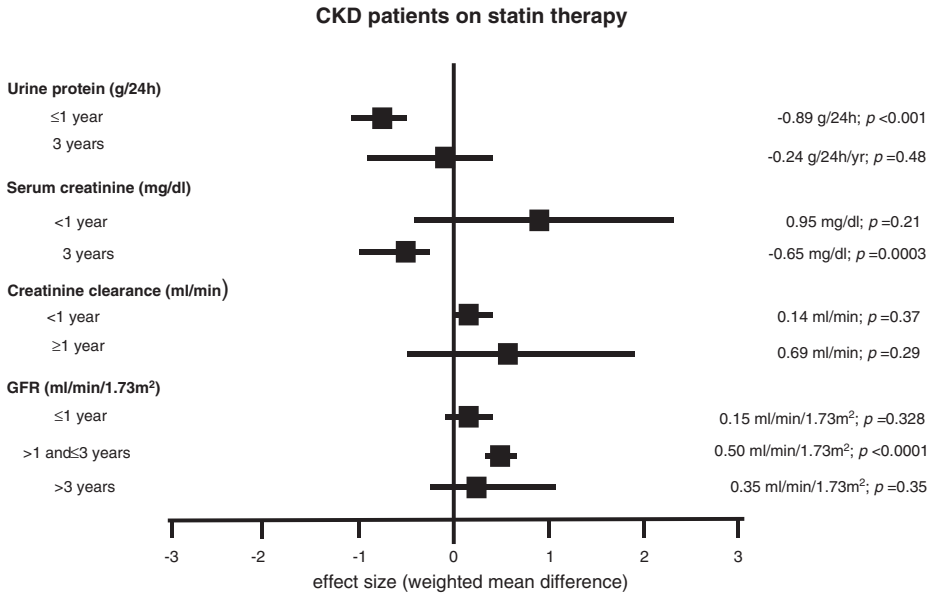

Fig. 4. The changes of the renal parameters depending on the duration of statin therapy.

[31,32,36] was 0.14 ml/min (95%CI 0.16 to 0.43; $p = 0.37$) (Figs. 4, 7c). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.45$) and could be combined, thus the fixed effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔCrCl in CKD patients among statins vs. placebo therapy in short term follow up for evaluation of publication bias was −0.95 (95%CI −49.88–47.98, $p = 0.94$) and Begg–Mazumdar: Kendall's tau = −0.33, $p = 0.33$.

The summary for standardized effect size of mean differences of CrCl by Cockcroft–Gault method (ml/min/1.73 m^2) (ΔCrCl-CG) in CKD patients for 2 included trials comparing statin therapy to placebo [30,37] was 0.07 ml/min/1.73 m^2 (95%CI −0.23 to 0.36; $p = 0.65$) (Fig. 7d). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.76$) and could be combined but because of few included studies the random effects for individual and summary of effect size for standardized mean were applied. The Eger Regression test of normalized effect vs. precision for all included studies for ΔCrCl-CG in CKD patients among statins vs. placebo therapy for evaluation of publication bias could not be calculated because of too few strata.

3.7. Effect of statins on GFR in CKD patients

The summary for standardized effect size of mean differences of GFR [ml/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] formula)] (ΔGFR) in CKD patients comparing statins with placebo therapy for 12 included trials in 10 studies (2 groups in Atthobari et al. and Athyros et al. studies) [12,15,21,24,30,33–35,38,39] was 0.29 ml/min/1.73 m^2 (95%CI 0.01 to 0.58; $p = 0.04$) (Fig. 8a). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger Regression test (for evaluation of publication bias regression) of normalized effect vs. precision for all included studies for ΔGFR

