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ORIGINAL ARTICLE

Improvement of clinical outcomes in patients undergoing peritoneal dialysis using hydroxymethylglutaryl-CoA reductase inhibitors: A systematic review and meta-analysis

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Abstract

Background: It is unclear whether hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy decreases the risk of mortality and cardiovascular disease (CVD) in patients undergoing peritoneal dialysis (PD).

Methods: We performed a literature search of PubMed, Cochrane Library, Embase, and other databases for research publications up to June 2022. The outcomes of interest were fatal and nonfatal CVDs, all-cause mortality, and changes in the biochemical profiles. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled and synthesized using a random-effects model. The certainty of the evidence was determined using Grading of Recommendations, Assessment, Development, and Evaluation.

Results: Nine studies, including 2,933 patients undergoing PD, were included. Among them, three studies, including 2,099 patients, reported all-cause mortality, and three, including 1,571 patients, reported CVDs. In these patients, pooling results of two observational studies (very low-certainty evidence) showed that statin therapy significantly reduced CVDs (HR = 0.67; 95% CI = 0.54–0.84; p = 0.0004). Moreover, statin therapy was associated with significantly reduced low-density lipoprotein cholesterol, total cholesterol, and C-reactive protein levels (very low certainty of evidence). However, the effects of statin therapy on triglyceride, high-density lipoprotein, and albumin levels were not statistically significant.

Conclusion: Although statin therapy was associated with significantly reduced low-density lipoprotein cholesterol, total cholesterol, and C-reactive protein levels, the probable beneficial effect of statins on CVD risk in patients undergoing PD could not be concluded firmly. Additional high-quality studies are required to assess the potential beneficial effects of statin therapy in PD patients.

Keywords: All-cause mortality; Cardiovascular disease; Meta-analysis; Peritoneal dialysis; Statin

1. INTRODUCTION

Due to advances in diagnostic and treatment armamentarium, cardiovascular disease (CVD) mortality has steadily declined over the past decades.[1] However, the risk of cardiovascular (CV) events among patients undergoing dialysis remains 20–30 times higher than that in the general population.[2] Patients undergoing peritoneal dialysis (PD) have an increased risk of CV mortality than those undergoing hemodialysis (HD).[3]

Recent randomized controlled studies (RCTs), including patients undergoing dialysis, have failed to demonstrate that hydroxymethylglutaryl-CoA reductase inhibitor (statin) can reduce fatal and nonfatal CV events despite clinically relevant reductions in serum cholesterol levels.[4–6] Therefore, according to the Kidney Disease: Improving Global Outcomes guidelines, statin or statin/ezetimibe combination therapy was recommended in adults with dialysis-dependent chronic kidney disease (CKD) with evidence level 2A.[7] Although the SHARP trial has demonstrated that the statin effect on the major atherosclerotic event in patients undergoing PD is neutral,[6] some observational studies have shown the possible protective effect of statin therapy in patients undergoing PD.[8,9] Further subgroup analysis of statin effect focusing on patients undergoing PD in large RCTs is still lacking.

This systematic review and meta-analysis aimed to evaluate whether statins reduce the mortality and CVD risks in patients undergoing PD and investigate the effects of statins on biochemical markers.

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2. METHODS

The prespecified protocol of this systematic review was registered at PROSPERO (number CRD 42021242828), and the study was performed in accordance with the PRISMA guidelines (Supplemental Table 1, http://links.lww.com/JCMA/A165).

2.1. Search strategy

Three electronic databases (MEDLINE via PubMed, Cochrane, Embase, Scopus, and Airitilibrary) were searched on June 14, 2022, using the search strategies detailed in Supplemental Table 2, http://links.lww.com/JCMA/A165. The ClinicalTrials.gov website and Google Scholar were also searched for randomized trials registered as completed but not yet published. The search was limited to RCTs, clinical trials, and cohort studies (Supplementary Table 2, http://links.lww.com/JCMA/A165).

Three investigators (D.Y.L., C.J.H., and H.M.C.) used a three-step search strategy. An initial limited search of MEDLINE and PubMed was performed, followed by analyzing the text words in the title, abstract, and index terms used to describe the article. A second search using all identified keywords and index terms was performed across all included databases. Subsequently, the reference lists of all the identified reports and articles were searched for additional studies. Eligibility queries were resolved through discussion. In cases of missing data in the included studies, the authors were contacted by e-mail for further information. The search was repeated to ensure accuracy and completeness.

2.2. Inclusion and exclusion criteria

RCTs and cohort studies were deemed eligible if they included patients aged ≥18 years who underwent PD. The intervention and control groups received statin therapy and a placebo or standard treatment, respectively. The types of statins were not limited, except for cerivastatin, which was withdrawn from the market owing to serious side effects. RCTs, clinical trials, and cohort studies that reported one or more endpoints that met our primary or secondary outcomes were included. Our primary outcome of interest was the association between statin use and a reduction in all-cause mortality and CVD. The secondary outcomes of interest were the association between statin use, lipid profiles, and inflammatory profile changes.

