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The effect of statins on all-cause and cardiovascular mortality in patients with non-dialysis chronic kidney disease, patients on dialysis, and kidney transplanted recipients: an umbrella review of meta-analyses

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Abstract. – OBJECTIVE: Although some previous meta-analyses have demonstrated a relationship between statin therapy and all-cause mortality in patients with chronic kidney disease (CKD), conflicting results have been reported. Thus, we performed an umbrella review to understand the strength of evidence and validity of the claimed associations between statin use and all cause and cardiovascular mortality in CKD patients, including patients on dialysis (CKD stage 5D) and transplant recipients.

MATERIALS AND METHODS: We comprehensively re-analyzed the data of 14 meta-analyses of observational studies and randomized controlled trials on associations between statin use and different CKD groups – CKD, CKD stage 5D, and kidney transplant recipients. We also assessed the strength of evidence of the re-analyzed outcomes, which were determined from the criteria, including the statistical significance of the *p*-value of random-effects, as well as fixed-effects meta-analyses, small-study effects, between-study heterogeneity, and a 95% prediction interval.

RESULTS: For CKD patients, statin use showed suggestive evidence for an association with reduced all-cause mortality [relative risk (RR) 0.77, 95% confidence interval (0.69-0.87)]. For kidney transplant recipients, statin use showed suggestive evidence for an association with reduced cardiovascular mortality [RR 0.67, 95% CI (0.50-0.90)]. However, for patients on dialysis, statins showed neither cardiovascular [RR 0.93, 95% CI (0.86-1.01)] nor all-cause mortality [RR 0.98, 95% CI (0.89-1.08)] benefits.

CONCLUSIONS: Our finding indicates that statin could improve all-cause and cardiovascular mortality in patients with non-dialysis CKD.

Key Words:
CKD, Mortality, Statin, Umbrella review.

Introduction

Chronic kidney disease (CKD) affects up to 16% of the world's population[1]. It is often associated with debilitating morbidity and mortality, including but not limited to leading non-com-

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municable diseases, such as cardiovascular diseases and kidney failure. CKD contributes to the dreadful economic burden: its ever-increasing incidence, the economic burden it creates on society, and the financial strain it puts on healthcare systems have led CKD to be recognized as one of the most crucial public health emergencies of the 21st century[2,3]. Globally, it represents the 16th leading disease cause of the most years-of-life-lost and was responsible for a 33.7% increase in all-age deaths between 2007 and 2017[1,4]. CKD is defined as an alteration in either the renal structure, function, or both for a period of at least three months with implications on the person's health. This alteration usually leads to a fall in the glomerular filtration rate, below 60 mL/min/1.73 m^2, or albuminuria of more than 30 mg per day[5]. The causes of CKD are often diverse, but obesity, hypertension, and/or diabetes mellitus are major risk factors for both cardiovascular disease and CKD[6].

With the aging of the global population and the projected increase in the incidence of non-communicable diseases, such as obesity and diabetes, the prevalence of CKD is expected to increase even further[7-9]. The mortality rate among CKD patients is estimated to be 1.4 to 3.7-fold that in patients without CKD[10].

Statins are a group of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase used in preventing coronary heart disease by lowering plasma cholesterol[11]. Statin-based regimens have long been considered a component of the mainstay treatment for CKD patients. Most meta-analyses and post-hoc analyses have reported a benefit in using statin in decreasing all-cause mortality among people living with CKD[12-14]. However, recent prospective studies on statins challenged this anticipated beneficial effect on mortality among CKD patients[10].

To determine and assess the strength of the evidence of the effect of statins on the reduction of mortality in patients with CKD, we carried out an umbrella review and comprehensively re-analyzed the data of meta-analyses of randomized controlled trials (RCTs) and observational studies.

Materials and Methods

We conducted an umbrella review of meta-analyses and systematic reviews studying the effects and associations between statin use and the all-cause mortality in patients with CKD across the different stages of the disease. We performed this umbrella review per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search

We performed our search using the following keywords: '(hydroxymethyl glutaryl-coa reductase inhibitor OR statin) AND (mortality OR chronic kidney disease) AND (meta-analysis OR systematic review)'. We limited our search to articles written in English. We performed the search in January 2020. We sought for meta-analyses of either RCTs or observational studies in our search strategy. Each retrieved article was reviewed in detail, from the title, through the abstract, to the full texts. Subsequently, we used inclusion and exclusion criteria in the decision to include the articles or not. We also conducted a supplementary EMBASE database search for completion. Eligible meta-analyses that did not overlap with the PubMed search were included.

Eligibility Criteria and Data Extraction

Meta-analyses and systematic reviews of both RCTs and observational studies (cohort and case-control studies) investigating the association between statin use and mortality rates of CKD patients were included. We added articles containing multiple meta-analyses and independently assessed each separate meta-analysis for inclusion. Review articles, *in-vitro* studies, and genetic studies were excluded.

Two of our investigators (G.H.J. and J.I.S) individually performed data search and extraction. Discrepancies were resolved *via* consensus. We gathered information regarding the articles' first author, year of publication, CKD stages, study design, number of included studies, mortality rates, total number of participants, and the random-effects with a 95% confidence interval (CI). We analyzed the raw data of each study considering all data on mortality rates of CKD patients, statins use, and study design. We reported the results of articles containing both RCTs and observational studies separately.