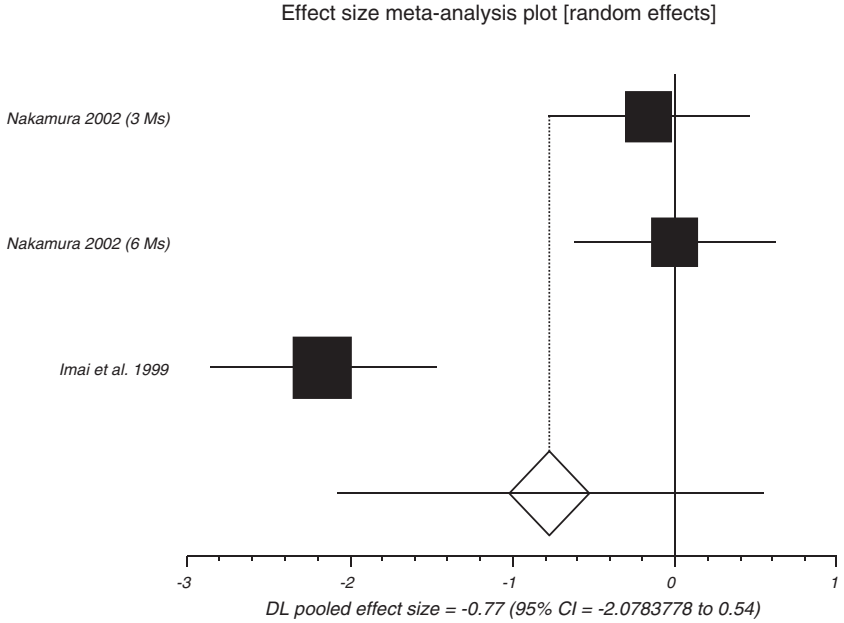

Fig. 5. Individual and pooled effect size for standardized mean for the outcome of ΔBUN in the studies considering statins compared to placebo therapy in CKD patients.

