Pharmacological Research 72 (2013) 35–44

Contents lists available at SciVerse ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—A meta-analysis of 11 randomized controlled trials involving 21,295 participants

Marcin Barylski[a], Shekoufeh Nikfar[b,c], Dimitri P. Mikhailidis[d], Peter P. Toth[e], Pooneh Salari[f], Kausik K. Ray[g], Michael J. Pencina[h], Manfredi Rizzo[i,j], Jacek Rysz[k], Mohammad Abdollahi[l], Stephen J. Nicholls[m], Maciej Banach[k,*], Lipid and Blood Pressure Meta-Analysis Collaboration Group

[a] Department of Internal Medicine and Cardiological Rehabilitation, Medical University of Lodz, Poland
[b] Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Iran
[c] Food and Drug Laboratory Research Center, Ministry of Health and Medical Education, Tehran, Iran
[d] Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London (UCL), London, UK
[e] University of Illinois College of Medicine, Peoria, IL, USA
[f] Medical Ethics and History of Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran
[g] Cardiovascular Sciences Research Centre, St George's University of London, UK
[h] Department of Biostatistics, Boston University, Harvard Clinical Research Institute, Boston, MA, USA
[i] BioMedical Department of Internal Medicine and Medical Specialties, University of Palermo, Italy
[j] Euro-Mediterranean Institute of Science and Technology, Italy
[k] Department of Hypertension, Medical University of Lodz, Poland
[l] Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
[m] South Australian Health & Medical Research Institute, University of Adelaide, Australia

ARTICLE INFO

Article history:
Received 7 March 2013
Received in revised form 20 March 2013
Accepted 20 March 2013

Keywords:
Cardiovascular events
Chronic kidney disease
Dialysis
Mortality
Statins
Stroke

ABSTRACT

The available studies have reported the benefits of statins on all-cause and cardiovascular mortality in chronic kidney disease (CKD) patients. However studies in end-stage renal disease patients on dialysis yielded conflicting results. Therefore, we performed a meta-analysis and provide the most reliable trial data to date on the impact of statin therapy on cardiovascular events and death from all causes in CKD patients. Data from PubMed, Web of Science, Cochrane Library, and Scopus for the years 1966 to October 2012 were searched. The final meta-analysis included 11 randomized controlled trials involving 21,295 participants with CKD. Among them 6857 were on dialysis. The use of statins in subjects with non-dialysis-dependent CKD resulted in a marked reduction in death from all causes (relative risk [RR]: 0.66; 95% confidence interval [CI]: 0.55–0.79; $p < 0.0001$), cardiac causes (RR: 0.69; 95%CI: 0.55–0.68; $p = 0.0012$), cardiovascular events (RR: 0.55; 95%CI: 0.4–0.75; $p = 0.0001$) and stroke (RR: 0.66; 95%CI: 0.5–0.88; $p = 0.0022$). The use of statins in dialysis-dependent CKD patients resulted in a non-significant effect on death from all causes (RR: 0.99; 95%CI: 0.88–1.11; $p = 0.85$) and stroke (RR: 1.31; 95%CI: 0.9–1.89; $p > 0.05$), but had the effect of reducing death from cardiac causes (RR: 0.79; 95%CI: 0.64–0.98; $p < 0.05$) and cardiovascular events (RR: 0.81; 95%CI: 0.7–0.94; $p < 0.05$). In conclusion, the use of statins should be indicated in cardiovascular disease prevention especially in patients with non-dialysis-dependent CKD. According to the very limited data the obtained results suggest caution in expecting a reduction in cardiovascular events in patients on dialysis.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality not only among the general population, but also in patients with chronic kidney disease (CKD) [1]. Several clinical trials have demonstrated that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) are gaining widespread acceptance as a principal therapy for the primary and secondary prevention of atherosclerosis and CVD [2–4]. The role of statins in

* Corresponding author at: Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland. Tel.: +48 42 639 37 71; fax: +48 42 639 37 71.
E-mail address: maciejbanach@aol.co.uk (M. Banach).

1043-6618/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.phrs.2013.03.007

primary prevention of CVD risk in CKD patients still remains to be clarified. No large randomized clinical trials have provided evidence that statins as a primary prevention strategy reduce CVD in these patients. It has been suggested that these agents are effective and appear safe for secondary prevention of cardiovascular (CV) events in individuals with mild chronic renal insufficiency (especially stages 1–3 of CKD) [5,6].

There are potential explanations for the putative effects of statins on the rate of CV events in patients with CKD. Statins may exert their protection against kidney disease through a variety of immunomodulatory effects [3–6]. Statin therapy attenuates endothelial dysfunction, enhances renal perfusion and reduces abnormal permeability to plasma proteins [7]. In experimental models, statins have been shown to inhibit the progression of renal damage, but in humans there are only observational studies, which do not provide definite information [8].

In several animal models, the beneficial effects of statins on renal disease associated with hypertension and vascular injury have been described [8,9]. Moreover, in a rat model of glomerulonephritis statin treatment prevented macrophage glomerular infiltration and suppressed mesangial cell proliferation and mesangial matrix expansion [10]. In consideration of the anti-inflammatory effects on vascular structure, regardless of cholesterol reduction, statins have experimentally been demonstrated to attenuate tumor necrosis factor-α induced angiogenesis *in vitro* and reverse myocardial expression of inflammatory and growth factors [11]. The inhibition of inflammatory cytokine-induced vascular endothelial growth factor expression was hypothesized [11]. Some investigators postulate that the benefit of statin therapy in patients with CKD is attributable to better kidney perfusion secondary to improved endothelial and cardiac function and improved protein trafficking in the glomerulus and proximal tubular epithelium [12].

Meta-analyses and *post hoc* analyses have reported benefits of statins for all-cause and CV mortality in CKD patients [13,14]. It has been suggested that the absolute benefit of treatment with statins seems to be greater among individuals with non-dialysis-dependent CKD. Studies in end-stage renal disease (ESRD) patients on dialysis yielded conflicting results and such positive effects were not found in the 4D (*Die Deutsche Diabetes Dialyse*) (expect from the fatal stroke and cardiac events) and AURORA (*A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events*) studies [15,16]. Recently, however, the SHARP (*Study of Heart and Renal Protection*) study, despite its limitations (simvastatin + ezetimibe *vs.* placebo), showed an insignificant trend toward reducing CV events in dialysis patients [17]. Therefore, we performed a meta-analysis to evaluate the impact of statin therapy on CV events and death from all causes in patients with CKD.

