Journal of the American Heart Association

ORIGINAL RESEARCH

Effect of Statins in Patients With Hemodialysis-Dependent Chronic Kidney Disease: A Nationwide Cohort Study

Minyoul Baik, MD; Jimin Jeon, MS; Joonsang Yoo, MD, PhD; Jinkwon Kim, MD, PhD

BACKGROUND: Guidelines for lipid-lowering therapy in patients with dialysis-dependent chronic kidney disease remain ambiguous. We aimed to explore cardiovascular outcomes associated with statin use in patients with hemodialysis-dependent chronic kidney disease, stratified by prior statin use.

METHODS: This was a retrospective cohort study of patients with chronic kidney disease who initiated maintenance hemodialysis, using a nationwide health claims database in Korea between 2010 and 2021. A multivariate Cox regression analysis was performed, incorporating statin use throughout the follow-up period as a time-dependent variable. The primary outcome was a composite of stroke, myocardial infarction, and all-cause mortality. A subgroup analysis was conducted based on statin use before hemodialysis initiation.

RESULTS: Of the 49 868 study participants, the mean age at hemodialysis initiation was 65.5±11.2 years, and 32 225 (64.6%) were men. During a mean follow-up of 3.8 years, the primary composite outcome occurred in 20 345 patients (40.8%). Throughout the follow-up period, approximately 40% of patients received statin therapy. Statin use was significantly associated with a reduced risk of the primary composite outcome (adjusted hazard ratio, 0.51 [95% CI, 0.49–0.53]; $P<0.001$). This association was consistent regardless of prior statin use, although the benefit was less pronounced in statin-naïve patients (P for interaction <0.001).

CONCLUSIONS: Statin use was consistently associated with improved long-term cardiovascular outcomes in patients with hemodialysis-dependent chronic kidney disease, regardless of prior statin use. These findings suggest that continuing statin therapy is crucial for cardiovascular prevention in patients already receiving statins before hemodialysis initiation; initiating statin therapy may also provide clinical benefits in statin-naïve patients undergoing hemodialysis.

Key Words: cardiovascular outcome ■ chronic kidney disease ■ hemodialysis ■ statin

Lipid-lowering therapy remains challenging in patients with dialysis-dependent chronic kidney disease (CKD). Guidelines define CKD as a cardiovascular risk factor and recommend statin therapy for patients with non-dialysis-dependent CKD.[1–3] Although both all-cause and cardiovascular mortality rates increase with CKD progression,[4] recommendations for lipid-lowering therapy in patients with dialysis-dependent CKD remain ambiguous.[1–3] Specifically, current guidelines recommend against initiating statins or statin combinations in patients with dialysis-dependent CKD, although continuation is advised for those already receiving such treatment at the time of dialysis initiation.[1–3] These recommendations are based on randomized trials that have not demonstrated a significant benefit of statin therapy on composite cardiovascular outcomes in patients with dialysis-dependent CKD.[5–7]

Correspondence to: Jinkwon Kim, MD, PhD, Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, 363, Dongbaekjukjeon-daero, Yongin-si, Gyeonggi-do 16995, South Korea. Email: antithrombus@gmail.com

This article was sent to Charalambous C. Charalambous, PhD, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.043214

For Disclosures and Sources of Funding, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a nationwide cohort of nearly 50 000 patients initiating hemodialysis, statin use as a time-dependent exposure was associated with an approximately 50% lower risk of stroke, myocardial infarction, and all-cause mortality.

What Are the Clinical Implications?

- Continuation of statins after hemodialysis initiation is essential for improving cardiovascular and survival outcomes, with particularly strong benefits in patients already on statins before dialysis.
- Initiating statins in statin-naïve patients may also confer meaningful benefit, suggesting the need to reconsider current guidelines that discourage starting statins in this population.

Nonstandard Abbreviations and Acronyms

NHIS	National Health Insurance System

The benefits of statins in patients with dialysis-dependent CKD remain controversial, particularly regarding whether the effect of lipid-lowering therapy differs based on prior statin use.[3,5–7] Given the ambiguity in this field, we hypothesized that a time-dependent exposure analysis using a large population-based cohort could help evaluate the benefit of statins. Considering that medication use may vary over time, a time-dependent model is regarded as more reliable than a time-fixed model for accurately assessing the long-term effects of statin therapy in real-world clinical practice.[8]

This study aimed to investigate (1) the effect of statins on the risk of composite cardiovascular outcomes, considering the dynamic nature of statin use during follow-up, and (2) whether this association differs according to previous statin use, using Korean nationwide claims data.

METHODS

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (no. 9-2020-0148). The requirement for informed consent was waived because of the retrospective nature of the study, which was based on an anonymous health insurance claims database.

The data, analytical methods, and study materials will not be made available to other researchers to reproduce the results or replicate the procedure. The authors do not have the authority to share patient information because the National Health Insurance System (NHIS) data are derived from a nationwide administrative health claims database, in which the NHIS gives permission to researchers for access after reviewing each research topic. The NHIS data can be accessed through the NHIS website (https://nhiss.nhis.or.kr/).