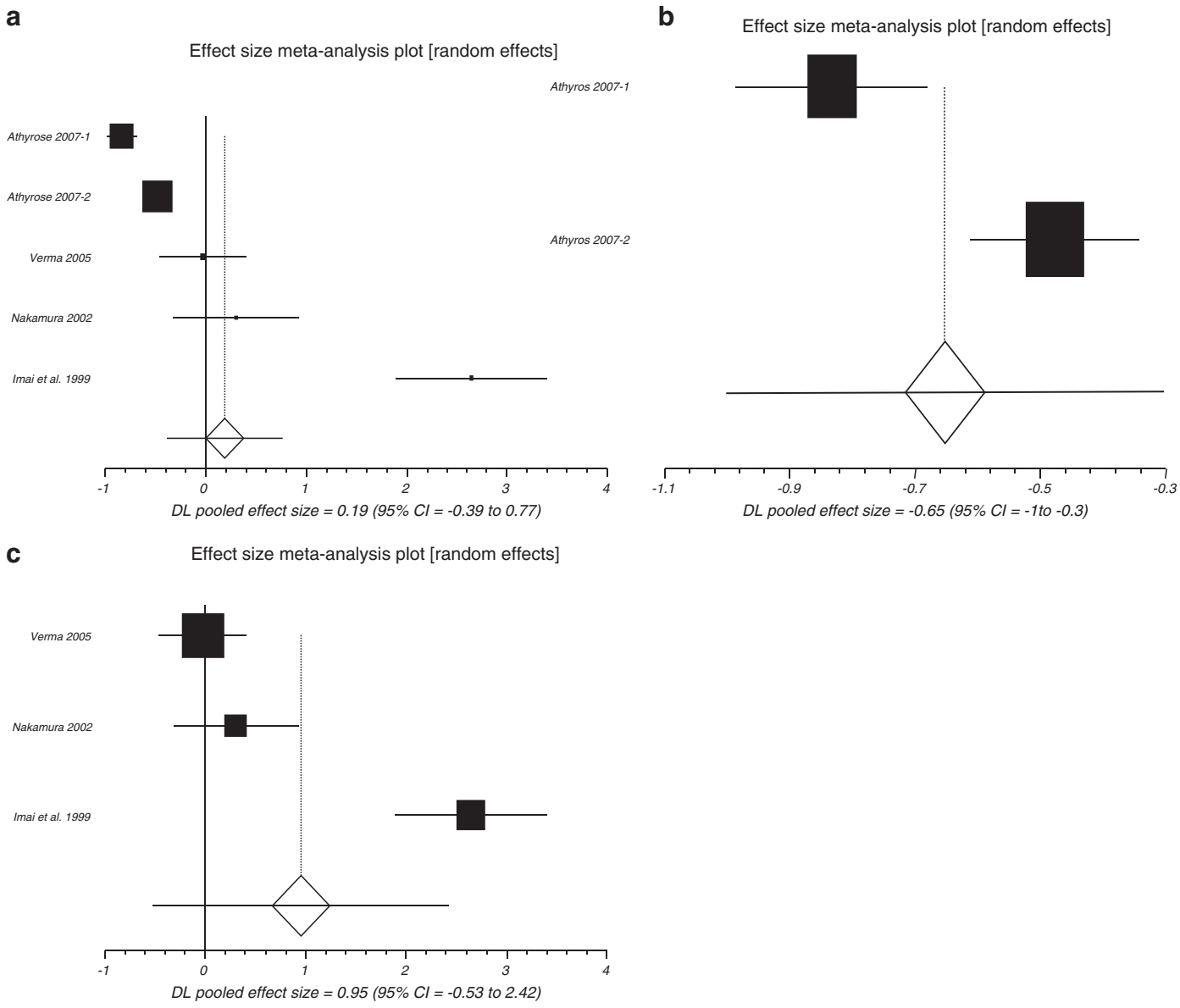

Fig. 6. Individual and pooled effect size for standardized mean for the outcome of ΔSCr (a), ΔSCr with long-term therapy (b), and ΔSCr with short-term therapy (c) in the studies considering statins compared to placebo therapy in CKD patients.

in CKD patients among statins vs. placebo in therapy in all studies was 0.95 (95%CI −4.43–6.33, $p = 0.70$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated that tau = 0.09, $p = 0.74$.

The summary for standardized effect size of ΔGFR in CKD patients with ≤1 year of statin therapy for 3 included trials compared to placebo [12,24,34] was 0.15 ml/min/1.73 m^2 (95%CI −0.15 to 0.45; $p = 0.328$) (Figs. 4, 8b). The Cochrane Q test for heterogeneity indicated that the studies turned to be homogeneous ($p = 0.99$) and could be combined, thus the fixed effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔGFR in CKD patients among statins vs. placebo with ≤1 year of the therapy for evaluation of publication bias could not be calculated because of too few strata.

The summary for standardized effect size ΔGFR in CKD patients with between 1 and 3 years of statin therapy for 6 included trials compared to placebo in 5 studies (2 groups in Athyros et al. study) [30,31,35,38,39] was 0.50 ml/min/1.73 m^2 (95%CI 0.40 to 0.60; $p < 0.0001$) (Figs. 4, 8c). The Cochrane Q test for heterogeneity indicated that the studies turned to be not heterogeneous ($p = 0.07$) and could be combined, thus the fixed effects for individual and summary of effect size for standardized mean were applied. For evaluation of publication bias regression of normalized effect vs. precision for all included studies for ΔGFR in CKD patients among statins vs. placebo with >1 year and ≤3 years of the therapy was −1.98 (95%CI −3.95–−0.01, $p = 0.05$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated that tau = −0.33, $p = 0.27$.

The summary for standardized effect size ΔGFR in CKD patients with >3 years of statin therapy for 3 included trials compared with placebo in 2 (2 groups in Atthobari et al. study) was 0.35 ml/min/1.73 m^2 (95%CI −0.38 to 1.08; $p = 0.35$) (Figs. 4, 8d). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean were applied. The Eger regression test of normalized effect vs. precision for all included studies for ΔGFR in CKD patients among statins vs. placebo in 3–5-year therapy for evaluation of publication bias could not be calculated because of too few strata.