2.3. Data extraction and quality assessment

Two reviewers (D.Y.L. and H.M.C.) independently extracted data. The data collected from each study included: (1) trial details (first author and year), (2) region of participating centers, (3) study design, (4) inclusion and exclusion criteria, (5) total number of patients in each group, (6) follow-up duration, (7) PD duration, (8) end-stage renal disease (ESRD) etiology, (9) baseline lipid profile, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglyceride (TG) levels, (10) changes in lipid profile, (11) baseline C-reactive protein (CRP) level, (12) baseline albumin level, and (13) provided estimates of each outcome of interest. This information was extracted in a predesigned form using Microsoft Excel. Any divergence between the reviewers was discussed with a third reviewer (C.J.H.). An agreement was reached through a consensus. The Newcastle-Ottawa scale was used to determine the quality of cohort studies,[10] and the Cochrane tool was used to assess the risk of bias for RCTs. The overall certainty of the evidence for each outcome depending on the risk of bias, indirect evidence, inconsistency, effect estimates imprecision, and potential publication bias, was analyzed using the grading of recommendations assessment, development, and evaluation (GRADE) approach.[11]

2.4. Data and statistical analyses

This meta-analysis and systematic review reported the number and proportion of patient characteristics. Studies by Cueto-Manzano et al[12] and Han et al[13] reported secondary outcomes as the median secondary outcomes. We converted the median to mean and standard deviation (SD), assuming the data distribution was symmetrical. The SD was considered approximately equal to the width of the interquartile range divided by 1.35.[14] Concerning the influence of small-study effects on the results of a meta-analysis where evidence of between-study heterogeneity ($I^2 > 0$) exists, we compared the fixed- and random-effects estimates of the intervention effect, and the result was similar.[15] Considering the variance between studies, the DerSimonian and Laird random-effects model was used to analyze the pooled hazard ratio (HR) and 95% confidence interval (CI) obtained in studies included for all-cause mortality and CVD evaluation.[16] Mean differences (MD) and 95% CIs of changes in lipid profiles and inflammatory biomarkers were selected as effect measures. Between-study heterogeneity was statistically assessed using Higgins's I^2 statistic.[17] A CI for I^2 was constructed using the noncentral chi-square method, and an I^2 value >50% showed substantial heterogeneity. A formal assessment of publication bias was performed using Egger's regression asymmetry test.[18] Sensitivity analysis was conducted using the leave-one-out meta-analysis function from the meta R package.[19] For secondary outcome analysis, we performed sensitivity analyses using different correlation coefficients due to the lack of change in SD in the included studies. The overall results of the sensitivity analyses showed no difference in the correlation coefficient range (0.5–0.9).[20] All analyses were performed using RevMan (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration [2014]).

3. RESULTS

3.1. Search results

The initial search strategy yielded 2,746 unduplicated studies; after conducting title research based on the inclusion and exclusion criteria, 2,729 studies were excluded. In the Cochrane Library, a systemic review of the effects of statins on clinical outcomes in dialysis patients was first reported in 2004 and updated in 2009 and 2013. The previous systematic review and meta-analysis were reviewed carefully, and seven additional studies from the reference list of two review articles were included.[21,22] Two reviewers (D.Y.L. and H.M.C.) independently assessed the 24 relevant studies included.[6,8,9,12,13,23–39] After excluding seven studies without full-text articles,[33–36,39] 17 studies were left. Subsequently, we critically appraised all 17 studies, and their inclusion was independently analyzed by two review authors (D.Y.L. and H.M.C.). Eight full-text articles were excluded for the reasons shown in Fig. 1. Among the remaining 9 studies for qualitative synthesis, six reported secondary outcomes,[12,13,23–26] and seven reported primary outcomes, including all-cause mortality or CVD. However, two studies had mixed HD and PD patients without further PD subgroup analysis,[30,31]and one study's endpoint was a composite of all-cause mortality, nonlethal acute myocardial infarction, coronary artery bypass graft surgery, and percutaneous transluminal coronary angioplasty.[27] Finally, four studies were included for primary outcome meta-analysis (two RCTs and two observational studies).[6,8,9,23] Table 1 summarizes the characteristics of the included studies. The entire search process is shown in the PRISMA flowchart (Fig 1).

3.2. Characteristics of the included studies

Among the 2,933 patients with PD in the nine included studies, 968 used statins. Two, one, one, one, and four studies used