Statistical Analysis

We analyzed each meta-analysis that satisfied the inclusion criteria and reported the association between statin use and mortality among CKD

patients. In the case of overlapping meta-analyses, we combined the individuals according to mortality, CKD, and study design. In this case, we conducted a re-meta-analysis after eliminating overlapping studies. The summary effect size was reported with a 95% CI and *p*-value with both random-effects and fixed-effects. All re-analyses in this study were performed using the Comprehensive Meta-Analysis software ver.3.3.070 (Borenstein, NH, USA).

Estimation of Summary Effects and Estimation of Prediction Interval

All individual studies were re-examined for each meta-analysis. We assessed the summary effects and 95% CI using both random- and fixed-effects methods. We also reported the 95% prediction interval (PI), which tackles the dispersion of effects and additionally takes into account the in-between-study heterogeneity. Our CI reflected the accuracy of the mean.

Evaluation of Between-Study Heterogeneity and Small-Study Effects

We used the I^2 metric of inconsistency and the *p*-value of the X^2-based Cochrane Q test to assess heterogeneity across the studies. I^2 values of <50% (low), 50%-75% (moderate), and >75% (high) were used to describe heterogeneity. Egger's regression test was used to interpret the publication biases. Small-study effects were used for detecting publication and reporting bias. We considered an article to have a small-study when Egger's test had a *p*-value < 0.10 in random-effects meta-analyses.

Determination of the Level of Evidence

The level of the evidence of the association between statin use and mortality among CKD patients was determined for each meta-analysis and re-analyzed based on the pooled meta-analysis. The criteria were based on several factors, including: the statistical significance by random and fixed-effects *p*-values, 95% PI, small-study effects, between-study heterogeneity, and concordance between the effect estimate of the most extensive study and a summary estimate of the meta-analysis.

The Criteria Were Stratified as Follows:

Convincing evidence: (1) Statistical significance for the random effect and fixed effect *p*-values at $p < 0.001$, (2) no small-study effects or large between-study heterogeneity, (3) the 95% PI rejected the null hypothesis, (4) concordance between the effect estimate of the largest study and the summary effect of the random effects meta-analysis.

Suggestive evidence: (1) Statistical significance of random effects at $p < 0.05$, (2) the 95% PI included the null hypothesis, (3) no small-study effects or large between-study heterogeneity.

Weak evidence: (1) Statistical significance of random effects at $p < 0.05$, (2) small-study effects, or large between-study heterogeneity found.

Non-significant association: there was no statistical significance by random effect meta-analysis ($p > 0.05$).

When significant heterogeneities were encountered, the results were reassessed to resolve whether heterogeneities were secondary to differences in the direction of the effect or if it could be due to differences in the size of the association (level of evidence recalculated in the latter case).

Results

Search Strategy and Selected Studies for Reanalysis

136 potentially eligible articles were retrieved by the literature search. After that, a stepwise screening was performed. Forty-eight articles were excluded (35 were duplicates and 13 were not meta-analysis) after assessing the titles, and forty-four articles were screened by the abstracts (23 were not investigating statin therapy, 7 were not including kidney disease patients, and 1 was high intensity statin therapy). Finally, after reviewing another 57 full-text articles for eligibility, 43 were excluded because they did not have a mortality outcome. The eligible 14 articles describing the associations or relationships between statin use and mortality or survival of CKD patients were finally included[15-28].

The outcomes evaluated in the meta-analyses included all-cause mortality and cardiovascular mortality of CKD patients (defined as 'not on dialysis'), CKD 5D (defined as 'on dialysis'), and of kidney transplant recipients (Tables I-VI). Eight (57%) of the 14 meta-analyses examined all-cause mortality, five (36%) examined cardiovascular mortality in CKD patients not receiving dialysis, seven (50%) studied all-cause mortality,

Table I. Effects of statin therapy in CKD patients (all-cause mortality).