Data Source and Participants

This retrospective observational cohort study was based on data from the Korean NHIS. The NHIS is an obligatory universal health insurance system covering the entire South Korean population.[9] When Korean citizens visit hospitals and use medical resources, their claims are submitted to the NHIS for billing. Thus, the NHIS database contains all citizens' demographic and medical information, including hospital visits, medical procedures, prescriptions, and diagnoses, as defined by the *International Classification of Diseases, Tenth Revision* (*ICD-10*). In addition, the NHIS provides a general health examination to all citizens aged ≥40 years every 2 years. This free-of-charge national health examination comprises a standard questionnaire (past medical history and lifestyle habits, including alcohol consumption, smoking, and exercise), anthropometric measurements (height, weight, body mass index, and blood pressure), and laboratory tests.[9]

Using the NHIS database, we screened patients diagnosed with advanced CKD between January 2010 and December 2021. Patients with advanced CKD were identified using *ICD-10* codes (end-stage renal disorder [N18.0], CKD stage 5 [N18.5], kidney transplantation [T86.1, Z94.0], and dialysis [Z99.2, Z49]) and a special claim code for hemodialysis of V001. To include patients with hemodialysis-dependent CKD, we selected those who consistently had claim codes for hemodialysis (O7020 and O9991) during the 3 months after HD initiation. The index date was defined as the first claim date for hemodialysis that satisfied the aforementioned continuity criteria. The health examination data of each individual were obtained from the most recent examination conducted within 2 years before the index date.

The claims database for this study has been available since 2002, and those who received hemodialysis before the index date (washout period) were excluded to ensure the inclusion of only patients who were newly initiating hemodialysis. Additionally, patients with a history of kidney transplantation before the index date, aged <40 years, missing health examination data, or inaccurate information regarding lipid-lowering therapy were excluded. Finally, patients with follow-up ≤90 days were excluded to account for the aim of this study on the long-term prognosis according to statin use and

the transiently increased risk of cardiovascular events after hemodialysis initiation,[10] which was not the focus of our study, and to avoid immortal bias.[11]

Outcomes and Follow-Ups

The primary outcome was defined as the composite development of stroke, myocardial infarction (MI), and all-cause death. Ischemic and hemorrhagic strokes were defined as admission with a primary diagnosis of relevant *ICD-10* codes (ischemic stroke [I63] and hemorrhagic stroke [I60–62]) and brain imaging during admission. MI was defined as an admission with a primary diagnosis based on the relevant *ICD-10* code [I21]. As described previously, patients who experienced events within 90 days of hemodialysis initiation were excluded.

Statin and Other Medications

Medication use during the follow-up period was collected as a time-dependent variable, which is considered more reliable than a time-fixed model for evaluating the effects of medications in real-world clinical practice.[8] On each day of the study period, medication use was determined by whether the day was covered by a prescription, based on the prescription records in the NHIS database. The primary variable of interest in this study was statin use, which was analyzed as a time-dependent variable. The use of statins, ezetimibe, oral antiplatelets, and oral anticoagulants was evaluated using this method, and these medications were incorporated as time-dependent variables. Previous statin use was defined as having a prescription of statins for more than 30 days within a 90-day period immediately preceding the index date (hemodialysis initiation) and was collected as a time-fixed variable.

Statistical Analysis

On each day of the follow-up period, the proportion of patients taking statins was calculated by dividing the number of at-risk patients using statins by the total number of at-risk patients on that day, to show the trend of statin use after hemodialysis initiation. Considering the dynamic change in statin use in clinical practice, the estimated event-free survival curve during follow-up after hemodialysis initiation was constructed using the Simon and Makuch method, which is an expansion of the Kaplan–Meier plot with respect to a time-dependent variable.[12] Differences between the curves according to statin use were evaluated using the Mantel–Byar test to compare survival data with a time-dependent variable.[13]

Using a Cox regression model incorporating the use of medications throughout the follow-up period as time-dependent variables, we calculated the adjusted hazard ratio (aHR) and 95% CI for statin use after hemodialysis initiation. Adjustments were made for sex, age, waist circumference, body mass index, systolic blood pressure, fasting glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, comorbidities (hypertension, diabetes, heart failure, cancer, atrial fibrillation, and history of cardiovascular disease), household income, smoking, alcohol consumption, physical activity, previous statin use as a time-fixed variable, and medication use (oral antiplatelet agents, anticoagulants, ezetimibe, and statins) during follow-up as time-dependent variables. We constructed individual time-dependent Cox regression models for each secondary outcome. The development of competing risks was censored at that time. Given that guidelines offer different recommendations regarding statin use based on whether patients were receiving statins before hemodialysis initiation,[1–3] we conducted a predetermined subgroup analysis according to prior statin use (prior statin users versus statin-naïve patients). Statistical analyses were performed using SAS (version 9.4.2; SAS Institute) and R (version 3.5.1; R Foundation for Statistical Computing) software. Statistical significance was set at $P<0.05$.