2. Materials and methods

2.1. Data sources

We searched PubMed, Web of Science (ISI), Cochrane Library, and Scopus using keywords such as statins, chronic kidney disease, chronic renal failure, hemodialysis, atorvastatin, lovastatin, pravastatin, simvastatin and rosuvastatin. We limited our search to randomized clinical trials written in English. Data were collected for the years 1966 to October 2012. Studies were chosen for the meta-analysis if they met the inclusion criteria including CKD, chronic renal failure, hemodialysis, peritoneal dialysis (and not kidney transplantation) and lipid lowering monotherapy with statins. Three reviewers assessed each article independently to diminish the probability of duplication, analyzing reviews, case studies and uncontrolled trials. Studies were precluded if they were uncontrolled or their results did not consider our goals.

2.2. 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 [18]. The quality scale ranges from 0 to 5 points, with a low quality report scoring ≤ 2 and a high quality report scoring at ≥ 3.

2.3. Statistical analysis

Data from selected studies were extracted in the form of 2×2 tables by study characteristics including age and sex of patients, their disease, type of statin, dosage per day, concomitant therapy and duration of follow-up in each study.

Included studies were weighted and pooled. Data were analyzed using StatsDirect version 2.7.9 (Altrincham, UK). Relative Risk (RR) and 95% confidence intervals (95%CI) were calculated using Mantel-Haenszel, Rothman-Boice (for fixed effects) or Der Simonian-Laird (for random effects) methods. The Cochran *Q* test was used to test heterogeneity and $p < 0.05$ was considered significant. In case of heterogeneity, the random effects model was used. The funnel plot was used as a publication bias indicator.

3. Results

The electronic searches yielded 667 items: 293 from PubMed, 63 from Web of Sciences, 300 from Scopus, and 11 from the Cochrane Library. Of these, 32 trials were scrutinized in the full text, of which 21 trials were considered unsuitable while 11 trials [14–16,19–26] were included in the analysis (Fig. 1). Of these 11 studies, 8 [14–16,19,23–26] obtained a Jadad score of ≥ 3 and the others [20–22] gained a Jadad score of ≤ 2. The final meta-analysis included 21,295 subjects with CKD. Among them 14,202 were not on dialysis, 6,857 required renal replacement therapy (RRT), and 236 patients both on dialysis and not requiring RRT were not separately reported. The following statins were investigated in the meta-analysis: atorvastatin (4 trials), lovastatin (1 trial), pravastatin (3 trials), simvastatin (1 trial), and rosuvastatin (2 trials). Duration of treatment ranged between 24 weeks and 5.1 years. Patient characteristics, renal disease, statin type, dosage, and duration of treatment for each study are reported in Table 1. The impact of statin therapy on the occurrence of selected adverse events in CKD patients is reported in Table 2.

3.1. Effect of statins on death from all causes in CKD patients both on dialysis and not requiring dialysis

The summary for relative risk (RR) of death from all causes in CKD patients for 9 included trials comparing statins with placebo [14–16,19–24] was 0.86 with 95% confidence interval (CI) 0.75–0.98 ($p = 0.02$, Fig. 2a). The Cochrane *Q* test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined; thus the random effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for death from all causes in CKD patients both on dialysis and not on dialysis between statin therapy and placebo therapy was −2.38 (95%CI = −4.21 to −0.55, $p = 0.02$) and Begg–Mazumdar Kendall's test on standardized effect *vs.* variance indicated $\tau = -0.44$, $p = 0.08$ (unbiased meta-analysis).

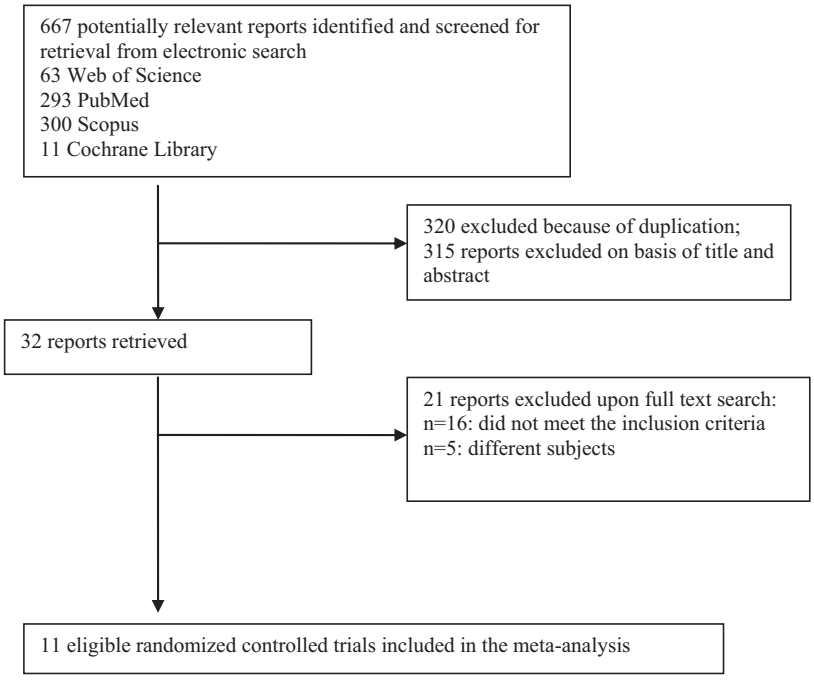

Fig. 1. Flow diagram of the study selection process.

3.2. Effect of statins on death from all causes in CKD patients who are not on dialysis

The summary for RR of death from all causes in CKD patients for 5 included trials comparing statins with placebo [14,19–22] was 0.66 with 95%CI: 0.55–0.79 ($p < 0.0001$, Fig. 2b). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.19$) and could be combined; thus the fixed effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for death from all causes in CKD patients who are not on dialysis between statin therapy and placebo therapy was −0.72 (95%CI: −5.73 to 4.29, $p = 0.68$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = -0.4$, $p = 0.23$ (unbiased meta-analysis).

3.3. Effect of statins on death from all causes in CKD patients who are on dialysis

The summary for RR of death from all causes in CKD patients for 3 included trials comparing statins with placebo [15,16,24] was 0.99 with 95%CI: 0.88–1.11 ($p = 0.85$, Fig. 2c). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous ($p = 0.003$) and could not be combined; thus the random effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for death from all causes in CKD patients who are on dialysis between statin therapy and placebo therapy could not be calculated because of too few strata.