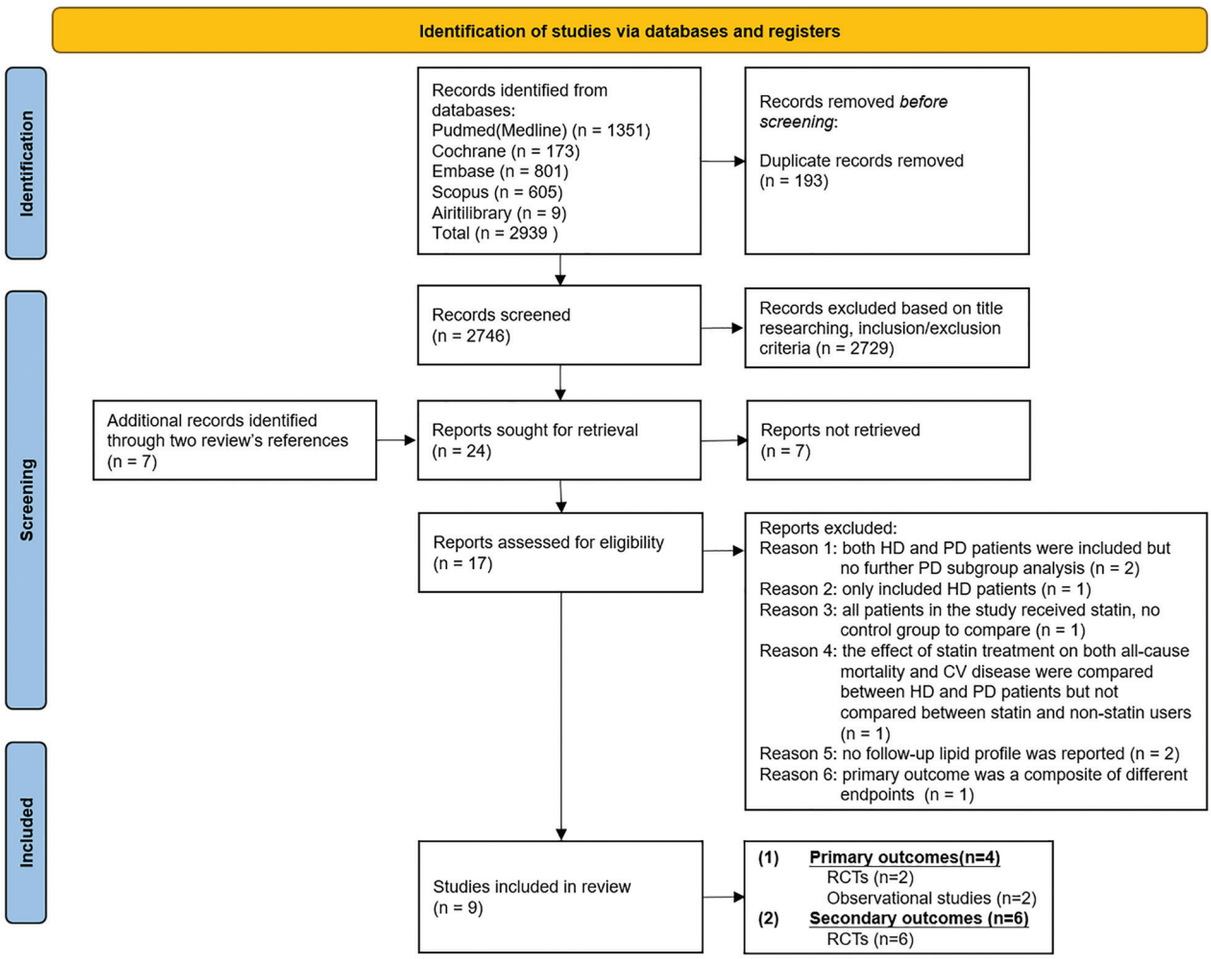

Fig. 1 Flowchart of literature selection. CV = cardiovascular; CRP = C-reactive protein; HD = hemodialysis; PD = peritoneal dialysis; RCT = randomized controlled trial.

simvastatin 20 mg daily, simvastatin 5 mg daily, atorvastatin 40 mg daily, pravastatin 20 mg daily, and statins, respectively. The mean age of the study participants ranged from 48 to 59 years. There was no significant difference in age or male percentage between the statin and nonstatin groups. The follow-up duration ranged from 6 months to 4.9 years. One RCT required patients to receive either pravastatin or placebo orally for 2 months during the first treatment period. After a 1-month washout period, the patients were crossed over to receive another drug (or placebo) for an additional 2 months. The etiologies of ESRD in these patients were diabetes mellitus (14.3–74%), hypertensive glomerulosclerosis (11–62.5%), chronic glomerulonephritis (9.3–50%), polycystic kidney disease (2.6–15%), and unknown or other causes (9–24.9%). Baseline lipid profiles, albumin levels, and CRP levels are shown in Table 2. Table 3 summarizes the characteristics of the six studies with available data on prespecified secondary outcomes. Among the four included studies with available data on prespecified primary outcomes, one RCT and two observational cohort studies provided the desired data on all-cause mortality, and two RCTs and one observational cohort study provided the desired data on CVD.

3.3. Risk of bias in the included studies

Generally, all included RCTs were randomly assigned to a statin or placebo group. In these RCTs, two studies used open-label designs instead of double-blind designs.[13,23] An unclear blinding design was reported in three RCTs.[24–26] All analyses were performed on an intention-to-treat (ITT) basis, except for two studies that did not mention whether they were based on the ITT population.[12,25] Supplemental Figure 2, http://links.lww.com/JCMA/A165 shows the risk of bias assessed using the Cochrane risk of bias tool for RCTs. The quality of the two observational studies was assessed using the Newcastle-Ottawa scale (Supplemental Table 3, http://links.lww.com/JCMA/A165). The certainty of evidence from these trials was appraised using the GRADE method, in which an assessment was made for each reported outcome. The certainty of the evidence was rated very low for primary outcomes due to two observational studies, insufficient sample size, serious indirectness, and strongly suggested publication bias. As for the secondary outcomes, all included studies were RCTs, but the certainty of the evidence was also rated very low due to incomplete outcome data, unclear blinding designs reported by the RCTs, insufficient sample size, serious indirectness, and strongly suggested publication bias (Supplemental Table 4, http://links.lww.com/JCMA/A165). Sensitivity analyses were not performed because of the limited number of primary outcomes. Although a sensitivity analysis of secondary outcomes was performed, similar findings were also seen in our sensitivity analysis by omitting one study at a time.