RESULTS

Between January 2010 and December 2021, 249 196 patients with advanced CKD were screened, and 196 932 were initiated on maintenance hemodialysis (Figure 1). After excluding 147 064 patients according to the study criteria, 49 868 patients with hemodialysis-dependent CKD who newly initiated maintenance hemodialysis were included in the study. Of the included patients, the mean age at hemodialysis initiation was 65.5±11.2 years, and 32 225 (64.6%) patients were men (Table 1). When we evaluated the use of statins throughout the period following hemodialysis initiation, the overall proportion of patients receiving statins remained approximately 40% (Figure 2 and Table S1).

During the mean 3.8±2.8 years of follow-up (mean±SD), 20 345 (40.8%) patients experienced the primary composite outcome (698 [1.4%] ischemic stroke, 644 [1.3%] hemorrhagic stroke, 789 [1.6%] MI, and 18 214 [36.5%] all-cause deaths). The Simon and Makuch plot showed a reduced risk of the primary composite outcome with statin use ($P<0.001$; Figure 3). In the multivariable time-dependent Cox regression model, statin use was associated with a 49% reduced risk of the primary composite outcome (aHR, 0.51 [95% CI, 0.49–0.53]; $P<0.001$; Table 2). Unlike statins, ezetimibe was not associated with the risk of the primary composite outcome ($P>0.05$, Table S2). In the analysis of secondary outcomes, statin use was significantly associated with a reduced risk of stroke

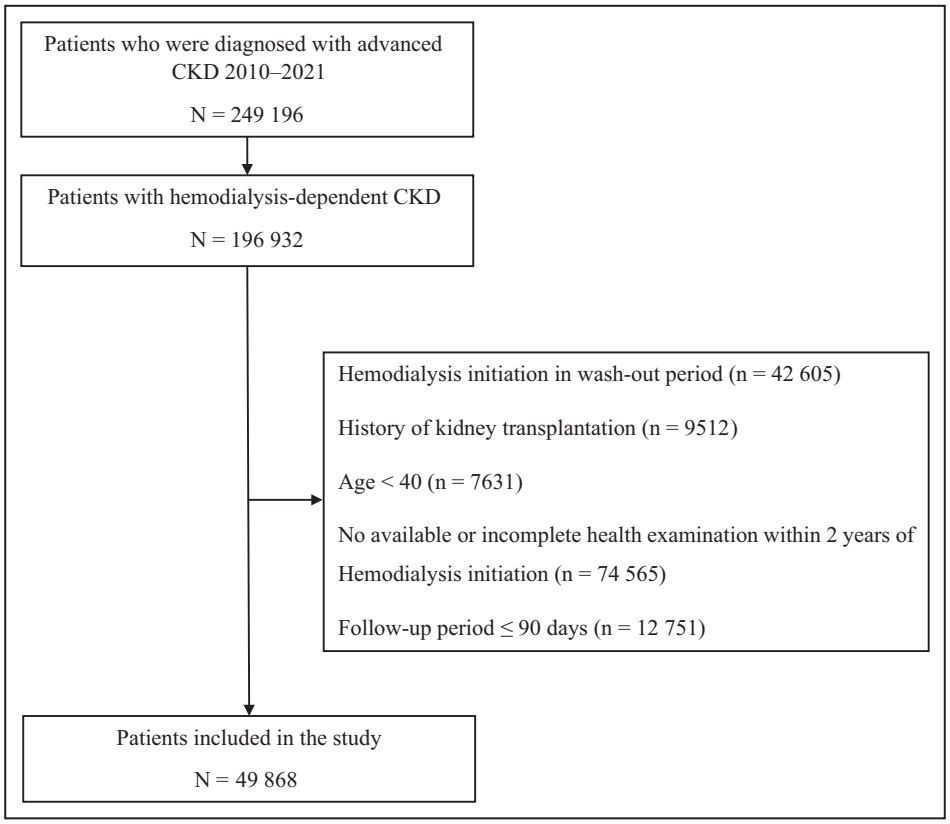

Figure 1. Flow diagram of patient selection.
CKD indicates chronic kidney disease.

and MI (especially ischemic stroke) and all-cause mortality (Table 2 and Table S3).

Given that current guidelines have different recommendations depending on statin use before hemodialysis initiation, we conducted subgroup analyses by dividing the patients into prior statin users and statin-naïve patients before hemodialysis initiation. When we investigated the proportion of patients receiving statin therapy at 6 months after hemodialysis initiation, statins were more frequently prescribed to prior statin users than to statin-naïve patients (68% versus 15%, $P<0.001$). In both groups, statin therapy after hemodialysis was consistently associated with a reduced risk of the primary composite outcome (Table 2). Interestingly, a significant interaction was observed with respect to prior statin use before hemodialysis initiation (P for interaction <0.001); the risk reduction was more pronounced in prior statin users (aHR, 0.44 [95% CI, 0.42–0.46]; $P<0.001$) compared with that in statin-naïve patients (aHR, 0.67 [95% CI, 0.63–0.72]; $P<0.001$) (Table 2). The benefits of statin therapy for stroke and MI, and for all-cause death, were consistent regardless of prior statin use; however, the benefit for stroke and MI was least pronounced and marginal in statin-naïve patients (aHR, 0.85 [95% CI, 0.73–1.00]; $P=0.048$; Table 2).