3.4. Effect of statins on death from cardiac causes in CKD patients both on dialysis and not on dialysis

The summary for RR of death from cardiac causes in CKD patients for 7 included trials comparing statins with placebo [14,15,19,22,23,25,26] was 0.76 with 95%CI: 0.66–0.88 ($p = 0.0003$, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.25$) and could be combined; thus the fixed effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for death from cardiac causes in CKD patients both on dialysis and not on dialysis between statin therapy and placebo therapy was −0.38 (95%CI: −2.25 to 1.48, $p = 0.62$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = -0.14$, $p = 0.56$ (unbiased meta-analysis).

3.5. Effect of statins on death from cardiac causes in CKD patients who are not on dialysis

The summary for RR of death from cardiac causes in CKD patients for 4 included trials comparing statins with placebo [14,19,22,25] was 0.69 with 95%CI: 0.55–0.68 ($p = 0.0012$, Fig. 3b). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.86$) and could be combined; thus the fixed effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for death from cardiac causes in CKD patients who are not on dialysis between statin therapy and placebo therapy was −0.52 (95%CI: −1.75 to 0.71, $p = 0.21$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = -0.33$, $p = 0.33$ (unbiased meta-analysis).

3.6. Effect of statins on death from cardiac causes in CKD patients who are on dialysis

The RR of death from cardiac causes in CKD patients on dialysis for only 1 trial comparing statins with placebo [15] was 0.79 with 95%CI = 0.64–0.98 ($p < 0.05$).

3.7. Effect of statins on all cardiovascular events in CKD patients both on dialysis and not on dialysis

The summary for RR of all cardiovascular events in CKD patients for 8 included trials comparing statins with placebo [14,15,19–23,25] was 0.63 with 95%CI: 0.51–0.78 ($p < 0.0001$,

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					
Tonelli et al. [14]	78.3/21.7*	78.2/21.8	64.4 ± 6.8	64.2 ± 6.7	CKD	Pravastatin	40 mg/d	ARBs, ACEIs, BBs	58.9 months
Wanner et al. [15]	53.8/46.2	54.1/45.9	65.7 ± 8.3	65.7 ± 8.3	HD, CKD	Atorvastatin	20 mg/d	ACEIs, ARBs, CCBs, BBs, erythropoietic therapy, APLTs	3.96 year
Fellström et al. [16]	61.3/38.7	63/37	64.1 ± 8.6	64.3 ± 8.7	HD, CKD	Rosuvastatin	10 mg/d	ACEIs, ARBs, CCBs, BBs, diuretics, Vit. D, Ca, Sevelamer, erythropoietic therapy, APLTs	3.8 year
Fassett et al. [19]	62/38	68/32	60 ± 15	60.3 ± 15.2	CKD	Atorvastatin	10 mg/d	Erythropoietic therapy, ACEIs, ARBs	2.5 year
Athyros et al. [20]	80/20	80/20	59 ± 8	58 ± 7	CKD, CHD, MetS	Atorvastatin	10 mg/d	ASA, BBs, ACEIs, Diuretics, HG	3 years
Nakamura et al. [21]	–	–	–	–	CKD	Pravastatin	10–20 mg/d	–	5 years
Ridker et al. [22]	–	–	–	–	CKD	Rosuvastatin	20 mg/d	–	1.9 year
Stegmayr et al. [23]	68.57/31.42	69.86/30.1	67.8 ± 12.4	69.4 ± 10.2	CKD ± HD	Atorvastatin	10 mg/d	–	5 years
Saltissi et al. [24]	26.31/73.68	31.57/68.42	–	–	HD, CKD	Simvastatin	5 mg/d	–	24 weeks
Kendrick et al. [25]	82/18	75/15	62 ± 8	62 ± 7	CKD	Lovastatin	20 mg/d	ASA, BBs, ACEIs, Diuretics, HG, αBs	5.1 year
Nanayakkara et al. [26]	51/49	63/37	54 ± 11	52 ± 13	CKD	Pravastatin	40 mg/d	BBs, ACEIs, ARBs, αBs	2 years

* Values are presented as mean difference ± standard deviation.

Fig. 4a). The Cochrane *Q* test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined; thus the random effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for all cardiovascular events in CKD patients both on dialysis and not on dialysis between statin therapy and placebo therapy was −1.89 (95%CI: −4.79 to 1.01, $p = 0.16$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = -0.21$, $p = 0.4$ (unbiased meta-analysis).

3.8. Effect of statins on all cardiovascular events in CKD patients who are not on dialysis

The summary for RR of all cardiovascular events in CKD patients for 6 included trials comparing statins with placebo [14,19–22,25] was 0.55 with 95%CI: 0.4–0.75 ($p = 0.0001$, Fig. 4b). The Cochrane *Q* test for heterogeneity indicated that the studies were heterogeneous ($p < 0.0001$) and could not be combined; thus the random effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for all cardiovascular events in CKD patients who are not on dialysis between statin therapy and placebo therapy was −2.84 (95%CI: −6.1 to 0.41, $p = 0.07$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = -0.33$, $p = 0.27$ (unbiased meta-analysis).

3.9. Effect of statins on all cardiovascular events in CKD patients who are on dialysis

The RR of all cardiovascular events in CKD patients for only 1 trial comparing statins with placebo [15] was 0.81 with 95%CI = 0.7–0.94 ($p < 0.05$).

3.10. Effect of statins on stroke in CKD patients both on dialysis and not on dialysis

The summary for RR of stroke in CKD patients for 6 included trials comparing statins with placebo [14,15,19,21–23] was 0.83 with 95%CI: 0.67–1.04 ($p = 0.08$, Fig. 5a). The Cochrane *Q* test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.11$) and could be combined; thus the fixed effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for stroke in CKD patients both on dialysis and not on dialysis between statin therapy and placebo therapy was −1.03 (95%CI: −3.86 to 1.79, $p = 0.37$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = 0.07$, $p = 0.72$ (unbiased meta-analysis).

3.11. Effect of statins on stroke in CKD patients who are not on dialysis

The summary for RR of stroke in CKD patients for 4 included trials comparing statins with placebo [14,19,21,22] was 0.66 with 95%CI: 0.5–0.88 ($p = 0.004$, Fig. 5b). The Cochrane *Q* test for heterogeneity indicated that the studies were not heterogeneous ($p = 0.91$) and could be combined; thus the fixed effects analysis for individual and summary of RR was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for stroke in CKD patients who are not on dialysis between statin therapy and placebo therapy was −0.59 (95%CI: −2.12 to 0.94, $p = 0.24$) and Begg–Mazumdar Kendall's test on standardized effect vs. variance indicated $\tau = -0.33$, $p = 0.33$ (unbiased meta-analysis).