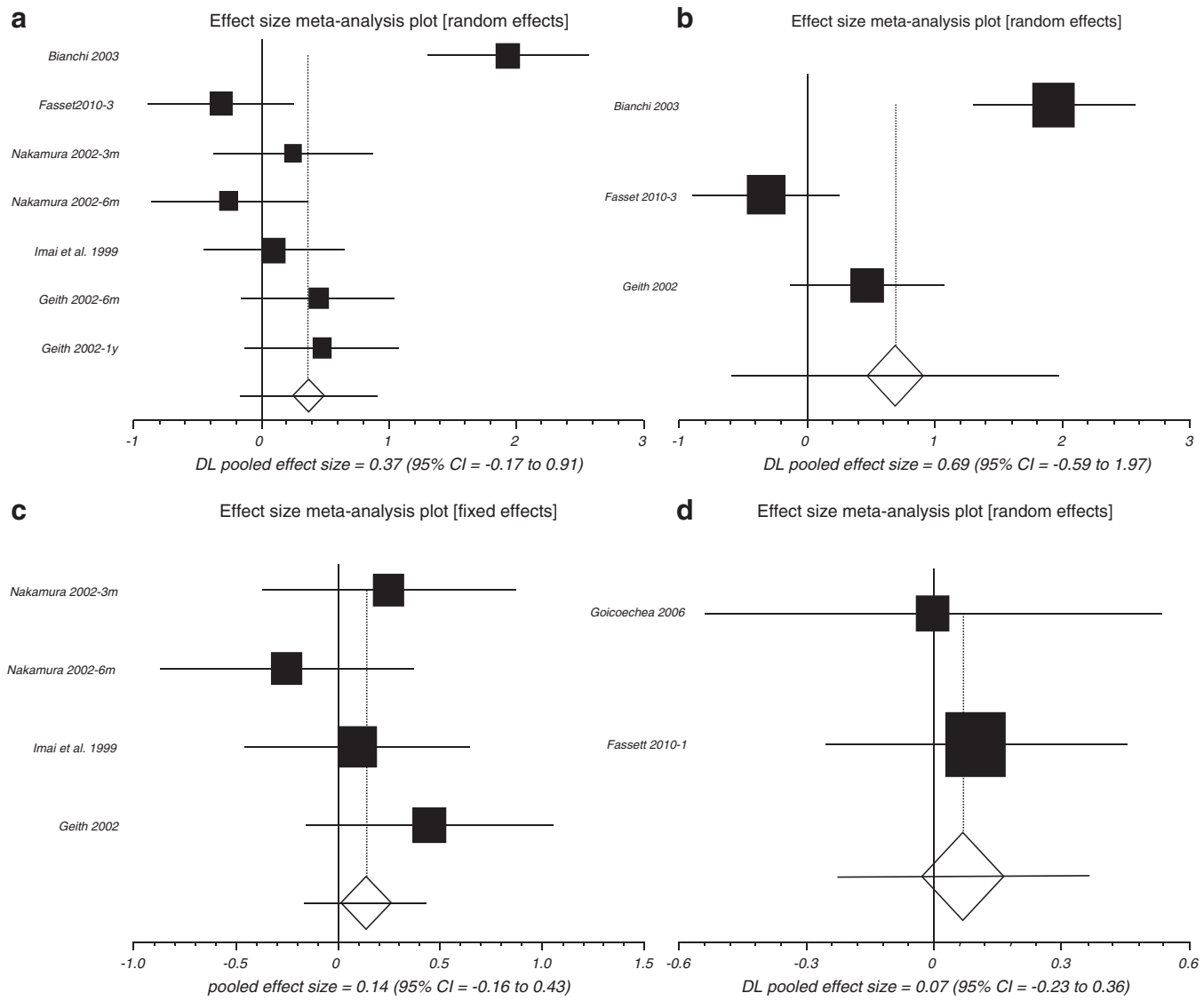

Fig. 7. Individual and pooled effect size for standardized mean for the outcome of ΔCrCl (a), ΔCrCl with long-term therapy (b), ΔCrCl with short-term therapy (c), and "ΔCrCl-Cockcroft–Gault" (d) in the studies considering statins compared to placebo therapy in CKD patients.

4. Discussion

This meta-analysis provides important information on the effects of statins on renal function in 6452 subjects with CKD treated with either statins or placebo. Our results support the conclusion that statins exert renoprotective effects, influencing hsCRP both in patients on and off dialysis therapy, urinary protein with the effect persisting for short-term therapy (≤12 months) and serum creatinine but only for long-term therapy (3 years). Also, statins modestly preserved GFR, with a significant increase for between 1 and 3 years.