DISCUSSION

Using a nationwide claims-based database, we investigated the effects of statin use on long-term outcomes in patients with hemodialysis-dependent CKD. This study, based on real-world practices in Korea, showed that statin use after hemodialysis initiation was associated with approximately a 50% reduction in the risk of composite cardiovascular outcomes, including stroke, MI, and all-cause death. We found a significant interaction between statin use before hemodialysis initiation and the beneficial effects of statin use after maintenance hemodialysis. The benefit of statin use was more pronounced in prior statin users than in statin-naïve patients, especially for all-cause death. However, even among statin-naïve patients, statin therapy after hemodialysis initiation was significantly associated with a one-third reduction in the risk of primary composite outcome.

Because of the lack of robust evidence, the current guidelines offer ambiguous recommendations regarding lipid-lowering therapy for patients with dialysis-dependent CKD.[1–3] The 2019 European Society of Cardiology and European Atherosclerosis Society guidelines defined stage 3 to 5 CKD as high or very-high risk of atherosclerotic cardiovascular disease and

Table 1. Baseline Characteristics of the Patients Included in the Study

Variable	Total (N=49868)
Sex, male	32225 (64.62)
Age, y	65.48±11.23
Household income, quartile	
Q1, lowest	10413 (20.88)
Q2	13948 (27.97)
Q3	11814 (23.69)
Q4, highest	13693 (27.46)
Health examination	
Body mass index	24.15±3.59
Waist circumference	84.71±9.98
Systolic blood pressure, 10 mm Hg	137.09±19.70
Fasting glucose, mmol/L	6.76±3.23
Triglyceride, mmoL	1.80±1.28
Total cholesterol, mmoL	4.62±1.39
Low-density lipoprotein cholesterol, mmoL	2.60±1.18
Current smoker	6437 (12.91)
Alcohol consumption	
0 d/wk	39697 (79.60)
1–2 d/wk	7359 (14.76)
≥3 d/wk	2812 (5.64)
Physical activity	
0 d/wk	28663 (57.48)
1–2 d/wk	9222 (18.49)
≥3 d/wk	11983 (24.03)
Comorbidities	
History of cardiovascular disease	20467 (41.04)
Hypertension	48758 (97.77)
Diabetes	39532 (79.27)
Heart failure	26321 (52.78)
Atrial fibrillation	7102 (14.24)
Cancer	6483 (13.00)
Previous use of statin	25878 (51.89)

Data are represented as numbers (%) or mean±SD.

recommended statin or statin–ezetimibe combination therapy in non-dialysis-dependent stage 3 to 5 CKD as Class I, Level of Evidence A.[2] In patients with dialysis-dependent CKD, the guidelines recommend statins, ezetimibe, or their combination in patients already on those medications at the time of dialysis initiation; however, commencement of lipid-lowering therapy in statin-naïve patients was not recommended (Class III, Level of Evidence A–B).[2] The 2018 American guidelines and 2013 Kidney Disease: Improving Global Outcomes guidelines have similar recommendations.[1,3] The recommendation against initiating lipid-lowering therapy for patients with dialysis-dependent CKD is based on a few prior randomized trials. In the 2005 4D (Die Deutsche Diabetes Dialyze Studie) trial, including 1255 patients with diabetes on maintenance hemodialysis, atorvastatin 20 mg did not reduce the primary composite outcome of death from cardiac causes, nonfatal MI, and stroke (relative risk [RR], 0.92 [95% CI, 0.77–1.10]; P=0.37).[5] In the 2009 AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial, including 2776 patients on maintenance hemodialysis, rosuvastatin 10 mg was not associated with the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR, 0.96 [95% CI, 0.84–1.11]; P=0.59).[6] In the 2011 SHARP (Study of Heart and Renal Protection) trial with 9270 patients with CKD (3023 on maintenance dialysis at randomization), use of simvastatin 20 mg plus ezetimibe 10 mg reduced the risk of the primary composite outcome in patients not on dialysis (RR, 0.78 [95% CI, 0.67–0.91]); however, it did not in patients on dialysis (RR, 0.90 [95% CI, 0.75–1.08]).[7]