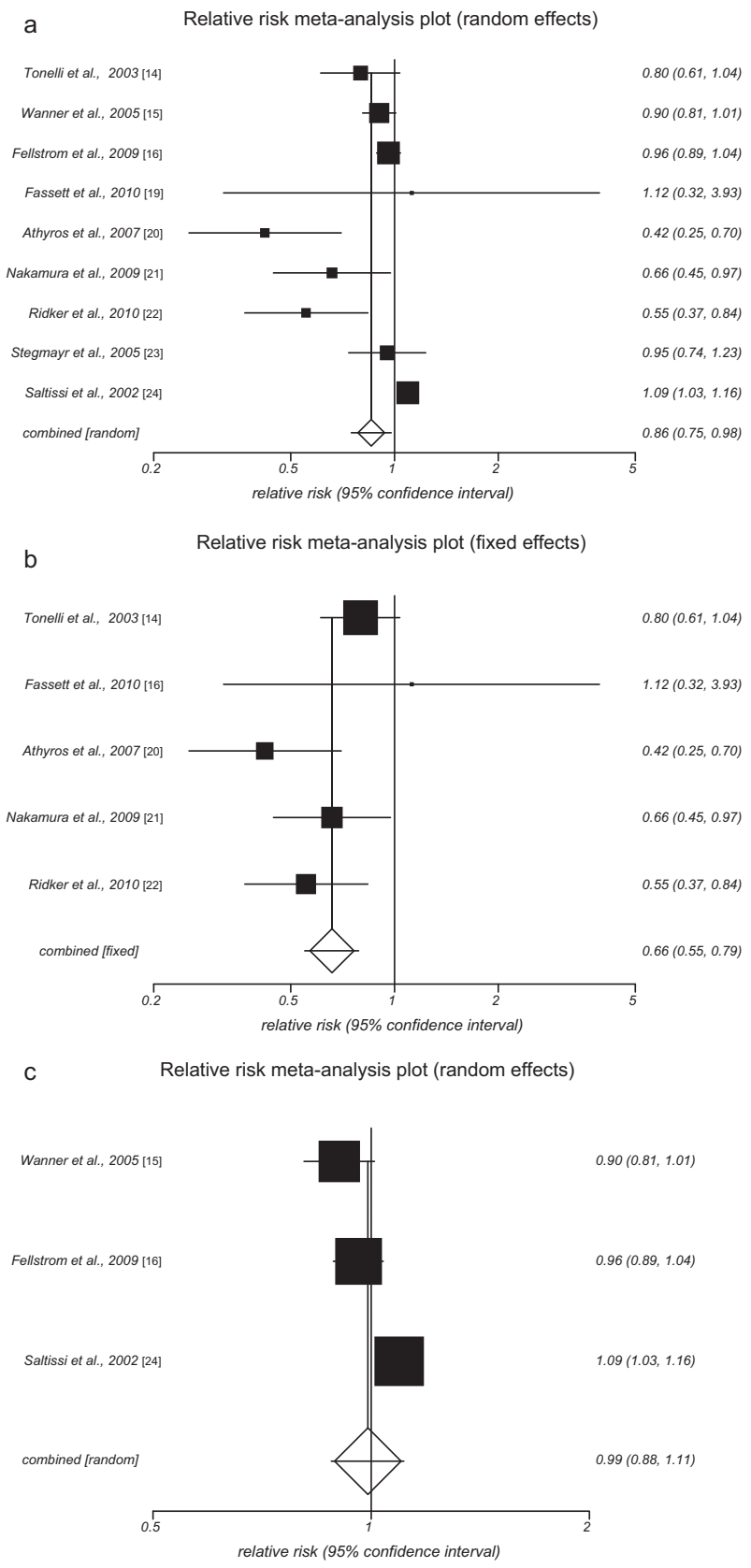

Fig. 2. Individual and pooled relative risk for the outcome of death from all causes in the studies considering statins compared to placebo therapy in CKD patients both on dialysis and not on dialysis (a) [14–16,19–24], in CKD patients who are not on dialysis (b) [14,19–22], and in CKD patients who are on dialysis (c) [15,16,24].

Table 2
The impact of statin therapy on the occurrence of selected adverse events in CKD patients.

Study	Death from all causes		Death from cardiac causes		All cardiovascular events		Stroke	
	Placebo n/N	Statins n/N	Placebo n/N	Statins n/N	Placebo n/N	Statins n/N	Placebo n/N	Statins n/N
Tonelli et al. [14]	111/868	86/844	126/868	89/844	619/844	474/844	46/868	29/844
Wanner et al. [15]	320/619	297/636	149/636)	121/619	246/636	205/619	44/636	59/619
Fellstrom et al. [16]	660/1384	636/1389	–	–	–	–	–	–
Fassett et al. [19]	4/65	4/58	2/65	1/58	7/65	4/58	2/65	0/58
Athyros et al. [20]	42/731	21/869	–	–	182/731	110/869	–	–
Nakamura et al. [21]	63/3663	40/3533	–	–	144/3663	98/3533	57/3663	37/3533
Ridker et al. [22]	61/1629	34/1638	40/1629	24/1638	76/1629	33/1638	14/1629	10/1638
Stegmayr et al. [23]	47/73	43/70	17/73	23/70	16/73	17/70	1/73	0/70
Saltissi et al. [24]	895/1592	760/1237	–	–	–	–	–	–
Kendrick et al. [25]	–	–	1/145	0/159	67/145	24/159	–	–
Nanayakkara et al. [26]	–	–	6/46	2/47	–	–	–	–