Author/ year	N	T	Type of patients	N/T	T/M	Model*	Effect size*	Random effect§	Fixed effect§	D/N/I	Egger's *p*-value	I^2 (*p*-value)	*p*-value (R)	*p*-value (F)	95% PI	S	Evidence
Messow, et al 2017	6	RCT	CKD	7601/ 15288	HR	Mixed	0.82 (0.73-0.91)	0.80 (0.68-0.93)	0.82 (0.73-0.91)	2/4/0	0.142	30.7 (0.205)	0.004	<0.001	0.55-1.14	No	Suggestive
Zhang, et al 2016	11	RCT	CKD	16160/ 32557	RR	Fixed	0.78 (0.72-0.84)	0.65 (0.50-0.84)	0.75 (0.69-0.81)	4/7/0	0.183	71.0 (< 0.001)	0.001	< 0.001	0.31-1.35	No	Weak
Zhang, et al 2014	7	RCT	Mild to moderate CKD	16722/ 33589	RR	Random	0.79 (0.72-0.86)	0.79 (0.72-0.86)	0.79 (0.73-0.85)	4/3/0	0.252	6.3 (0.380)	< 0.001	< 0.001	0.68-0.90	No	Convincing
Palmer, et al 2014	10	RCT	CKD not on dialysis	14063/ 28276	RR	Random	0.79 (0.69-0.91)	0.79 (0.69-0.91)	0.81 (0.75-0.87)	4/6/0	0.294	31.7 (0.155)	0.001	< 0.001	0.58-1.06	No	Suggestive
Barylski, et al 2013	9	RCT	CKD not on dialysis	10274/ 20898	RR	Random	0.86 (0.75-0.98)	0.86 (0.75-0.98)	0.99 (0.95 1.26	3/5/1	0.009	78.9 (< 0.001)	0.023	0.701	0.59--1.04)	Yes	Weak
Barylski, et al 2013	5	RCT	CKD not on dialysis	6942/ 13898	RR	Fixed	0.66 (0.55-0.79)	0.64 (0.50-0.82)	0.67 (0.56-1.23	3/2/0	0.338	35.1 (0.187)	< 0.001	< 0.001	0.33-0.80)	No	Suggestive
Navaneethan, et al 2009	5	RCT	CKD not on dialysis	9340/ 18762	RR	Random	0.81 (0.74 0.89)	0.81 (0.74-0.89)	0.81 (0.74-0.89)	1/4/0	0.391	0.0 (0.774)	< 0.001	< 0.001	0.70-0.93	No	Convincing
Strippoli, et al 2008	5	RCT	Pre-dialysis CKD	9049/ 18176	RR	Random	0.81 (0.74 0.89)	0.81 (0.74-0.89)	0.81 (0.74-0.89)	1/4/0	0.391	0.0 (0.774)	< 0.001	< 0.001	0.70-0.93	No	Convincing
Combined Analysis	15	RCT	CKD not on dialysis	–	RR	–	–	0.77 (0.69-0.87)	0.80 (0.75-0.86)	6/9/0	0.202	36.3 (0.079)	<0 .001	< 0.001	0.58-1.02	No	Suggestive

CKD, chronic kidney disease; D/N/I, decreasing risk/No difference/Increasing risk; F, fixed effect; HR, hazard ratio; N, number of studies; N/T, number of intervention/total; PI, prediction intervals; R, random effect; RCT, randomized controlled study; RR, risk ratio; S, small-study effect; T, type of studies; T/M, Type of metrics; *Value reported in the original article of the meta-analysis; §Value obtained from re-analysis of the original meta-analysis.

Table II. Effects of statin therapy in CKD patients (cardiovascular mortality).

Author/ year	N	T	Type of patients	N/T	T/M	Model*	Effect size*	Random effect§	Fixed effect§	D/N/I	Egger's *p*-value	I^2 (*p*-value)	*p*-value (R)	*p*-value (F)	95% PI	S	Evidence
Zhang, et al 2014	6	RCT	Mild to moderate CKD	9437/ 18974	RR	Random	0.83 (0.73-0.93)	0.83 (0.73-0.93)	0.83 (0.73-0.93)	1/5/0	0.170	0.0 (0.917)	0.002	0.002	0.69-0.98	No	Convincing
Palmer, et al 2014	6	RCT	CKD not on dialysis	9480/ 19059	RR	Random	0.77 (0.69-0.87)	0.77 (0.69-0.87)	0.77 (0.69-0.87)	1/5/0	0.096	0.0 (0.919)	<0.001	<0.001	0.65-0.92	No	Convincing
Barylski, et al 2013	4	RCT	CKD not on dialysis	2699/ 5406	RR	Fixed	0.69 (0.55-0.86)	0.69 (0.55-0.87)	0.69 (0.55-0.87)	2/2/0	0.104	0.0 (0.859)	0.001	0.001	0.42-1.13	No	Suggestive
Navaneethan, et al 2009	4	RCT	CKD not on dialysis	9334/ 18746	RR	Random	0.80 (0.70-0.90)	0.80 (0.70-0.90)	0.80 (0.70-0.90)	1/3/0	0.435	0.0 (0.810)	< 0.001	< 0.001	0.61-1.05	No	Suggestive
Strippoli, et al 2008	4	RCT	Pre-dialysis CKD	9001/ 18085	RR	Random	0.80 (0.70-0.90)	0.84 (0.74-0.94)	0.84 (0.74-0.94)	1/3/0	0.389	0.0 (0.815)	0.004	0.004	0.34-0.58	No	Convincing
Combined Analysis	10	RCT	CKD not on dialysis	-	RR	-	-	0.80 (0.72-0.88)	0.80 (0.72-0.88)	3/7/0	0.036	0.0 (0.910)	<0.001	<0.001	0.70-0.90	Yes	Weak

CKD, chronic kidney disease; D/N/I, decreasing risk/No difference/Increasing risk; F, fixed effect; N, number of studies; N/T, number of intervention/total; PI, prediction intervals; R, random effect; RCT, randomized controlled study; RR, risk ratio; S, small-study effect; T, type of studies; T/M, Type of metrics; *Value reported in the original article of the meta-analysis; §Value obtained from re-analysis of the original meta-analysis.

Table III. Effects of statin therapy in CKD 5D patients (all-cause mortality).