The lack of benefit observed in randomized trials initiating lipid-lowering therapy in dialysis-dependent CKD has traditionally been explained by competing risks, as nonatherosclerotic causes of death may overshadow the potential cardiovascular benefits.[1] Although patients on dialysis have the highest absolute cardiovascular risk, the large number of nonatherosclerotic or all-cause deaths and their short life expectancies may explain the limited effectiveness of statins in these patients.[1,5–7] Even if statins truly prevent cardiovascular events in prevalent dialysis patients, the magnitude of RR reduction is substantially smaller than in earlier stages of CKD.[14] In fact, meta-analyses showed that the relative reductions in major cardiovascular events observed with statin therapy diminish as estimated glomerular filtration rate declines, with little or no benefit in patients on dialysis.[14,15] In a meta-analysis of patients with CKD, the number needed to treat of statins to reduce 1 major cardiovascular event was 46 in CKD stage 5, 36 in CKD stage 4, and 24 in CKD stages 2 to 3.[16] If the speculative cardiovascular benefit among dialysis patients is confirmed in future studies, the absolute benefit may be comparable to that observed in patients with less severe CKD because of the higher cardiovascular event rate in the dialysis population.

Our study showed that statin use, treated as a time-varying variable throughout the follow-up period after hemodialysis initiation, was associated with a reduced risk of composite cardiovascular outcomes. This benefit was more pronounced in prior statin users than in statin-naïve patients; continuing statin therapy was associated with an approximately 56% reduction in the risk of cardiovascular outcomes. However, we found that the proportion of patients continuing statin therapy after hemodialysis initiation was consistently <70% throughout the study period. The low use of statin therapy may be attributed to previous reports

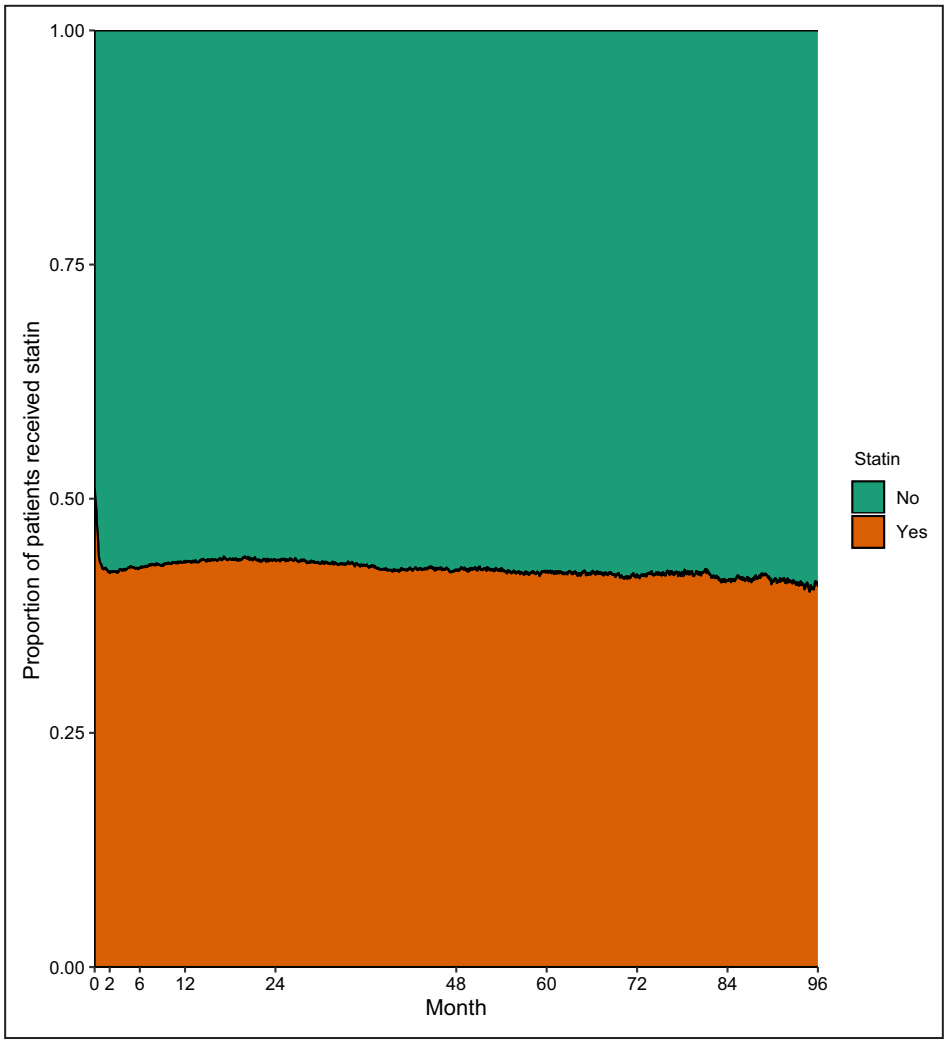

Figure 2. Daily changes in statin use after hemodialysis.
The diagram depicts the daily changes in statin use since the initiation of hemodialysis. The numbers and percentages at specific time points are shown in Table S1.

with inconsistent effects of statins in patients with dialysis-dependent CKD.[1,5–7] Considering that half of the patients with hemodialysis-dependent CKD exhibited moderate to poor treatment adherence,[17] and guidelines recommend continuing statin therapy in prior statin users,[1–3] continuous prescription of statins and educational efforts to improve adherence are important for preventing cardiovascular events in these patients. Given the significant risk reduction associated with statin therapy, the low proportion of patients taking statin therapy could be a potential treatment target in the high-risk group of patients with dialysis-dependent CKD who were already taking statins before hemodialysis.