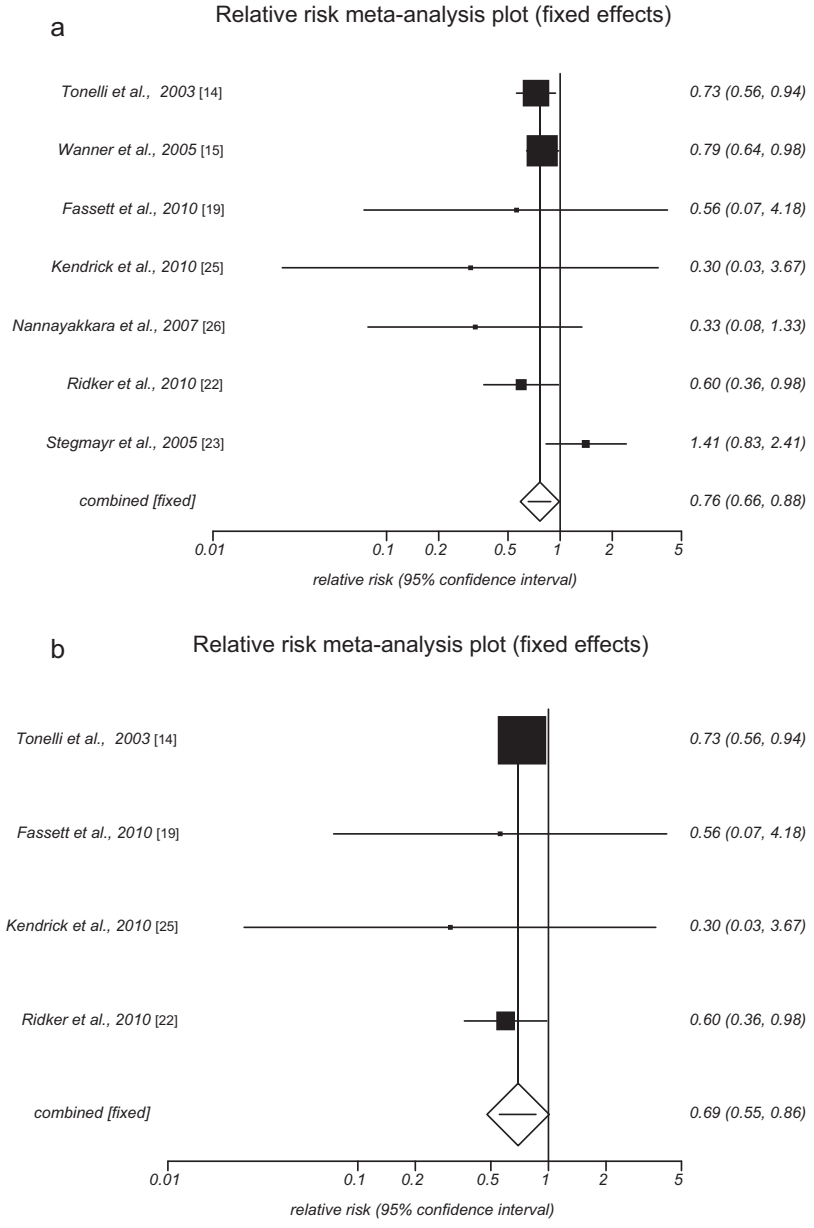

Fig. 3. Individual and pooled relative risk for the outcome of death from cardiac causes in the studies considering statins compared to placebo therapy in CKD patients both on dialysis and not on dialysis (a) [14,15,19,22,23,25,26], and in CKD patients who are not on dialysis (b) [14,19,22,25].

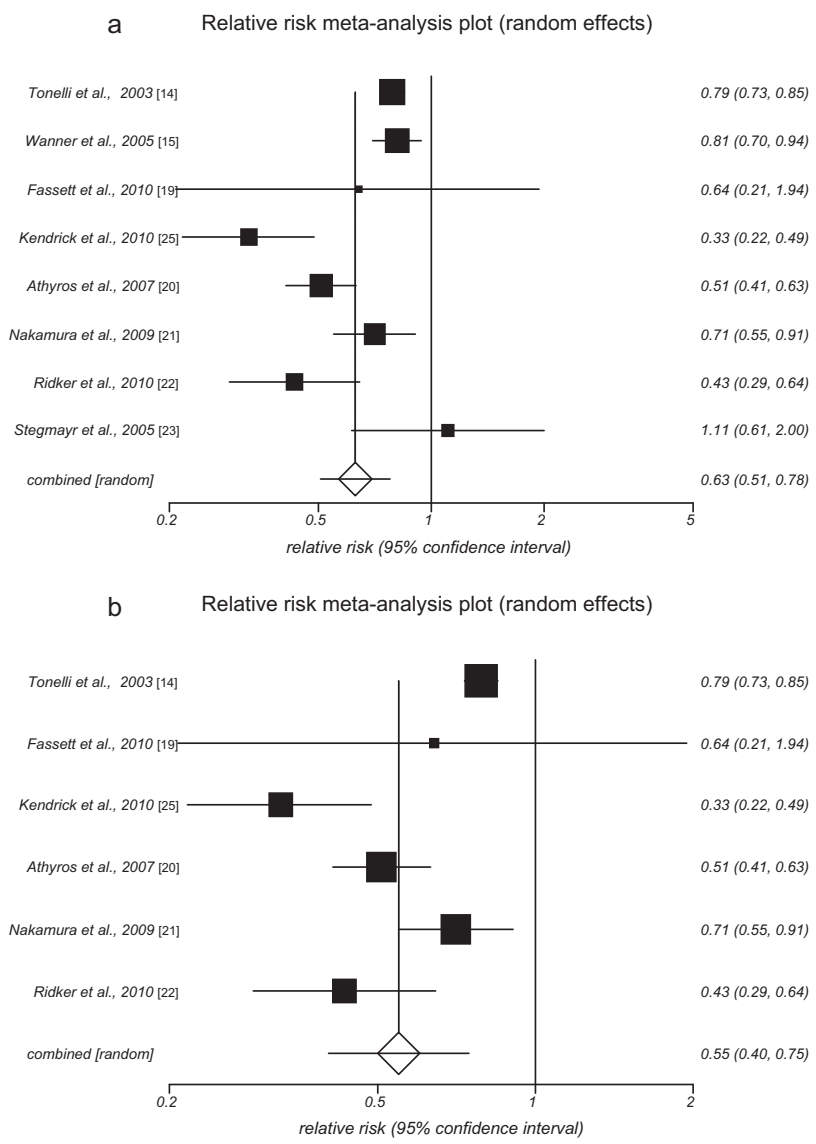

Fig. 4. Individual and pooled relative risk for the outcome of all cardiovascular events in the studies considering statins compared to placebo therapy in CKD patients both on dialysis and not on dialysis (a) [14,15,19–23,25], and in CKD patients who are not on dialysis (b) [14,19–22,25].

3.12. Effect of statins on stroke in CKD patients who are on dialysis

The relative risk of stroke in CKD patients for only 1 trial comparing statins with placebo [15] was 1.31 with 95%CI = 0.9–1.89 ($p > 0.05$).

4. Discussion

This meta-analysis is part of a group of meta-analyses assessing different aspects of the role of statins in patients with hypertension and its complications, including chronic kidney disease [5,27]. In the present study, we gathered the reliable evidence available to date including 21,295 patients with non-dialysis and dialysis-dependent CKD from 11 randomized trials assessing the specific effect of statins on cardiovascular events and death from all causes [14–16,19–26].