Renoprotective effects of statins have been shown by experimental studies [40,41] as well as suggested by randomized clinical trials [14,17,18,42–45]. This protective effect on renal function may be achieved by reducing the contribution of lipids to glomerulosclerosis and by mechanisms by which statins ameliorate vascular calcification in CKD subjects [46,47]). Additionally, statins may have other cholesterol-independent renoprotective actions, such as reducing neutrophil and macrophage infiltration [46], up-regulating endothelial nitric oxide (NO) synthase [48], inhibition of renal cell proliferation, antifibrotic and antioxidant effects, and down-regulation of inflammatory cytokines [47].

Microalbuminuria is an independent predictor of total and CV mortality in both hemo- (HD) and peritoneal dialysis (PD) subjects [49,50]. Recent evidence has shown decreased albuminuria in subjects treated with a statin [51–53]. Sandhu et al. in their meta-analysis showed a significant reduction in albuminuria and proteinuria (0.58 units of standard deviation [SD] greater in statin recipients; 95%CI 0.17–0.98) [22]. Douglas et al. showed that statin therapy reduced albuminuria or proteinuria depending on baseline levels: a change of 2% (95%CI, −32 to 35%) was observed for those with excretion <30 mg/day, −48% (95%CI, −71 to −25%) for those with excretion of 30–300 mg/day, and −47% (95%CI, −67 to −26%) for those with excretion >300 mg/day [54]. In our meta-analysis we did not see significant changes in urinary albumin levels (0.003 g/24 h, $p = 0.95$), but this could be because we included a limited number of studies (due to inclusion criteria). It is possible that the effect does not exist (statins may reduce only proteinuria), longer therapy might be necessary, and it has been suggested that angiotensin-converting-enzyme inhibitors (ACEI) may limit the benefits of statins [54]. The effect could also depend on the statin dose and baseline risk of CKD [55–57].

Proteinuria is a powerful predictor of kidney function loss, and dyslipidemia may further contribute to the progression of CKD [58,59].