Author/ year	N	T	Type of patients	N/T	T/M	Model*	Effect size*	Random effect§	Fixed effect§	D/N/I	Egger's *p*-value	I^2 (*p*-value)	*p*-value (R)	*p*-value (F)	95% PI	S	Evidence
Messow, et al 2017	2	RCT	CKD and dialysis	2008/ 4028	HR	Mixed	0.95 (0.87-1.04)	0.95 (0.87-1.04)	0.95 (0.87-1.04)	0/2/0	NA	0.0 (0.744)	0.262	0.262	NA	NA	No evidence
Yang, et al 2015	5	RCT, OS	Diabetic dialysis	6454/ 13081	HR	Random	0.81 (0.71-0.92)	0.81 (0.71-0.92)	0.83 (0.78-0.88)	3/2/0	0.183	54.7 (0.065)	0.002	<0.001	0.56-1.18	No	Weak
Sun, et al 2015	3	RCT	Dialysis	3541/ 7051	RR	Fixed	0.98 (0.93-1.04)	0.98 (0.93-1.03)	0.98 (0.93-1.03)	0/3/0	0.404	0.0 (0.533)	0.410	0.410	0.65-1.46	No	No evidence
Palmer, et al 2013	7	RCT	Dialysis	2352/ 4705	RR	Random	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0/7/0	0.182	0.0 (0.869)	0.184	0.184	0.88-1.04	No	No evidence
Barylski, et al 2013	3	RCT	CKD and dialysis	3262/ 6857	RR	Random	0.99 (0.88-1.11)	0.99 (0.88-1.11)	1.02 (0.97-1.06)	0/2/1	0.123	82.5 (0.003)	0.848	0.442	0.26-3.75	No	Weak
Navaneethan, et al 2009	5	RCT	Dialysis	928/ 1884	RR	Random	0.95 (0.86-1.06)	0.95 0.86-(1.06)	0.95 (0.86-1.06)	0/5/0	0.303	0.0 (0.652)	0.349	0.349	0.80-1.13	No	No evidence
Strippoli, et al 2008	3	RCT	CKD and dialysis	696/ 1404	RR	Random	0.95 (0.85-1.06)	0.95 (0.85-1.06)	0.95 (0.85-1.06)	0/3/0	0.046	0.0 (0.440)	0.372	0.372	0.47-1.91	Yes	No evidence
Combined Analysis	16	Combined	Dialysis	–	RR	–	–	0.93 (0.86-1.01)	0.96 (0.93-0.99)	3/12/1	0.135	70.1 (<0.001)	0.072	0.021	0.73-1.19	No	No evidence

CKD, chronic kidney disease; D/N/I, decreasing risk/No difference/Increasing risk; F, fixed effect; HR, hazard ratio; N, number of studies; NA, not applicable; N/T, number of intervention/ total; OS; observational study; PI, prediction intervals; R, random effect; RCT, randomized controlled study; RR, risk ratio; S, small-study effect; T, type of studies; T/M, Type of metrics; *Value reported in the original article of the meta-analysis; §Value obtained from re-analysis of the original meta-analysis.

Table IV. Effects of statin therapy in CKD 5D patients (cardiovascular mortality).

Author/ year	N	T	Type of patients	N/T	T/M	Model*	Effect size*	Random effect§	Fixed effect§	D/N/I	Egger's *p*-value	I^2 (*p*-value)	*p*-value (R)	*p*-value (F)	95% PI	S	Evidence
Messow, et al 2017	2	RCT	CKD and dialysis	2008/ 4028	HR	Mixed	0.92 (0.75-1.13)	0.92 (0.75-1.13)	0.94 (0.82-1.07)	0/2/0	NA	52.6 (0.146)	0.409	0.342	NA	NA	No evidence
Sun, et al 2015	3	RCT	Dialysis	3541/ 7051	RR	Fixed	0.97 (0.88-1.07)	0.97 (0.86-1.08)	0.97 (0.88-1.07)	0/3/0	0.343	20.3 (0.285)	0.538	0.523	0.39-2.37	No	No evidence
Palmer,	6	RCT	Dialysis	2315/ 4627	RR	Random	0.94 (0.84-1.06)	0.94 (0.84-1.06)	0.94 (0.84-1.06)	0/6/0	0.075	0.0 (0.654)	0.312	0.312	0.81-1.10	No	No evidence
Navaneethan, et al 2009	4	RCT	Dialysis	906/ 1839	RR	Random	0.96 (0.65-1.40)	0.96 (0.65-1.40)	0.89 (0.73-1.08)	0/4/0	0.460	27.1 (0.249)	0.817	0.242	0.28-3.30	No	No evidence
Strippoli, et al 2008	3	RCT	CKD and dialysis	696/ 1404	RR	Random	0.83 (0.67-1.02)	0.83 (0.67-1.02)	0.83 (0.67-1.02)	0/3/0	0.027	0.0 (0.672)	0.078	0.078	0.21-3.33	Yes	No evidence
Combined Analysis	8	RCT	Dialysis	–	RR	–	–	0.98 (0.89-1.08)	0.98 (0.89-1.08)	0/8/0	0.259	0.0 (0.559)	0.644	9,644	0.88-1.09	No	No evidence

CKD, chronic kidney disease; D/N/I, Decreasing risk/No difference/Increasing risk; F, fixed effect; HR, hazard ratio; N, number of studies; NA, not applicable; N/T, number of intervention/ total; PI, prediction intervals; R, random effect; RCT, randomized controlled study; RR, risk ratio; S, small-study effect; T, type of studies; T/M, Type of metrics; *Value reported in original article of the meta-analysis; §Value obtained from re-analysis of original meta-analysis.