CKD is recognized as an important independent predictor of CVD [28]. Even patients with a mild to moderate degree of kidney function, without other CV risk factors, show an increased incidence of CV events [29]. However, to date, in patients with renal impairment (especially with ESRD requiring renal replacement therapy [RRT]), large studies specifically designed to evaluate the effect of statins on CV and renal outcomes are surprisingly not available. Most available data on the effects of statins in CKD patients are extrapolated from *post hoc* analysis of large prospective interventional trials carried out on subjects with established CV diseases, but notably, they do not specifically concern CKD patients [30–33]. All these subanalyses of patients with CKD showed the effectiveness of statin therapy in reducing CV events, comparable to that in patients without impaired renal function.

In 2009 a *post hoc* analysis of the ALLIANCE (*Aggressive Lipid Lowering Initiation Abates New Cardiac Events*) study, atorvastatin therapy, compared with usual care, reduced the relative risk of the first CV event by 28% in patients with CKD and 11% in patients without CKD [34]. The absolute benefit of treatment with a statin seems to be greater among individuals with non-dialysis-dependent CKD [35]. In a meta-analysis including 25,017 participants with CKD not requiring dialysis from 26 randomized controlled trials, statins decreased the risk of both all-cause mortality and cardiovascular events [RR 0.81 (95%CI: 0.74–0.89) and RR 0.80 (95%CI: 0.70–0.90), respectively] [36]. In a meta-analysis of Strippoli et al., including

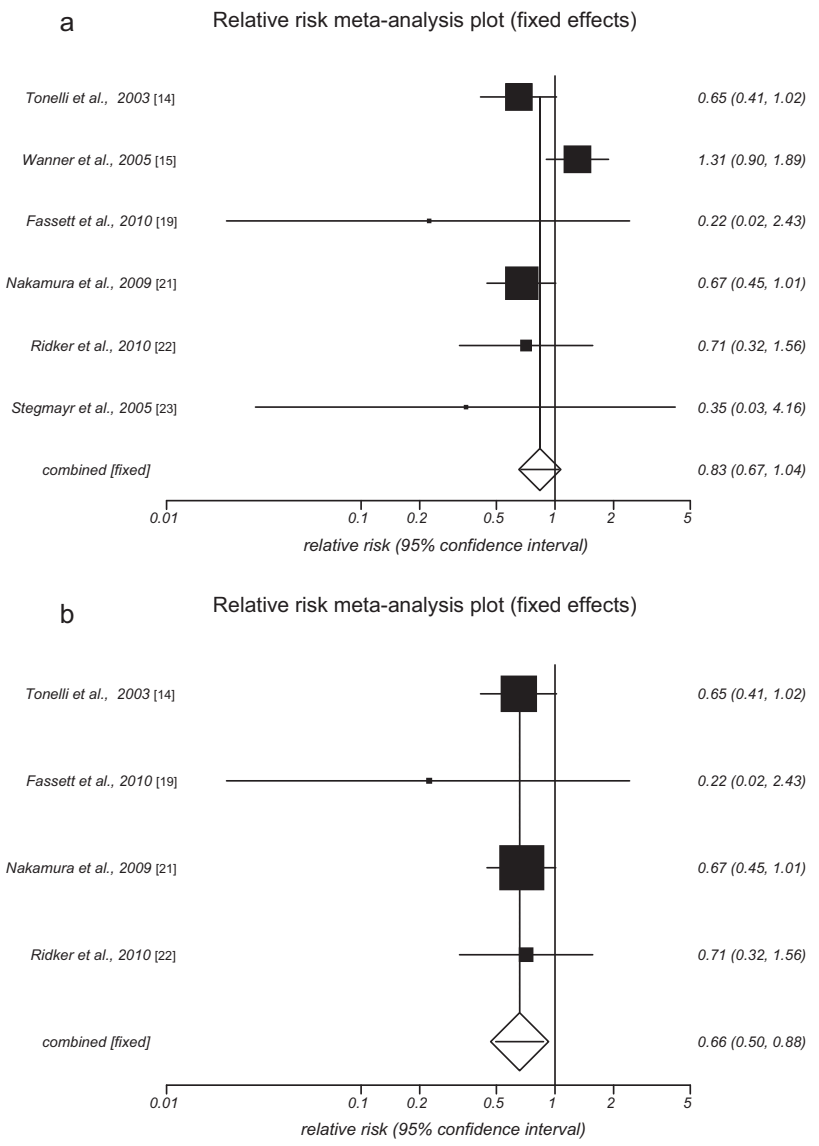

Fig. 5. Individual and pooled relative risk for the outcome of stroke in the studies considering statins compared to placebo therapy in CKD patients both on dialysis and not on dialysis (a) [14,15,19,21–23], and in CKD patients who are not on dialysis (b) [14,19,21,22].

30,144 patients with CKD (pre-dialysis, dialysis, and transplant populations), the risk of new fatal and non-fatal CV events was significantly reduced by 20% with statins [fatal cardiovascular events: RR 0.81 (95%CI: 0.73–0.90) and non-fatal cardiovascular events: RR 0.78 (95%CI: 0.73–0.84)]. Statins had no significant effect on all-cause mortality [37]. In a *post hoc* analysis from the CARDS (*Collaborative Atorvastatin Diabetes Study*) trial, which enrolled patients with type 2 diabetes but without previous history of CVD, patients with a glomerular filtration rate (GFR) from 30 to 60 ml/min/1.73 m^2 treated with atorvastatin 10 mg/day had a statistically significant reduction of new CV events after a median follow-up period of 3.9 years. A similar reduction rate was observed in patients without renal disease [38]. Several randomized controlled trials produced even more convincing findings concerning the effects of statins on CV events in patients with early stages of CKD. In a *post hoc* analysis of the CARE (*Cholesterol And Recurrent Events*) trial, involving patients with chronic renal insufficiency, the incidence of CV events was lower in participants receiving pravastatin than in those receiving placebo (HR (hazard ratio): 0.72; 95%CI: 0.55–0.95; $p = 0.02$) [14]. Pravastatin was associated with lower adjusted HR for major coronary events (HR: 0.72; 95%CI: 0.59–0.88; $p = 0.001$) and coronary revascularization (HR: 0.65; 95%CI: 0.50–0.83; $p = 0.001$), but not total mortality (HR: 0.81; 95%CI: 0.61–1.08; $p = 0.14$) or stroke (HR: 0.62; 95%CI: 0.39–1.00; $p = 0.051$) [14]. Interestingly, these results have not been confirmed in the PREVEND IT (*Prevention of Renal and Vascular Endstage Disease Intervention Trial*) study. In 864 microalbuminuric subjects treatment with pravastatin did not result in a significant reduction in cardiovascular mortality or hospitalization for cardiovascular morbidity (HR: 0.87; 95%CI: 0.49–1.57; $p = 0.649$) [39].