The significant interaction according to previous statin use, showing less benefit in statin-naïve patients, may help explain the inconsistent findings of previous studies on the effectiveness of statins in statin-naïve patients and may partly account for the failure of earlier trials to demonstrate a clear benefit of statin therapy in dialysis-dependent CKD.[5–7] The SHARP trial showed that a simvastatin and ezetimibe combination safely reduced the incidence of major cardiovascular events in a wide range of patients with advanced CKD (HR, 0.83 [95% CI, 0.74–0.94]), and subgroup analysis did not show a significant interaction based on dialysis status (P=0.21).[7] This finding suggests that future randomized trials may reveal the benefits of lipid-lowering therapy even in statin-naïve patients. Another explanation for the stronger association observed in prior statin users may be the different baseline characteristics of prior statin users and statin-naïve patients. Because prior statin users have higher levels of dyslipidemia and more underlying cardiovascular risk factors than those of statin-naïve patients, the preventive effects of statins may differ. These characteristics of statin-naïve patients

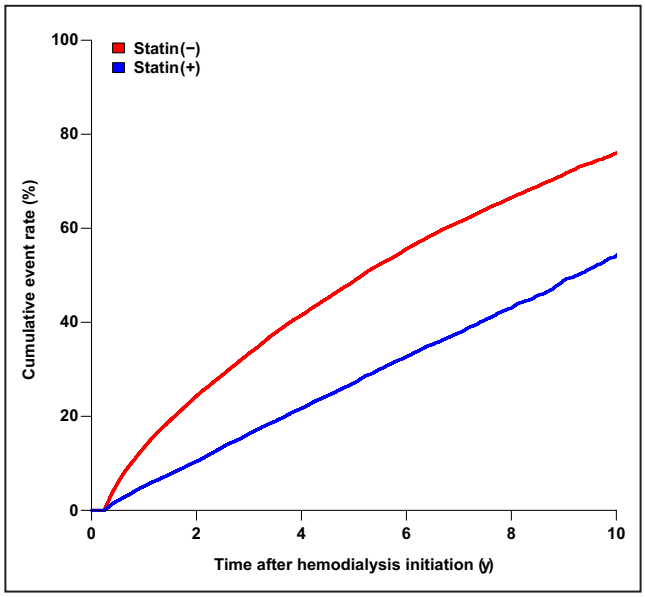

Figure 3. Cumulative incidence of primary composite outcome according to statin use.
Statin use decreased the risk of the primary composite outcome during follow-up (Mantel–Byar test, $P<0.001$).

before hemodialysis may obscure the clinical benefits of statin therapy. Further studies are needed to explore the underlying mechanisms behind the differences in the effectiveness of statins according to previous statin use before hemodialysis and to support future clinical trials in this population.

In our study, lipid-lowering therapy was also associated with a reduced risk of stroke and MI (especially ischemic stroke) and all-cause death in the secondary outcome analyses. In secondary outcome analyses of previous randomized trials, lipid-lowering therapy did not reduce all-cause death or ischemic stroke.[5–7] Accumulating epidemiologic evidence has shown that lipid-lowering therapy is effective in reducing cardiovascular morbidity and mortality in various diseases and general populations.[1,2] Statins, a representative lipid-lowering therapy, have been associated with a reduced risk of all-cause mortality, suggesting the pleiotropic benefits of statins. In 326 981 older US veterans without known CVD, statin use was associated with a 25% reduction in the risk of all-cause mortality (HR, 0.75 [95% CI, 0.74–0.76]).[18] Similarly, statin therapy reduced all-cause mortality in 96 162 matched nursing home residents.[19] A meta-analysis of randomized trials demonstrated that statins reduced the risk of all-cause death by 9% per 1.0 mmol/L reduction in low-density lipoprotein cholesterol (HR, 0.91 [95% CI, 0.88–0.93]).[20] A previous Korean health claims database study showed that statin initiation was associated with a reduced risk of all-cause mortality in incident statin-naïve dialysis patients.[21] The multinational observational study, DOPPS (Dialysis Outcomes and Practice Patterns Study), which included 17 221 hemodialysis patients, showed that statin users had a 31% lower relative risk of death compared with nonusers.[22] Our study showed that the benefit of statin therapy was more pronounced for all-cause death than for stroke and MI, with the least benefit for stroke and MI observed in statin-naïve patients. This relatively weak effect on stroke and MI may partly explain why previous randomized trials initiating lipid-lowering therapy in dialysis-dependent CKD have failed to demonstrate a benefit of statins.[1–3] In our data, the reason why statins decreased the incidence of ischemic stroke but not MI remains unclear and is inconsistent with the results of a previous study.[20] This discrepancy should be further investigated in future studies.