Table 1

Characteristics of the included studies

Study	Design/country/facility number	Group	N	Study follow-up duration	Outcome of interest
Wu et al (2017)[23]	(1) prospective, randomized, open-labeled trial (2) Taiwan (3) Single center	Total	32	6 months	1. Diastolic function (E/e) 2. Systolic function 3. CVD: cardiac disease, cerebrovascular disease, severe ischemic events
	(4)	Atorvastatin 40 mg daily	16		4. MACE: hospitalization b/c heart failure, MI, recurrent CAD, stroke, PAOD, arrhythmia
	1.	Placebo	16		5. Lipid profile 6. TNF-alfa 7. IL-6 8. CRP
Cueto-Manzano et al (2013)[12]	(1) Randomized, double-blind, controlled, and crossover clinical trial (2) Mexico (3) Single center	Total	76	(1) 2 months (2) 1-month washout period (3) crossed over for an additional 2 months	1. CRP 2. Lipid profile 3. Other biochemical variables
	(4)	Pravastatin 20 mg daily then placebo	41		
	(5)	Placebo then Pravastatin 20 mg daily	35		
Doh et al (2012)[24]	(1) Prospective, open, randomized trial (2) Korea (3) single center	Total	70	6 months	1. Insulin resistance 2. Serum inflammatory markers and adipokines (hsCRP, IL-6, adiponectin, leptin, resistin) 3. Lipid profile
	(6)	Statins	35		4. Other biochemical variables
	(7)	Nonstatin users	35		
Sezer et al (2012)[25]	(1) Prospective, randomized, controlled trial (2) Turkey single center	Total	48	1 month	1. hsCRP, IL-6, TNF-alfa 2. Lipid profile
	(1)	Simvastatin 20mg daily	25		
	(2)	Placebo	23		
Han et al (2011)[13]	(1) Prospective, randomized, open-label trial (2) Korea (3) single center	Total	124	6 months	1. Flow-mediated dilatation (FMD)and nitroglycerin-mediated dilatation 2. Brachial–ankle pulse wave velocity (BaPWV) 3. Volume status:
	1.	Only valsartan	57		Intracellular fluid (ICF)
	2.	Rosuvastatin 10mg daily + Valsartan	57		Extracellular fluid (ECF) Total body weight 4. CRP, IL-6, fibrinogen, 8 isoprostane
Baigent SHARP trial (2011)[6]	(1) Randomized double-blind trial (2) United Kingdom	Total	496	4.9 years	1. Major atherosclerotic events (defined as nonfatal myocardial infarction or coronary death, non-hemorrhagic stroke, or arterial revascularization excluding dialysis process procedures)
	(3)	Simvastatin 20mg plus ezetimibe	258	5.	6.
	(4)			7.	8.
	(5)	Placebo	238	9.	10.
Saltissi et al (2002)[26]	(1) double-blind, stratified, placebo-controlled, randomized study (2) Australia	Total	23	6 months	1. Efficacy assessment: percentage change from baseline in non-HDL cholesterol, LDL-cholesterol, total cholesterol, HDL cholesterol, total cholesterol to HDL cholesterol ratio, triglycerides, apolipoproteins A1 and B (ApoA1 and ApoB100), and lipoprotein (Lp) (a)
	3.	Simvastatin 5mg daily	16		
	4.	Placebo	7		2. Safety assessment: adverse events

(Contined)

Table 1 (Continued)

Study	Design/country/facility number	Group	N	Study follow-up duration	Outcome of interest
Lee et al (2011)[8]	(1) 1:1 matched cohort (2) Korea (3) 7 PD centers	Total	1024	2.7 years	1. All-cause mortality Death within 3 months of transfer to HD was deemed to be PD-related mortalities
	(4)	Statins	387		
	(5)	Nonstatin users	637		
Goldfarb-Rumyantzev et al (2007)[9]	(1) Retrospective cohort from DMMS Wave 2 study (2) United States of America (3) 259 facilities	Total	1053	3 years	1. Cause of death (hypertensive disease, ischemic heart disease, other heart diseases, cerebrovascular disease) 2. All-cause mortality
	1.	Lipid-modifying medications	143 (n= 10 gave other than statins, eg. Gemfibrozil or niacin)		3. Cardiovascular mortality
	2.	Placebo	910		

ALT = alanine transaminase; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = coronary heart disease; CK = creatine kinase; CRP = C-reactive protein; CVD = cardiovascular disease; HD = hemodialysis; HDL = high-density lipoprotein cholesterol; IL-6 = Interleukin 6; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAOD = peripheral arterial occlusive disease; PD = peritoneal dialysis; PTCA = percutaneous transluminal coronary angioplasty; TC = total cholesterol; TNF-alfa = tumor necrosis factor-alpha.

3.4. Primary and secondary outcomes

The primary outcomes were the major CVD and all-cause mortality rates. The secondary outcomes included changes in the lipid profiles and inflammatory biomarkers (Table 3). All reported results were analyzed using a random-effects model. We separated the RCTs and observational studies for the respective meta-analyses per the GRADE guidelines, and the results were presented separately.

3.4.1. All-cause mortality

Data for all-cause mortality were available from one RCT and two observational cohort studies.[8,9,23] In one small RCT that included 32 patients who reported all-cause mortality in patients undergoing PD, there was no significant difference between the two groups (HR = 3.23, 95% CI = 0.41–25.45; p = 0.27) (Fig. 2a). In the meta-analysis of two observational studies, including 2,067 patients undergoing PD who reported all-cause mortality, patients in the statin group at any time point during the study were 33% less likely to have all-cause mortality than those in the control group (HR = 0.67, 95% CI = 0.54–0.84; p = 0.0004) without evidence of heterogeneity (I^2 = 6%, p = 0.30) (Fig. 2b).

3.4.2. Cardiovascular disease

Data for CVD were assessed from two RCTs and one observational cohort study. In the meta-analysis of two RCTs, including 528 patients reporting CVD in patients undergoing PD, there was a trend of statins' beneficial effect in reducing CVD risks, but this was not significant (HR = 0.71; 95% CI = 0.48–1.06; p = 0.09) without evidence of heterogeneity (I^2 = 0%, p = 0.83) (Fig. 3a). One observational study including 1,043 patients showed that statins might be associated with improved clinical outcomes in patients undergoing PD (HR = 0.67; 95% CI = 0.47–0.96; p = 0.03) (Fig. 3b).