In our meta-analysis we confirmed the protective effect of statins on the CV system in non-dialysis-dependent CKD patients. The use of statins resulted in a marked 34% reduction in death from all causes ($p < 0.0001$), 31% reduction in death from cardiac causes ($p = 0.0012$), 45% reduction in CV events ($p = 0.0001$) and 34% reduction in stroke ($p = 0.004$). Clinical studies in ESRD patients on dialysis did not confirm these results, what was also connected to the lack of suitable data in this group of patients. In the 4D study, a multicenter, randomized, double-blind, prospective study of 1255 subjects with type 2 diabetes mellitus receiving maintenance hemodialysis randomly assigned to receive 20 mg of atorvastatin/day or matching placebo for a median follow-up

period of 4 years, atorvastatin yielded a non-significant 8% reduction in the prespecified primary outcome of CV death, nonfatal myocardial infarction and stroke [15]. It was remarked by the authors that statins permitted an 18% reduction of combined cardiac events (469 cardiac events in total during the study), but not combined with cerebrovascular events or total mortality [15]. Similarly, the AURORA study showed no benefits of statin therapy compared to placebo in CKD patients on hemodialysis [16]. During a median follow-up period of 3.8 years, 10 mg of rosuvastatin/day yielded a non-significant 4% reduction in the primary outcome of CV death, nonfatal myocardial infarction or nonfatal stroke. There was also no significant effect on all-cause mortality [16]. Our meta-analysis also indicates that in dialysis-dependent CKD patients, statins do not exert a significant effect on death from all causes ($p = 0.85$) and stroke ($p > 0.05$), but have the effect of reducing death from cardiac causes and cardiovascular events ($p < 0.05$), however these results should be treated with caution as they are based only on one available study (besides death from all causes). Recently, the SHARP (*Study of Heart and Renal Protection*) study enrolled 9270 patients with CKD, of whom 3023 patients were receiving maintenance dialysis at randomization [17]. The key outcome was major atherosclerotic events, defined as the combination of myocardial infarction, coronary death, ischemic stroke or any revascularization procedure. The final results of the study showed that after a median follow-up of 4.9 years, patients randomized to an ezetimibe/simvastatin (10/20 mg) combination experienced a 17% reduction in major atherosclerotic events compared with the placebo group (RR: 0.83; 95%CI: 0.74–0.94; $p = 0.0021$) [17,40–42]. Such positive effects were not found in the aforementioned 4D and AURORA studies.

The results of our meta-analysis and the trials mentioned above (4D and AURORA) suggest a different pathogenetic mechanism in ESRD patients for the primary outcomes compared with mild or moderate CKD [6,40–42]. The pathophysiological basis of the disease has not been completely elucidated. It has been hypothesized that CV disease in patients undergoing hemodialysis differs from that in other patients: it has been confirmed that half of deaths in hemodialysis patients were due to cardiac events not related to atherosclerosis, such as sudden death, arrhythmia, valvular disease, and importantly vascular calcifications, all conditions known not to be influenced by statin therapy [6,42]. Probably CVD in hemodialysis patients may happen in another scenario of CV risk, more and more compromised than in the general, non-renal population, so it is uncertain whether a single pharmacological agent may alter the rate of progression of this process [5,6,40,42–45].

The present meta-analysis has some inevitable limitations because of principle of meta-analysis that is dependent on type of data recruited. The studies included in this quantitative review were rather heterogeneous, because they were carried out in a variety of settings, with different methods, using various criteria and different comparator groups. We were unable to examine a possible dose-effect relationship of different statins given the relatively small number of trials and the limited sample size available. The only data that could be extracted from AURORA study to be technically included in our meta-analysis was death from all causes. Other data (death from cardiac causes, all cardiovascular events and stroke) were reported in AURORA trial, but in a way that it was not possible to accurately find numerator and denominator that is necessary for meta-analysis. Therefore, we excluded these 3 outcomes from our meta-analysis, not only for dialysis patients but for all CKD patients. We also excluded the clinical trials which were conducted on kidney transplant patients. In kidney transplant subjects the renal function can be normal or decreased. Also, the inflammatory status of the patients after transplantation and receiving specific medications, such as cyclosporine and others, is far different from patients with CKD or patients on hemodialysis. This fact can be explained by comparing pathophysiological differences between these two conditions.

In conclusion, our meta-analysis provides evidence that the use of statins should be indicated in CV prevention especially in patients with non-dialysis-dependent CKD. Available data from large randomized trials suggest caution in expecting a reduction in CV events after starting statin therapy in patients on hemodialysis; however, it seems that patients who were already on statins when starting on dialysis should be left on statins. Starting statin therapy in hemodialysis patients seems to be late, when the cardiac, cerebral, and vascular organ damage is already done. Moreover, although not proved by randomized trials, administering statins in patients on dialysis with established coronary artery disease should be suggested, as indicated in general patients at high CV risk. Finally, the current meta-analysis showed that we still need large, randomized trials in well-selected CKD patients on dialysis, in order to finally confirm or refute the limited benefits of statin therapy.

Conflict of interest statement

M.B. (Marcin Barylski), **S.N.**, **P.S.**, **J.R.**, **M.A.** have no conflict of interest. **D.P.M.** has given talks, attended conferences and participated in trials and advisory boards sponsored by MSD, Genzyme and Abbott. **P.P.T.** has given talks for AbbVie, Amarin, Astra-Zeneca, Genzyme, Kowa, Merck and is consultant for Amgen, Atherotech, Genzyme, Kowa, Liposcience, Merck. **K.K.R.** 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. **M.J.P.** is a member of DSMB for AbbVie. **M.R.** has given talks and participated in conferences sponsored by Astra-Zeneca, Bracco, Bromatech, Chiesi Farmaceutici, Novartis, Novo-Nordisk, Rikrea and Servier. **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. **M.B.** (Maciej Banach) has given talks, attended conferences and has received research support from MSD, Abbott, AstraZeneca, KRKA, Roche, Synageva, Polfarmex and Amgen.