This study has several strengths. First, we included a large number of patients with CKD who were initiated on continuous hemodialysis using real-world data from a nationwide health claims database. Our sample size (N=49 868) was larger than that reported in a previous meta-analysis (N=7053 on dialysis).[15] Second, the use of prescription data from the nationwide health claims database allowed for the detailed assessment of statin use, reflecting the dynamic change throughout the study period as a time-dependent variable. This approach is known to be more reliable than a time-fixed model for evaluating the effects of medications that may change over time on long-term outcomes in clinical practice.[8] A previous study showed that the association between statin use and all-cause death was not observed in a fixed summary measure but was evident in repeatedly measured covariates.[23] However,

Table 2. Impact of Statin Use on the Outcomes According to Previous Statin Use

	Whole population (N=49868)		Previous use of statin			
			Yes; prior statin user (n=25878)		No; statin-naïve patients (n=23990)	
	aHR [95% CI]	*P* value	aHR [95% CI]	*P* value	aHR [95% CI]	*P* value
Primary composite outcome						
Stroke, MI, and all-cause death	0.51 [0.49–0.53]	<0.001	0.44 [0.42–0.46]	<0.001	0.67 [0.63–0.72]	<0.001
Secondary outcomes						
Stroke, MI	0.81 [0.73–0.89]	<0.001	0.78 [0.68–0.88]	<0.001	0.85 [0.73–1.00]	0.048
All-cause death	0.48 [0.46–0.50]	<0.001	0.41 [0.39–0.43]	<0.001	0.66 [0.61–0.70]	<0.001

Data were obtained from a multivariable time-dependent Cox proportional hazards regression model for the development of the outcome. Adjustments were made for sex, age, waist circumference, body mass index, systolic blood pressure (10 mm Hg), fasting glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, hypertension, diabetes, heart failure, cancer, atrial fibrillation, history of cardiovascular disease, household income, smoking, alcohol consumption, physical activity, previous use of statins, oral antiplatelets, oral anticoagulants, and ezetimibe. aHR indicates adjusted hazard ratio; and MI, myocardial infarction.

this study has certain limitations. First, the possibility of residual confounding and bias cannot be ruled out, as this was a retrospective cohort study without intervention based on a claims database. In particular, a large proportion of patients on hemodialysis were excluded because they had not undergone a health examination, which was necessary for defining key covariates such as low-density lipoprotein cholesterol. Although this exclusion was methodologically unavoidable, it may have introduced selection bias. Second, the findings may not be generalizable to other populations, as the study was conducted solely on Korean participants. Third, serum albumin level, a key marker of nutritional status in patients on hemodialysis,[24] was not available in the Korean health examination data, making it difficult to rule out confounding by inflammation and malnutrition. Substantial evidence suggests that the inverse association between cholesterol levels and mortality in patients on hemodialysis is largely driven by such confounding rather than a true protective effect of high cholesterol.[25,26] Future studies with more comprehensive data and prospective designs are warranted to validate these findings.

CONCLUSIONS

Among patients with hemodialysis-dependent CKD, statin use may be a reasonable approach to improve long-term prognosis, including reducing the risk of stroke, MI, and all-cause death. Our findings suggest that statin use is associated with an approximately 50% reduction in composite cardiovascular outcomes. Although previous studies have not proven the beneficial effects of initiating statins in statin-naïve patients on hemodialysis, our study showed that in patients with and without prior statin use before hemodialysis initiation, statin use consistently demonstrated a favorable long-term prognosis, with a more pronounced benefit in prior statin users. These results highlight the need for further clinical trials to evaluate the potential benefits of lipid-lowering therapies in this population.

ARTICLE INFORMATION

Received April 20, 2025; accepted September 17, 2025.

Affiliation

Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin-si, Gyeonggi-do, South Korea.

Acknowledgments

This study was conducted using data from the NHIS (Research Management Number: NHIS-2023-1-823). We thank NHIS employees for providing this data set. Minyoul Baik and Jinkwon Kim contributed to the concept and design of the study. Minyoul Baik, Jimin Jeon, Joonsang Yoo, and Jinkwon Kim contributed to the acquisition and analysis of data; Minyoul Baik and Jinkwon Kim contributed to drafting the article and preparing the figures.

Sources of Funding

This study was supported by a faculty research grant from the Yonsei University College of Medicine (6–2024-0144) and a National Research Foundation of Korea grant funded by the Korean Government (MSIT) (Grant No. RS-2024-00345524).

Disclosures

Dr Baik received a research grant from Daewoong and HK inno.N Pharmaceuticals. Dr Yoo received a research grant from the Chong Kun Dang Pharmaceutical. Dr Kim received research grants from Chong Kun Dang and Myung in Pharmaceutical. J. Jeon declares no conflicts of interest.