3.4.3. Lipid profile

Six studies, including 360 patients, reported changes in LDL-C and TG levels. Five studies, including 328 patients, reported changes in cholesterol levels. Five studies, including 284 patients, reported changes in HDL-C levels. Statins significantly reduced LDL-C and cholesterol levels with substantial heterogeneity (MD = –39.74; 95% CI = –54.60–24.89; p < 0.001; I^2 = 65% and MD = –43.12; 95% CI = –60.79–25.45; p < 0.001; I^2 = 68%, respectively; Supplemental Figs. 2–3, http://links.lww.com/JCMA/A165). The heterogeneity of LDL-C and cholesterol decreased (I^2 = 0% and 25%, respectively) after removing the studies by Cueto-Manzano et al and Doh et al, respectively, without affecting the overall result. The effect of statins on TG and HDL-C levels was not significant (MD = –35.22; 95% CI = –87.87–17.44; p = 0.19; I^2 = 0% and MD = 2.35; 95% CI = –1.31–6.01; p = 0.21; I^2 = 0%, respectively; Supplemental Figures 4–5, http://links.lww.com/JCMA/A165).

3.4.4. Inflammatory biomarkers

CRP and albumin levels were used as representative inflammatory biomarkers. Five studies, including 337 patients, reported changes in the CRP levels. Statins reduced CRP levels (MD = –0.83; 95% CI = –1.13–0.53; p < 0.001), but this result must be interpreted with caution because of the substantial heterogeneity (I^2 = 88%; Supplemental Fig. 6, http://links.lww.com/JCMA/A165), even after sensitivity analysis. Five studies, including 305 patients, reported changes in albumin levels. However, the effect of statins on albumin levels was not significant (MD = 0.08; 95% CI = –0.02–0.17; p = 0.14; I^2 = 0%; Supplemental Fig. 7, http://links.lww.com/JCMA/A165).

4. DISCUSSION

In our systematic review and meta-analysis of nine studies and 2,933 patients, the possible protective effects of statin use on CVD and all-cause mortality in patients undergoing PD could not be concluded firmly because of the small number of included studies and the very low certainty of the evidence. In contrast, statin therapy was significantly associated with reduced LDL-C, cholesterol, and CRP levels. More high-quality RCTs on this particular population are required for a firm conclusion.

All previous RCTs, including the 4-D,[4] AURORA,[5] and SHARP trials,[6] demonstrated that cholesterol-lowering medication could not reduce fatal and nonfatal CV events in patients undergoing dialysis despite clinically relevant reductions in serum cholesterol levels.[40] In contrast, statins were associated

Table 2

Characteristics of participants in the included studies

Studies	Treatment group	Patient, N	Age, year	Male, N, %	PD duration, Months	Diabetic Mellitus	Hypertensive nephrosclerosis
Wu et al (2017)[23]	Atorvastatin 40mg daily	16	57.6 ± 13.6	8, 50%	60.2 ± 26.4	4, 24%	10, 62.5%
	Placebo	16	59.3 ± 16.1	6, 37.5%	76.2 ± 37.4	3, 18.8%	6, 37.5%
Cueto-Manzano et al (2013)[12]	Pravastain 20 mg daily	41	53.4 ± 13.8	25, 61%	16(10-24)	23, 56%	3, 7%
	Placebo	35	55.5 ± 10.7	18, 52%	13.5(9.5-26)	26, 74%	4, 11%
Doh et al (2012)[24]	Statins	35	48.9 ± 11.7	16, 45.7%	76.5 ± 53.0	5, 14.3%	10, 62.5%
	Nonstatin users	35	48.5 ± 11.3	16, 45.7%	83.5 ± 50.3	6, 17.1%	6, 37.5%
Sezer et al (2012)[25]	Simvastatin 20mg daily	25	51.2 ± 13.1	12, 48.0%	35.6 ± 23.1	10, 40.0%	6, 24.0%
	Placebo	20	57.4 ± 11.6	7, 35.0%	36.9 ± 19.1	6, 30.0%	8, 40.0%
Han et al (2011)[13]	ARB + Statin	57	48.8 ± 10.6	29, 51.2%	77.6 ± 49.0	NR	32, 25.6%
	ARB alone	57	48.9 ± 11.5	26, 45.9%	75.7 ± 52.9		
Baigent (2011) SHARP trial[6]	Simvastatin 20mg plus ezetimibe	258	NR	NR	NR	NR	NR
	Placebo	238					
Saltissi et al (2002)[26]	Simvastatin 5mg daily	16	51.2 ± 13.1	12, 48.0%	35.6 ± 23.1	10, 40.0%	6, 24.0%
	Placebo	7	57.4 ± 11.6	7, 35.0%	36.9 ± 19.1	6, 30.0%	8, 40.0%
Lee et al (2011)[8]	Statin users	387	57 ± 13	206, 53.2%	continued therapy at	207, 53.5%	79, 20.4%
	Non-users	637	55 ± 15	390, 61.2%	least for 1 month	245, 38.5%	153, 24%
Goldfarb-Rumyantzev et al (2007)[9]	Statin users	133	58.5 ± 13.6	73, 51%	67.9 ± 23.5	67,46.9%	35, 24.4%
	Non-users	910	57.0 ± 15.5	473, 52%	67.6 ± 22.2	401,44.1%	197, 21.7%

ARB = angiotensin II receptor blocker; CRP = C-reactive protein; HDL = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NR = not reported; TC = total cholesterol.