References

[1] Banach M, Mikhailidis DP, Kjeldsen SE, Rysz J. Time for new indications for statins? Medical Science Monitor 2009;15:MS1–5.
[2] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
[3] Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. New England Journal of Medicine 1998;339:1349–57.
[4] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
[5] Nikolic D, Nikfar S, Salari P, Rizzo M, Ray KK, Pencina MJ, et al. Effects of statins on lipid profile in chronic kidney disease patients: a meta-analysis of randomized controlled trials. Current Medical Research and Opinion 2013, http://dx.doi.org/10.1185/03007995.2013.779237.
[6] Rysz J, Aronow WS, Stolarek RS, Hannam S, Mikhailidis DP, Banach M. Nephroprotective and clinical potential of statins in dialyzed patients. Expert Opinion on Therapeutic Targets 2009;13:541–50.
[7] O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation 1997;95:1126–31.
[8] Keane WF, Kasiske BL, O'Donnell MP, Kim Y. The role of altered lipid metabolism in the progression of renal disease: experimental evidence. American Journal of Kidney Diseases 1991;17(Suppl. 1):8–42.
[9] Vieira JM, Rodrigues LT, Mantovani E, Dellê H, Mattar AL, Malheiros DM, et al. Statin monotherapy attenuates renal injury in a salt-sensitive hypertension model of renal disease. Nephron Physiology 2005;101:82–91.
[10] Yoshimura A, Nemoto T, Sugenoya Y, Inui K, Watanabe S, Inoue Y, et al. Effect of simvastatin on proliferative nephritis and cell-cycle protein expression. Kidney International Supplement 1999;71:S84–7.

[11] Zhu XY, Daghini E, Chade A, Napoli C, Ritman EL, Lerman A, et al. Simvastatin prevents coronary microvascular remodelling in renovascular hypertensive pigs. Journal of the American Society of Nephrology 2007;18:1209–17.
[12] Tonelli M. Statins for slowing kidney disease progression: an as yet unproven indication. American Journal of Kidney Diseases 2008;52:391–4.
[13] Seliger SL, Weiss NS, Gillen DL, Kestenbaum B, Ball A, Sherrard DJ, et al. HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. Kidney International 2002;61:297–304.
[14] Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. Annals of Internal Medicine 2003;138:98–104.
[15] Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. New England Journal of Medicine 2005;353:238–48.
[16] Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. New England Journal of Medicine 2009;360:1395–407.
[17] Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 2011;377:2181–92.
[18] Jadad AR. Randomised controlled trials. London, UK: BMJ Books; 1998.
[19] Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Coombes JS. Effect of atorvastatin on kidney function in chronic kidney disease: a randomized double-blind placebo-controlled trial. Atherosclerosis 2010;213:218–24.
[20] Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome. a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrology, Dialysis, Transplantation 2007;22:118–27.
[21] Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y, et al. Pravastatin and cardiovascular risk in moderate chronic kidney disease. Atherosclerosis 2009;206:512–7.
[22] Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. Journal of the American College of Cardiology 2010;55:1266–73.
[23] Stegmayr BG, Brännstrom M, Bucht S, Crougneau V, Dimeny E, Ekspong A, et al. Low-dose atorvastatin in severe chronic kidney disease patients: a randomized controlled endpoint study. Scandinavian Journal of Urology and Nephrology 2005;39:489–97.
[24] Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. American Journal of Kidney Diseases 2002;39:283–90.
[25] Kendrick J, Shilpak MG, Targher G, Cook T, Lindeneld J, Chonchol M. Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study Trial. American Journal of Kidney Diseases 2010;55:42–9.
[26] Nanayakkara PWB, van Guldener C, ter Wee PM, Scheffer PG, van Ittersum FJ, Twisk JW, et al. Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on carotid intima-media thickness, endothelial function and renal function in patients with mild to moderate chronic kidney disease. Archives of Internal Medicine 2007;167:1262–70.
[27] Banach M, Nikfar S, Rahimi R, Bielecka-Dabrowa A, Pencina MJ, Mikhailidis DP, et al. The effects of statins on blood pressure in normotensive or hypertensive subjects – a meta-analysis of randomized controlled trials. International Journal of Cardiology, in press, http://dx.doi.org/10.1016/j.ijcard.2013.03.068
[28] Franczyk-Skóra B, Gluba A, Banach M, Kozłowski D, Małyszko J, Rysz J. Prevention of sudden cardiac death in patients with chronic kidney disease. BMC Nephrology 2012;13:162.
[29] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. New England Journal of Medicine 2004;351:1296–305.
[30] Tonelli M, Keech A, Shepherd J, Sacks F, Tonkin A, Packard C, et al. Effect of pravastatin in people with diabetes and chronic kidney disease. Journal of the American Society of Nephrology 2005;16:3748–54.
[31] Shepherd J, Kastelein JP, Bittner VA, Carmena R, Deedwania PC, Breazna A, et al. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clinic Proceedings 2008;83:870–9.
[32] Athyros VG, Hatzitolios AI, Karagiannis A, Savopoulos C, Katsiki N, Tziomalos K, et al. IMproving the imPlemEntation of cuRrent guidelines for the mAnagement of major coronary hearT disease rIsk factors by multifactorial interVEntion. The IMPERATIVE renal analysis. Archives of Medical Science 2011;7:984–92.
[33] Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. American Journal of Kidney Diseases 2007;49:373–82.
[34] Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP. Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. American Journal of Kidney Diseases 2009;53:741–50.
[35] Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110:1557–63.
[36] Navaneethan SD, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database of Systematic Reviews 2009;2:CD007784.
[37] Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ 2008;22:645–51.
[38] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). American Journal of Kidney Diseases 2009;54:810–9.
[39] Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110:2809–16.
[40] Barylski M, Małyszko J, Rysz J, Myśliwiec M, Banach M. Lipids, blood pressure, kidney – what was new in 2011? Archives of Medical Science 2011;7:1055–66.
[41] Banach M, Hering D, Narkiewicz K, Mysliwiec M, Rysz J, Malyszko J. Lipids, blood pressure, kidney – what was new in 2012? International Journal of Pharmacology 2012;8:659–78.
[42] Gluba A, Rysz J, Banach M. Statins in patients with chronic kidney disease: why, who and when? Expert Opinion on Pharmacotherapy 2010;11:2665–74.
[43] Cicero AFG, Reggi A, Parini A, Borghi C. Application of polyunsaturated fatty acids in internal medicine: beyond the established cardiovascular effects. Archives of Medical Science 2012;8:784–93.
[44] Poli A, Casula M, Tragni E, Brignoli O, Filippi A, Cricelli C, et al. Reaching LDL-c targets in high-risk patients requires high-efficacy cholesterol-lowering drugs in more than 50% of cases. The results of the CHECK study. Pharmacological Research 2011;64:393–6.
[45] Wanner C, Krane V. Uremia-specific alterations in lipid metabolism. Blood Purification 2002;20:451–3.