Supplemental Material

Tables S1–S3

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid

modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. 2020;41:111–188. doi: 10.1093/eurheartj/ehz455
3. Wanner C, Tonelli M. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85:1303–1309. doi: 10.1038/ki.2014.31
4. Consortium CKDP. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081. doi: 10.1016/S0140-6736(10)60674-5
5. Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248. doi: 10.1056/NEJMoa043545
6. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae D-W, Chevaile A, Cobbe SM, Grönhagen-Riska C, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395–1407. doi: 10.1056/NEJMoa0810177
7. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, 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 randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192. doi: 10.1016/S0140-6736(11)60739-3
8. Bijlsma MJ, Janssen F, Hak E. Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method. *Pharmacoepidemiol Drug Saf*. 2016;25:325–332. doi: 10.1002/pds.3935
9. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, Do CH, Song JS, Hyon Bang J, Ha S, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol*. 2017;46:799–800. doi: 10.1093/ije/dyw253
10. Baik M, Jeon J, Yoo J, Nam HS, Heo JH, Kim J, Kim YD. Risk of cardiovascular events following hemodialysis initiation: a self-controlled case series study. *Kidney Res Clin Pract*. Published online ahead of print September 2024. doi: 10.23876/j.krcp.24.097
11. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087. doi: 10.1136/bmj.b5087
12. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. *Stat Med*. 1984;3:35–44. doi: 10.1002/sim.4780030106
13. Cantor AB. A test of the association of a time-dependent state variable to survival. *Comput Methods Prog Biomed*. 1995;46:101–105. doi: 10.1016/0169-2607(94)01604-e
14. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GFM. Benefits and harms of statin therapy for persons with chronic kidney disease. *Ann Intern Med*. 2012;157:263–275. doi: 10.7326/0003-4819-157-4-201208210-00007
15. Collaboration CTTC. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol*. 2016;4:829–839. doi: 10.1016/S2213-8587(16)30156-5
16. Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, Cass A, Zhang H, Wang H. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J*. 2013;34:1807–1817. doi: 10.1093/eurheartj/eht065
17. Lnu A, Rathee G, Sharma R, Dahiya S, Vaibhav F, Kumar P. Treatment adherence and factors influencing it in end-stage renal disease patients on maintenance hemodialysis: a study from a tertiary care hospital in North India. *Cureus*. 2024;16:e73335. doi: 10.7759/cureus.73335
18. Orkaby AR, Driver JA, Ho Y-L, Lu B, Costa L, Honerlaw J, Galloway A, Vassy JL, Forman DE, Gaziano JM, et al. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. *JAMA*. 2020;324:68–78. doi: 10.1001/jama.2020.7848
19. O'Sullivan JL, Kohl R, Lech S, Romanescu L, Schuster J, Kuhlmey A, Gellert P, Yasar S. Statin use and all-cause mortality in nursing home residents with and without dementia. *Neurology*. 2024;102:e209189. doi: 10.1212/WNL.0000000000209189
20. Collaboration CTTC. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet*. 2015;385:1397–1405. doi: 10.1016/S0140-6736(14)61368-4
21. Kim JE, Park S, Kim M-s, Kang SJ, Lee JW, Kim KS, Kim YC, Kim DK, Joo KW, Kim YS, et al. Statin initiation and all-cause mortality in incident statin-naïve dialysis patients. *Atherosclerosis*. 2021;337:59–65. doi: 10.1016/j.atherosclerosis.2021.08.026
22. Andreucci VE, Fissell RB, Bragg-Gresham JL, Ethier J, Greenwood R, Pauly M, Wizemann V, Port FK. Dialysis Outcomes and Practice Patterns Study (DOPPS) data on medications in hemodialysis patients. *Am J Kidney Dis*. 2004;44:61–67. doi: 10.1053/j.ajkd.2004.08.013
23. Alsabbagh MW, Eurich D, Lix LM, Wilson TW, Blackburn DF. Does the association between adherence to statin medications and mortality depend on measurement approach? A retrospective cohort study. *BMC Med Res Methodol*. 2017;17:66. doi: 10.1186/s12874-017-0339-z
24. Bossola M, Muscaritoli M, Tazza L, Giungi S, Tortorelli A, Fanelli FR, Luciani G. Malnutrition in hemodialysis patients: what therapy? *Am J Kidney Dis*. 2005;46:371–386. doi: 10.1053/j.ajkd.2005.05.031
25. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA*. 2004;291:451–459. doi: 10.1001/jama.291.4.451
26. Chang TI, Streja E, Ko GJ, Naderi N, Rhee CM, Kovesdy CP, Kashyap ML, Vaziri ND, Kalantar-Zadeh K, Moradi H. Inverse association between serum non-high-density lipoprotein cholesterol levels and mortality in patients undergoing incident hemodialysis. *J Am Heart Assoc*. 2018;7:7. doi: 10.1161/jaha.118.009096