Table 3

Changes in lipid and inflammatory profiles

			LDL, mg/dl		HDL, mg/dl	
Studies	Treatment group	Patient, N	Baseline	Follow-up	Baseline	Follow-up
Wu et al (2017)[23]	Atorvastatin	16	97.2 ± 52.6	57.4 ± 19.2	29.1 ± 12.8	37.6 ± 8.4
	Placebo	16	104.9 ± 27.3	101.5 ± 39.1	32.4 ± 13.3	35.3 ± 14.3
Cueto-Manzano et al (2013)[12]	Pravastain /Placebo	41	99 (77-138)	90 (67-121)	NR	NR
	Placebo /Pravastain	35	96 (73-126)	98 (72-124)		
Doh et al (2012)[24]	Rosuvastatin	35	117.9 ± 28.6	68.8 ± 21.6	52.9 ± 15.0	49.8 ± 15.8
	Placebo	35	116.0 ± 37.1	122.2 ± 38.2	52.9 ± 18.1	49.1 ± 16.6
Sezer et al (2012)[25]	Simvastatin	25	149.4 ± 39.9	96.8 ± 34.7	31.9 ± 14.8	33.6 ± 34.7
	Placebo	20	136.7 ± 53.7	120.5 ± 32.5	31.5 ± 11.4	36.3 ± 12.6
Han et al (2011)[13]	ARB + Statin	57	110.8 ± 29.61	65.6 ± 21.2	47.8 ± 13.2	49.7 ± 14.8
	ARB alone	57	120.2 ± 32.8	121.4 ± 37.4	50.7 ± 16.5	48.3 ± 16.4
Saltissi et al (2002)[26]	Simvastatin	16	170 ± 23	111 ± 20	39 ± 14	39 ± 13
	Placebo	7	203 ± 76	209 ± 53	45 ± 14	49 ± 13

All data are expressed as mean ± standard deviation or median (percentiles 25%–75%).
ARB = angiotensin II receptor blocker; CRP = C-reactive protein; HDL = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NR = not reported; TC = total cholesterol.

Cause of ESRD N, %			Baseline lipid profile				Others	
Chronic glomerulonephritis	Polycystic kidney	Others and Unknown	LDL (mg/dl)	HDL (mg/dl)	Cholesterol (mg/dl)	TG (mg/dl)	Baseline CRP (mg/l)	Baseline albumin (g/dl)
NR	NR	NR	97.2 ± 52.6	29.1 ± 12.8	NR	211 ± 196	3.52 ± 1.01	NR
			104.9 ± 27.3	32.4 ± 13.3		122 ± 52	2.77 ± 1.32	
NR	6, 15%	9, 22%	99 ± 45.18	NR	188 ± 67.40	176 ± 108.1	7.4(2-21)	3.1 ± 0.6
	2, 6%	3, 9%	96 ± 39.25		176 ± 43.7	190 ± 96.2	3.9(2-10)	3.2 ± 0.6
NR	NR	NR	117.9 ± 28.6	52.9 ± 15.0	190.6 ± 25.5	95.6 (71-152)	2.05 ± 1.57	3.7 ± 0.3
			116.0 ± 37.1	52.9 ± 18.1	191 ± 46.4	107.1 (84-167)	1.90 ± 1.33	3.8 ± 0.4
NR	NR	NR	149.4 ± 39.9	31.9 ± 14.8	217.4 ± 50.3	199.8 ± 116.3	4.9 (2.1-14.9)	4.0 ± 0.2
			136.7 ± 53.7	31.5 ± 11.4	202.4 ± 46.2	157.8 ± 58.9	6.3 (3.3-12.2)	4.1 ± 0.3
62, 50%	3, 2.6%	27, 23.6%	110.8 ± 29.6	47.8 ± 13.2	182.7 ± 33.4	94.0 (30-564)	1.63 ± 1.1	3.7 ± 0.4
			120.2 ± 32.8	50.7 ± 16.5	185.2 ± 46.1	97.0 (35-932)	1.43 ± 1.14	3.8 ± 0.4
NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	170 ± 23	39 ± 14	218 ± 42	262 ± 139	NR	NR
			203 ± 76	45 ± 14	253 ± 92	256 ± 117		
61, 15.8%	NR	40, 10.3%	NR	NR	182 ± 65	NR	NR	3.4 ± 0.56
144, 22.6%		95, 14.9%			180 ± 42			3.4 ± 0.53
14, 9.8%	NR	27, 18.9%	NR	NR	225 ± 70	257 ± 218	NR	3.4 ± 0.6
85, 9.3%		227, 24.9%			205 ± 56	204 ± 151		3.4 ± 0.6