Table V. Effects of statin therapy among kidney transplant recipients (all-cause mortality).

Author/ year	N	T	Type of patients	N/T	T/M	Model*	Effect size*	Random effect§	Fixed effect§	D/N/I	Egger's *p*-value	I^2 (*p*-value)	*p*-value (R)	*p*-value (F)	95% PI	S	Evidence
Rostami, et al 2017	5	RCT, OS	Kidney transplant recipient	6973/ 13916	HR	Random	0.75 (0.63-0.88)	0.76 (0.64-0.89)	0.78 (0.69-0.87)	4/2/0	0.033	48.3 (0.085)	0.001	< 0.001	0.48-1.18	Yes	Weak
Palmer, et al 2014	6	RCT	Kidney transplant recipients	1382/ 2760	RR	Random	1.08 (0.63-1.83)	1.08 (0.63-1.84)	1.05 (0.80-1.30)	0/6/0	0.475	9.0 (0.359)	0.783	0.680	0.36-3.22	No	No evidence
Navaneethan, et al 2009	4	RCT	Kidney transplant recipients	1542/ 3045	RR	Random	1.30 (0.54-3.12)	1.30 (0.54-3.11)	1.06 (0.85-1.31)	0/4/0	0.313	31.2 (0.225)	0.558	0.609	0.06-26.88	No	No evidence
Strippoli,	4	RCT	Kidney transplant recipients	1309/ 2619	RR	Random	1.30 (0.54-3.12)	1.30 (0.54-3.11)	1.06 (0.85-1.31)	0/4/0	0.313	31.2 (0.225)	0.558	0.609	0.06-26.88	No	No evidence
Combined Analysis	14	Combined	Kidney transplant recipients	–	RR	–	–	0.84 (0.72-0.98)	0.86 (0.79-0.94)	4/10/0	0.392	50.7 (0.015)	0.03	0.001	0.54-1.30	No	Weak

D/N/I, decreasing risk/No difference/Increasing risk; F, fixed effect; HR, hazard ratio; N, number of studies; NA, not applicable; N/T, number of intervention/total; OS; observational study; PI, prediction intervals; R, random effect; RCT, randomized controlled study; RR, risk ratio; S, small-study effect; T, type of studies; T/M, Type of metrics; *Value reported in the original article of the meta-analysis; §Value obtained from re-analysis of the original meta-analysis.

Table VI. Effects of statin therapy among kidney transplant recipients (cardiovascular mortality).

Author/ year	N	T	Type of patients	N/T	T/M	Model*	Effect size*	Random effect§	Fixed effect§	D/N/I	Egger's *p*-value	I^2 (*p*-value)	*p*-value (R)	*p*-value (F)	95% PI	S	Evidence
Palmer, et al 2014	4	RCT	Kidney transplant recipients	1161/ 2322	RR	Random	0.68 (0.45-	0.68 (0.45- 1.01)	0.68 (0.45- 1.01)	0/4/0 1.01)	0.421	0.0 (0.559)	0.057	0.057	0.28- 1.63	No	No evidence
Navaneethan, et al 2009	3	RCT	Kidney transplant recipients	1360/ 2681	RR	Random	0.68 (0.46-	0.69 (0.46- 1.03)	0.69 (0.46- 1.03)	0/3/0 1.03)	0.356	0.0 (0.395)	0.067	0.067	0.05- 9.54	No	No evidence
Strippoli, et al 2008	3	RCT	Kidney transplant recipients	1127/ 2255	RR	Random	0.68 (0.46-	0.69 (0.46- 1.03)	0.69 (0.46- 1.03)	0/3/0 1.03)	0.356	0.0 (0.395)	0.067	0.067	0.05- 9.54	No	No evidence
Combined Analysis	5	RCT	Kidney transplant recipients	–	RR	–	–	0.67 (0.50- 0.90)	0.67 (0.50- 0.90)	0/5/0	0.398	0.0 (0.723)	0.007	0.007	0.42- 1.08	No	Suggestive

D/N/I, decreasing risk/No difference/Increasing risk; F, fixed effect; N, number of studies; NA, not applicable; N/T, number of intervention/total; OS; observational study; PI, prediction intervals; R, random effect; RCT, randomized controlled study; RR, risk ratio; S, small-study effect; T, type of studies; T/M, Type of metrics; *Value reported in original article of the meta-analysis; §Value obtained from re-analysis of original meta-analysis.

and five (36%) studied cardiovascular mortality in CKD%D patients. Also, the number of meta-analyses that examined the effect of statin therapy on all-cause mortality was four (29%) and cardiovascular mortality was three (21%) in kidney-transplant recipients.