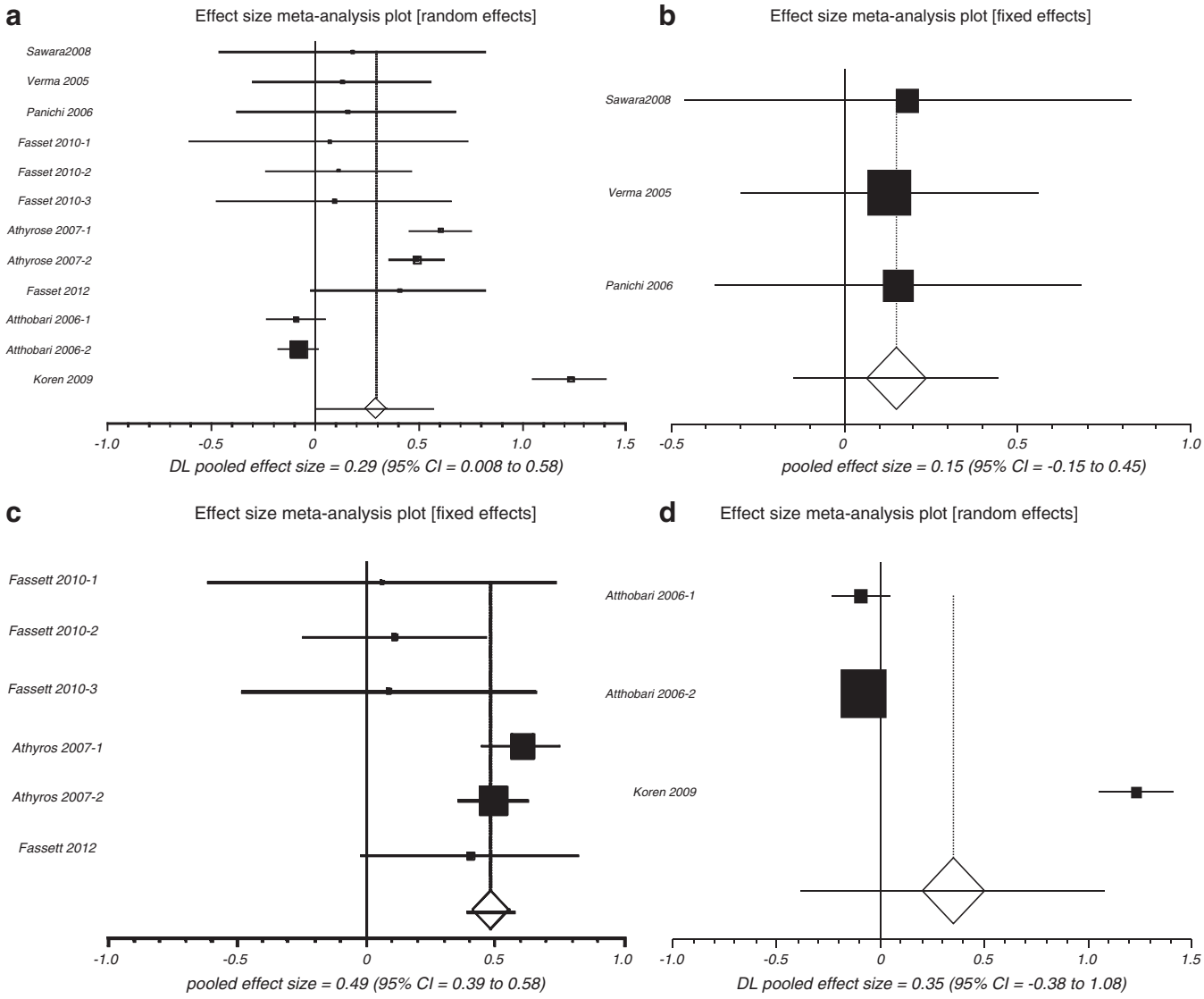

Fig. 8. Individual and pooled effect size for standardized mean for the outcome of ΔGFR (a), ΔGFR with ≤1 year of statin therapy (b), ΔGFR with >1 year and ≤3 years of statin therapy (c), ΔGFR with >3 years of statin therapy (d) in the studies considering statins compared to placebo therapy.

In accordance with our results in the meta-analysis (significant urinary protein reduction [−0.77 g/24 h, $p < 0.02$], the effect persisted also for treatment ≤12 months [−0.89 g/24 h, $p < 0.0001$]), a reduction in urinary protein excretion was shown in earlier meta-analyses and studies [18,22,42,54]. Recent studies suggest that these effects may be cholesterol-independent [18,23,60–63]. However, well-designed, large, randomized, controlled studies are needed to confirm these findings. It is still not clear why, despite significant reductions in 24 h urinary protein excretion, the statins do not influence creatinine clearance (which was also seen in our meta-analysis: 0.37 ml/min, $p = 0.18$) [60]. As already mentioned, Douglas et al. reported beneficial effects of statins in patients with proteinuria [54], while Fassett et al. failed to show this beneficial effect of statins possibly due to the use of ACEIs and ARBs in their study [30].

Reducing inflammation may prevent renal function loss [64]. This has been shown in individuals on hemodialysis [64,65]. Previous data demonstrated anti-inflammatory effects of statins in these individuals [27,51,53,66,67], while our results show significantly reduced levels of hsCRP both in dialysis and non-dialysis patients (−0.46 mg/dl, $p = 0.03$, and −0.28 mg/dl, $p < 0.05$, respectively), but not CRP. The anti-inflammatory effects of statins have been shown to be independent of statin effects on lipids, and seem to be dose-dependent [12,24,34,37,66,68,69]. Athyros et al. [33,70] suggested that improved endothelial function, renal blood flow, and the level of LDL-C reduction may be mechanisms by which statins improve renal function.