Cholesterol, mg/dL		TG, mg/dL		CRP, mg/L		Albumin, g/dL	
Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
NR	NR	211 ± 196	108.9 ± 50.7	3.52 ± 1.01	2.18 ± 1.13	NR	NR
		122 ± 52	144.1 ± 50.7	2.77 ± 1.32	3.96 ± 0.88		
188 (152-243)	171 (133-201)	176 (114-260)	178 (99-288)	7.4(2-21)	2.6(1-6)	3.1 ± 0.6	3.0 ± 0.6
176 (133-201)	177 (145-203)	190 (120-250)	175 (104-282)	3.9(2-10)	6.8(3-12)	3.2 ± 0.6	3.2 ± 0.7
190.6 ± 25.5	138.4 ± 25.9	95.6 (71-152)	91.2 (62-134)	2.05 ± 1.57	1.21 ± 0.84	3.7 ± 0.3	3.8 ± 0.4
191 ± 46.4	202.6 ± 50.2	107.1 (84-167)	113.3 (81-148)	1.90 ± 1.33	1.85 ± 1.14	3.8 ± 0.4	3.8 ± 0.4
217.4 ± 50.3	157.1 ± 33.4	199.8 ± 116.3	157.8 ± 87.9	4.9 (2.1-14.9)	4.4 (1.4-13.5)	4.0 ± 0.2	4.0 ± 0.3
202.4 ± 46.2	190.4 ± 47.3	157.8 ± 58.9	158.3 ± 60.5	6.3 (3.3-12.2)	5.1 (1.4-1.93)	4.1 ± 0.3	4.0 ± 0.6
182.7 ± 33.4	135.7 ± 26.4	94 (30-564)	86 (23-454)	1.63 ± 1.1	1.24 ± 0.87	3.7 ± 0.4	3.8 ± 0.5
197.6 ± 48.1	185.2 ± 46.1	97 (35-932)	113 (45-976)	1.43 ± 1.14	1.41 ± 1.10	3.8 ± 0.4	3.8 ± 0.4
218 ± 42	158 ± 33	262 ± 139	251 ± 135	NR	NR	NR	NR
253 ± 92	261 ± 62	256 ± 117	261 ± 87				

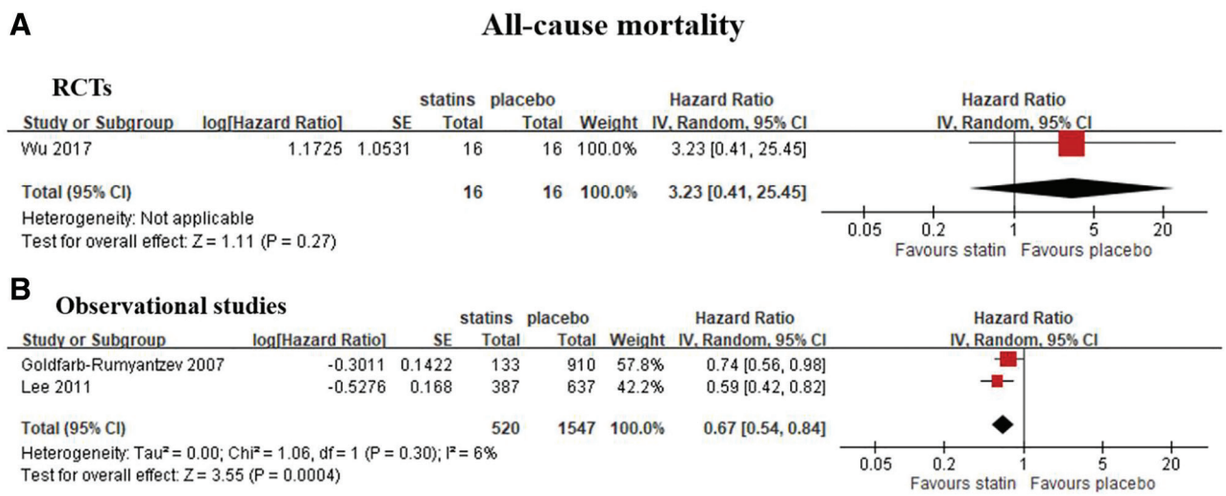

Fig. 2 Effects of stain on all-cause mortality in patients undergoing peritoneal dialysis. (A) Forest plot based on randomized controlled trials, (B) forest plot based on observational studies.

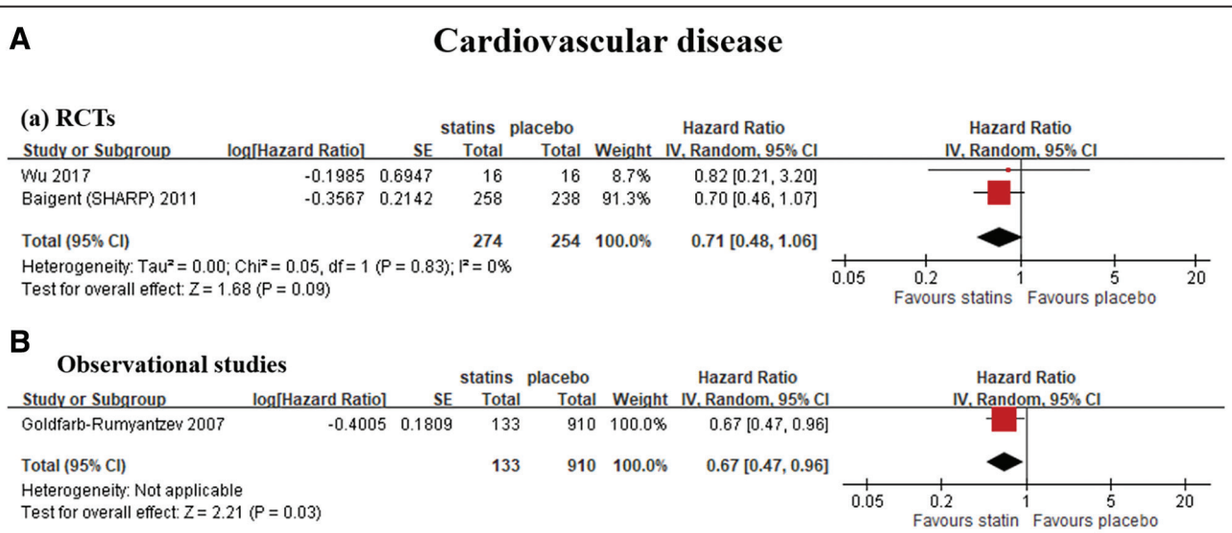

Fig. 3 Effects of stain on cardiovascular disease in patients undergoing peritoneal dialysis. (A) Forest plot based on randomized controlled trials, (B) forest plot based on observational studies.