The Effect of Statin on Mortality and of CKD Patients

The individual meta-analysis and pooled meta-analysis results of the association between statin use and mortality among CKD patients are summarized in Table I, II, Figure 1, and Figure 2. All meta-analyses revealed the beneficial effects of statins with convincing evidence in three meta-analyses, suggestive evidence in three meta-analyses, and weak evidence in two meta-analyses due to moderate-to-high heterogeneity and small-study effects. In the overall pooled analysis (n = 8), there was suggestive evidence of statin use on all-cause mortality of non-dialysis CKD patients (Table I and Figure 1).

When we assessed cardiovascular mortality, there were three meta-analyses with convincing evidence, and two with suggestive evidence in favor of the benefit of statins. However, the pooled meta-analysis of five articles resulted in weak evidence for the use of statins in preventing cardiovascular mortality in patients with CKD not on dialysis due to small-study effects (Table II and Figure 2).

The Effect of Statin on Mortality of CKD Patients on Dialysis

The individual meta-analysis and pooled meta-analysis results of the association between statin use and mortality among CKD 5D patients are summarized in Table III, IV, Figure 3, and Figure 4. When all-cause mortality was measured as an outcome of interest, two meta-analyses indicated weak evidence due to large heterogeneity, and no associations were found in five of them. In the combined analysis (n=7), there was no supporting evidence of a beneficial effect of statins on all-cause mortality in CKD 5D (Table III and Figure 3).

None of the five meta-analyses showed a significant effect of statin use on cardiovascular mortality in CKD 5D patients. This was observed by pooled analysis (Table IV and Figure 4).

The Effect of Statin on Mortality Among Kidney Transplant Recipients

The individual meta-analysis and pooled meta-analysis results of the association between statin

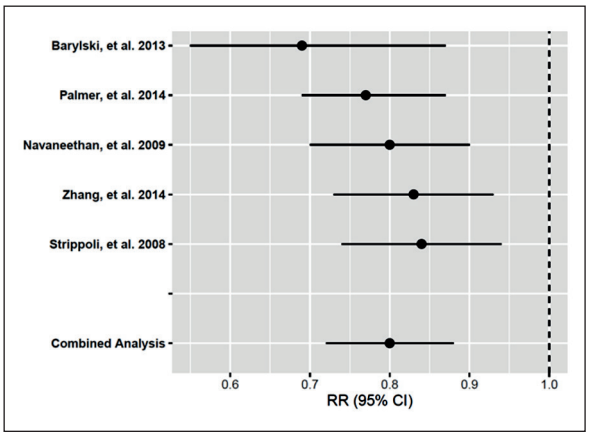

Figure 2. Effects of statin therapy in CKD patients (cardiovascular mortality).

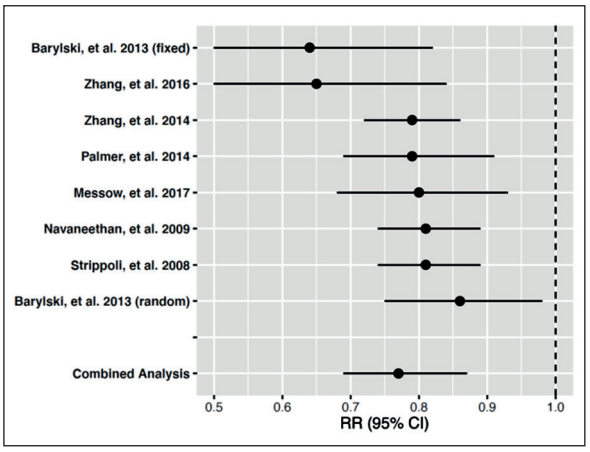

Figure 1. Effects of statin therapy in CKD patients (all-cause mortality).

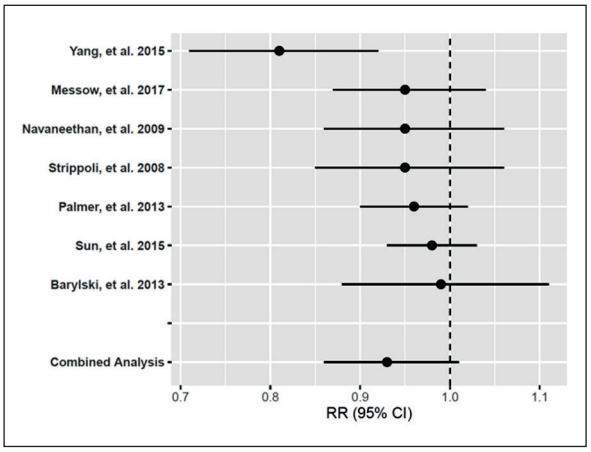

Figure 3. Effects of statin therapy in CKD 5D patients (all-cause mortality).