Statins may slow the decline in GFR [22,42,71,72]. Some authors reported only a modest, but favorable effect [22], while others reported significantly increased GFR with statin treatment [34]. Some RCTs and meta-analyses have also indicated a benefit of statins on eGFR [22,42], while others failed to demonstrate such an effect [21,60,73]. Our results suggest an overall significant increase of GFR after statin therapy (increase by 0.29 ml/min/1.73 m^2, $p = 0.04$), with the greatest GFR improvement after between 1 and 3 years of statin therapy (0.50 ml/min/1.73 m^2; $p < 0.0001$). Fassett et al. [30] reported a discrepancy between the eGFR and creatinine clearance; thus atorvastatin changed serum creatinine (and hence eGFR) without altering its clearance. Our meta-analysis provides similar results: statin therapy significantly influences GFR and serum creatinine (however, only after long-term therapy: −0.65 mg/dl, $p = 0.0003$). Additionally, although GFR decline was reduced during the first 2 years, at the end of the study there was no difference [30]; this is partially in accordance with our results concerning statin treatment between 1 and 3 years.

The beneficial effects of statin therapy might also be diminished by disease progression or the statin dose might be too low [30]. Dose-dependent effects, duration of treatment and improved renal blood flow are also possible relevant factors [33]. Of interest, this increase in GFR was accompanied by a decrease in serum uric acid level that could further reduce the risk for vascular events, though this is certainly controversial [33].

In a previous meta-analyses we reported the effects of statins on the lipid profile and CV endpoints (as well as all-cause mortality) especially in patients with CKD not requiring dialysis, showing a trend for greater effectiveness with longer therapy [3,7]. Similarly, a more effective trend has been confirmed on some renal parameters such as urinary protein and serum creatinine, as well as for GFR (between 1 and 3 years of therapy. However, that needs to be further investigated. Due to the lack of well-designed studies that include dialysis patients we still cannot answer the question on the renoprotective role of statins in these patients. Therefore, we cannot recommend using statins in CKD patients requiring dialysis. What is more our previous data suggests that we might predict the reverse effects of long-term statin therapy in this group of subjects [3].

One should notice that data from two recent meta-analyses [74,75] are not strictly in accordance with the findings in our meta-analysis. In Palmer et al. meta-analysis [74] the authors suggested that statins might be effective on CV outcomes especially in CKD patients without dialysis therapy, that is in line with the results of our previous meta-analysis [7]. The authors, however, did not evaluate the effect of statins on renal outcomes [74]. Upadhyay et al. meta-analysis [75] suggests that lipid-lowering therapy does not improve kidney outcomes but decreases the risk for CV events. The differences between the meta-analyses might be a result of different studies included as well as inclusion and exclusion criteria. Despite the results of these analyses there is still a question whether statin therapy might effectively prevent the progression of renal impairment. In the Study of Heart and Renal Protection (SHARP) study [76] the authors used a low dose of a statin (simvastatin 20 mg daily) and ezetimibe (10 mg daily), and despite 5-year follow-up and more than 9000 CKD patients included, reductions in renal disease progression were not shown. The decreased effect of statins on renal outcomes in CKD patients might depend on at least few factors, including the stages of CKD (the effect of statins diminishes with the renal impairment progression), and dose-dependent effects of statins (usually too low dose of statin) [3,7,30]. The results of our meta-analysis indicate that therapy duration might be important for achieving the renoprotective effects of statin therapy (*the longer the better* trend, especially for serum creatinine, creatinine clearance and GFR up to 3 years). The reduction of this effect for urine protein and GFR for the therapy $\geq$3 years requires further investigations.

The present meta-analysis has limitations. Some studies were heterogeneous. According to the carefully selected inclusion and exclusion criteria, a limited number of studies were available (especially for CKD patients on dialysis). On the other hand, a few studies directly addressed the effect of statins on renal function in CKD patients. In addition, different statins, at various doses and therapy duration were included. In some studies, patients also received concomitant therapy. Finally, duration of follow up was different (range: 8 weeks–4.5 years) and some studies had small patient populations (range: 12–477 in the statin groups).

In conclusion, our findings support potentially significant renoprotective effects of statins in CKD patients not requiring dialysis therapy. This effect might depend on the duration of statin therapy; this requires further investigation. More studies are necessary in dialysis patients to credibly evaluate the renal effects of statin therapy. Further well-designed, large, randomized controlled trials are required to provide definitive insights into the effect of statins on renal outcomes in patients with CKD.

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Declaration of interest

This meta-analysis was written independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies. No professional writer was involved in the preparation of this meta-analysis.

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