with a reduced risk of all-cause mortality in patients undergoing PD, as shown by propensity score matching and multivariate analysis to reduce potential selection bias in an observational study (HR = 0.55; 95% CI = 0.38–0.79; p = 0.001).[8] Another observational study showed that patients undergoing PD treated with lipid-lowering agents showed a decreased risk of all-cause (HR, 0.74; 95% CI, 0.56–0.98) and CV (HR = 0.67; 95% CI = 0.47–0.95) mortality compared with the controls.[9] However, this information supported the use of statin therapy in patients undergoing PD from retrospective cohort studies. Our results were inconsistent with those of previous RCTs, which mainly recruited patients undergoing HD instead of PD. The different characteristics of dyslipidemia, inflammatory status, and albumin levels between patients undergoing HD and PD may explain the biological plausibility of our findings.

Hypertriglyceridemia is common in HD but is more severe in patients undergoing PD.[41] This may be secondary to glucose absorption from the peritoneal dialysate and a higher prevalence of hypoalbuminemia in patients undergoing PD because of higher peritoneal protein loss, which is similar to the pathogenesis of lipid abnormalities in nephrotic syndrome.[42,43] However, our systematic review showed that statins did not affect TG and albumin levels in PD patients. The appropriate explanation for this finding could be that most studies included in this review used statins rather than fibrate, which can markedly lower TG levels (40–60%) and modestly increase HDL-C levels.[44] A meta-analysis has reported that fibrates are more effective than statins in lowering plasma lipoprotein(a) concentrations, which are usually higher in patients undergoing PD.[45] Moreover, combination therapy with statins and fibrates has emerged as an option for many high-risk patients, especially those with atherogenic dyslipidemia.[46,47] Although the ACCORD-Lipid study found no benefit of fenofibrate versus placebo, a beneficial reduction in major CVD events was found in a prespecified subgroup analysis

of study participants with dyslipidemia (TG level >204 mg/dL and HDL level <34 mg/dL).[48,49] These findings suggest that fibrate treatment effectively reduces the residual CV risk in high-risk patients.[50] However, fenofibrate is contraindicated in individuals with eGFR<30 mL/min/1.73 m^2, and there are not much data about the safety of gemfibrozil in patients with advanced CKD. Further RCTs of fibrates in patients with CKD to clarify its benefits and risks in this population are recommended in the commentary of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF DKOQI).[51]

Both hypoalbuminemia and inflammation are highly prevalent in patients undergoing PD and are independent risk factors for mortality in ESRD patients. Hypoalbuminemia causes hypertriglyceridemia and results in a paradoxical association between cholesterol level and all-cause and CV mortality, as discovered by Liu et al.[45] In contrast, the association between total cholesterol level and mortality was similar to that in the general population in the absence of hypoalbuminemia or inflammation.[52] The beneficial masking effect of statin due to hypoalbuminemia and inflammation might explain why previous RCTs reported neutral results for dialysis patients. In the present study, statins did not improve albumin levels, but the baseline albumin and CRP levels indicated hypoalbuminemia and an absence of a heightened inflammatory status in the study participants according to the definition of hypoalbuminemia and inflammation (serum albumin levels <3.6 mg/dL and CRP<10 mg/dL, respectively) in the study by Liu et al,[45] which interpreted the effect of statins on all-cause mortality and CVD more comprehensively. In contrast, statins significantly decreased CRP levels in this study, consistent with statins' widely accepted anti-inflammatory effect in previous studies.[53–57] Kang et al demonstrated that the anti-inflammatory effect directly influences arterial plaque.[58] The anti-inflammatory effect and ability of statins to lower cholesterol showed a probable beneficial effect on CVD and all-cause mortality, which may be amplified significantly in the absence of hypoalbuminemia.

Our study had several limitations. First, the number of studies included for primary outcomes was small (n = 3 for all-cause mortality and n = 2 for CVD). Second, the most significant limitation was that these meta-analyses included RCTs and observational studies. After separating the results of the RCTs and observational studies, the number of included studies was even smaller. Only one RCT with a small sample size was identified for all-cause mortality evaluation. However, quality assessment of the RCT suggested that it had a low risk of bias, and only two RCTs were identified for CVD evaluation. The other two observational studies for primary outcome evaluation had a high risk of bias, including selection bias, unmeasured confounders, and information bias. Third, although there was no evidence of heterogeneity for primary outcomes, higher doses of statins or statins with higher potency may affect the magnitude of the treatment effect, which may underestimate the benefit of statins. Due to the very low certainty of the evidence in primary and secondary outcomes, the influence of clinical and methodological diversity may be masked by the small number of included studies. Thus, this study's results should be interpreted cautiously despite reflecting the current body of evidence. Finally, only English and Chinese literature were included in our study, and some other language publications were missing. Therefore, further high-quality studies are required to investigate the exact role of statins in PD patients.

In conclusion, our analyses based on RCTs and observational studies indicated a probable beneficial effect of statins on CVD with very low certainty, which could not be concluded firmly because of the small number and limited quality of the included studies. Larger RCTs are required to evaluate whether statins can be routinely used to treat patients undergoing PD to prevent CV outcomes. In addition, statins-fibrates combination therapy may lower TG levels more efficiently in patients undergoing PD, which may further improve the clinical outcomes of these patients. Finally, the nutritional status of inflammation may modify the beneficial effects of statins on the CV outcomes of patients undergoing PD, which requires further consideration in future studies.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A165.

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