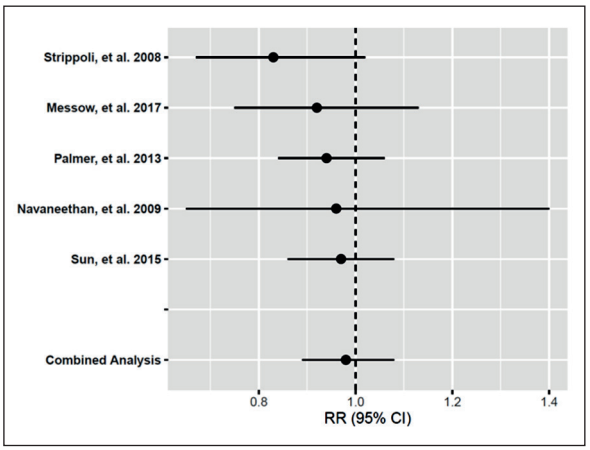

Figure 4. Effects of statin therapy in CKD 5D patients (cardiovascular mortality).

use and kidney transplant recipients' mortality are summarized in Table V, Table VI, Figure 5, and Figure 6. When all-cause mortality was analyzed, only one meta-analysis with the type of RCTs and cohort studies showed weak evidence supporting the effect of statins. The validity is still limited due to a small-study effect. The other three meta-analyses of RCTs showed no significant association between statin use and all-cause mortality. In the overall pooled analysis (n = 4), there was weak evidence supporting the beneficial effects of statin use on all-cause mortality among kidney transplant recipients (Table V and Figure 5).

The cardiovascular mortality of kidney transplant recipients and statin therapy included three meta-analyses, and they all showed no evidence of the preventive role of statins. Combined analysis (n = 3) revealed suggestive evidence for the effect of statin treatment in preventing cardiovascular mortality in patients who had undergone kidney transplantation (Table VI and Figure 6).

Discussion

We identified and comprehensively analyzed 32 meta-analyses from 14 articles. While 24 associations were statistically significant, only 11 of them were corroborated by convincing evidence from RCTs. In meta-analyses, statin showed suggestive and weak evidence for an association with beneficial effects on all-cause and cardiovascular mortality in CKD patients, respectively. For kidney-transplant patients, statins showed weak and suggestive evidence for reduced all-cause and cardiovascular mortality, respectively. However, in dialyzed patients, combined analyses showed no beneficial effects of statins on all-cause and cardiovascular mortality.

Patients with CKD are considered to be at high or very high risk of atherosclerotic cardiovascular disease according to 2019 ESC guidelines, and the use of statins or the statin/ezetimibe combination is recommended in non-dialyzed CKD patients with a high level of evidence[29]. However, two major RCTs (the Die Deutsche Diabetes Dialyse Studies (4D) trial and a study to evaluate the use of rosuvastatin in subjects on regular hemodialysis an assessment of survival and cardiovascular events (AURORA) trial) fail to show a significant reduction in cardiovascular mortality in patients on hemodialysis[30,31]. There are no RCTs on peritoneal dialysis patients. Some observational stud-

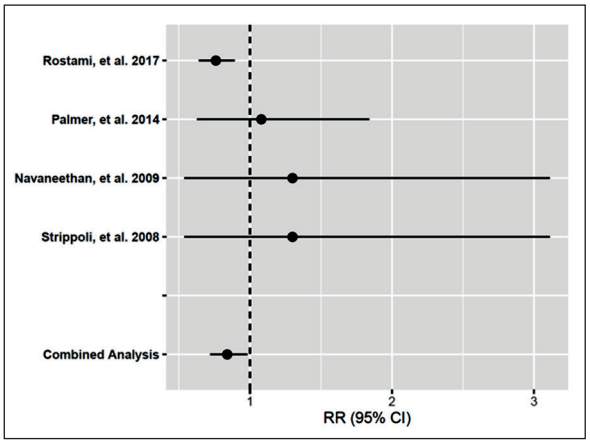

Figure 5. Effects of statin therapy among kidney transplant recipients (all-cause mortality).

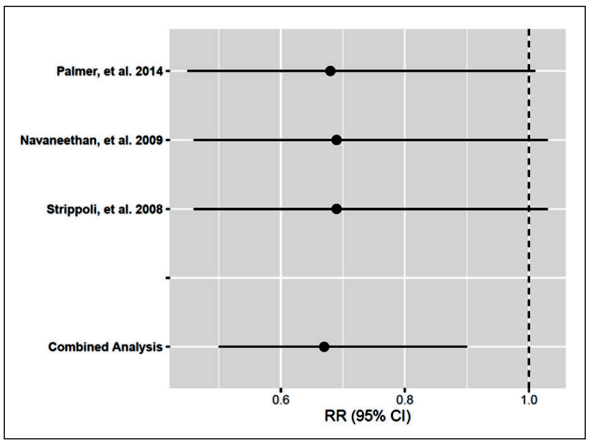

Figure 6. Effects of statin therapy among kidney transplant recipients (cardiovascular mortality).

ies showed that statin therapy reduced all-cause mortality in hemodialysis patients[32,33]. However, meta-analyses and guidelines do not recommend statins or statin/ezetimibe combination initiation in dialysis-dependent CKD patients[14,21,29,34]. Our study confirmed that in patients, on hemodialysis, statin use was correlated with neither a reduction in all-cause nor cardiovascular mortality[19,21,24-26,35]. However, further evidence is required to establish a protective correlation between these specific effects of patients on hemodialysis.

It is well proven in the scientific and medical community that dyslipidemia contributes to the development of cardiovascular disease in CKD patients[36]. Cardiovascular disease is the leading cause of mortality in patients with CKD, with a majority of these patients also suffering from hypertension and type 2 diabetes mellitus[37]. The mechanism of action of statins, in principle, consists of reducing endothelial dysfunction and decreases abnormal permeability to plasma proteins[38]. Interestingly, although not the subject of this study, we did not observe a significant increase in the adverse or side effects of statins, such as rhabdomyolysis, hepatotoxicity, and cancer, among CKD patients[20,24]. Therefore, our findings are in conformance with the current Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for Lipid Management in Chronic kidney disease (2013). The following guidelines recommend statin treatment for all CKD patients aged ≥ 50 years and not on dialysis or going for kidney transplantation (GFR categories G1-5). Our data provide further evidence in support of these recommendations. For CKD patients aged 18-49 years, statin treatment is suggested only for those with additional risk factors, such as coronary artery disease, diabetes mellitus, previous ischemic stroke, estimated 10-year incidence of coronary death, or more than 10% risk of non-fatal myocardial infarction[34]. In the recently published guidelines by the European Society of Cardiology (2019) and American College of Cardiology (2018), patients with CKD were considered to be at high (CKD G3) or very-high (CKD G4-5) risk of atherosclerotic cardiovascular disease[29,39].

As a result, ambitious and aggressive treatment goals were set. Such recommendations included using statin regimens to achieves more than 50% reductions in low-density lipoprotein (LDL) cholesterol from baseline for all patients with CKD and an LDL cholesterol goal of <55 mg/dL for very-high risk and <70 mg/dL for high-risk patients. Hence, the use of statins or the statin/ezetimibe combination was recommended in all CKD patients with a Class I recommendation and an A level of evidence. In transplant recipients, statin treatment may be considered with a Class IIa recommendation and a B level of evidence[29].

Although evidence supporting the use of statins in kidney transplant recipients is generally weak, statins had positive and protective effects. These findings are supported by the general medical community recommendation of statin use among patients with a transplanted kidney. In kidney transplant recipients, cardiovascular diseases are the major cause of mortality. Dyslipidemia is thus a common causal pathway leading to cardiovascular mortality, similarly to patients with CKD[40]. This commonality may explain the protective correlation of statins used in transplanted patients. However, the role of statins in kidney transplant recipients is multidimensional and affected by several factors. In contrast to patients with CKD, kidney transplant recipients are under continuous immunosuppressive therapy, including corticosteroids and calcineurin inhibitors (CNIs). Long-term corticosteroid and CNI use are well proven to increase LDL cholesterol, total cholesterol, and triglycerides in a dose-dependent manner[41,42], explaining in part the beneficial effects of statins on CV mortality among these patients. Pharmacokinetic interaction between CNIs and statins should be deliberated. The Assessment of Lescol in Renal Transplant (ALERT) study is the major RCT that assessed cyclosporine interaction and fluvastatin[43]. Unlike most other statins, fluvastatin is not metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. CYP3A4 is inhibited by CNIs, potentially leading to an increase in the bioavailability of fluvastatin[10,29]. Therefore, when patients on long term immune suppression are prescribed statins, pharmacokinetic interactions between the two drugs should always be considered. Further pharmacologic research is necessary to establish safe and practical guidelines in the case of dual immunosuppressant regimen and statin therapy.

Our study has several limitations. We only included meta-analyses that could be re-analyzed, potentially limiting our ability to control confounding variables that differed across the individual studies. Additionally, individual observational studies themselves have biases, possibly transferring these biases into the meta-analysis that included those different studies. The dose-effect of statins was beyond the scope of our analysis and such was not reported in our results or

discussion. Similarly, combination therapies such as statins with ezetimibe were also beyond our research and so were not performed due to a lack of studies and robust analysis. However, this is the first performed umbrella review of meta-analyses about statin use in CKD patients made through the recently published data.

Conclusions

Our umbrella review extensively re-analyzed the meta-analyses in search of the association between statin use and all-cause mortality and cardiovascular mortality, which was not analyzed in the other recently published umbrella review[14]. 6 of 15 studies showed a significantly reduced mortality among CKD patients. Five of eleven studies on statins and cardiovascular mortality were significant. The beneficial effects of statin were shown in CKD patients not on dialysis for both all-cause mortality and cardiovascular mortality and in kidney transplant recipients for cardiovascular mortality but not for all-cause mortality. For patients on dialysis, the beneficial effects of statin treatment could not be confirmed, neither for all-cause mortality nor for cardiovascular mortality. These results help to understanding the real effects of statins on CKD patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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The authors' responsibilities were as follows- R.A.G. and J.I.S designed this study, G.H.J, S.Y, and C.H.H. collected data. G.H.J, C.H.H., and S.Y. did the analyses. R.A.G., J.Y.L., K.H.L., J.W.Y., P.G., A.K., and J.I.S wrote the first draft of the manuscript and gave critical comments on the manuscript draft. All authors had full access to all the study data. All authors reviewed, wrote, and approved the final version. The corresponding author had the ultimate responsibility for the decision to submit for publication.

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