Statin Therapy Before Transition to End-Stage Renal Disease With Posttransition Outcomes

Melissa Soohoo, MPH; Hamid Moradi, MD; Yoshitsugu Obi, MD, PhD; Connie M. Rhee, MD, MSc; Elvira O. Gosmanova, MD; Miklos Z. Molnar, MD, PhD; Moti L. Kashyap, MD, MSc; Daniel L. Gillen, PhD; Csaba P. Kovesdy, MD; Kamyar Kalantar-Zadeh, MD, MPH, PhD; Elani Streja, MPH, PhD

Background—Although studies have shown that statin therapy in patients with non–dialysis-dependent chronic kidney disease was associated with a lower risk of death, this was not observed in dialysis patients newly initiated on statins. It is unclear if statin therapy benefits administered during the predialysis period persist after transitioning to end-stage renal disease.

Methods and Results—In 47,720 veterans who transitioned to end-stage renal disease during 2007 to 2014, we examined the association of statin therapy use 1 year before transition with posttransition all-cause and cardiovascular mortality and hospitalization incidence rates over the first 12 months of follow-up. Associations were examined using multivariable adjusted Cox proportional hazard models and negative binomial regressions. Sensitivity analyses included propensity score and subgroup analyses. The cohort’s mean±SD age was 71±11 years, and the cohort included 4% women, 23% blacks, and 66% diabetics. Over 12 months of follow-up, there were 13,411 deaths, with an incidence rate of 35.3 (95% CI, 34.7–35.8) deaths per 100 person-years. In adjusted models, statin therapy compared with no statin therapy was associated with lower risks of 12-month all-cause (hazard ratio [95% CI], 0.79 [0.76–0.82]) and cardiovascular (hazard ratio [95% CI], 0.83 [0.78–0.88]) mortality, as well as with a lower rate of hospitalizations (incidence rate ratio [95% CI], 0.89 [0.87–0.92]) after initiating dialysis. These lower outcome risks persisted across strata of clinical characteristics, and in propensity score analyses.

Conclusions—Among veterans with non–dialysis-dependent chronic kidney disease, treatment with statin therapy within the 1 year before transitioning to end-stage renal disease is associated with favorable early end-stage renal disease outcomes. (J Am Heart Assoc. 2019;8:e011869. DOI: 10.1161/JAHA.118.011869)

Key Words: end-stage renal disease • lipids • mortality • statin

Dyslipidemia is an established risk factor for cardiovascular events and mortality in the general population, and cholesterol-lowering drugs, especially statins, have been shown to improve outcomes among such patients at risk of cardiovascular events. Chronic kidney disease (CKD) is a progressive and irreversible condition associated with a high risk of cardiovascular morbidity and mortality, and current guidelines recommend treatment with statins irrespective of cholesterol levels and kidney function among adult patients with non–dialysis-dependent (NDD) CKD. The benefits of statin therapy in patients with NDD-CKD were observed in the subgroup analysis of the SHARP (Study of Heart and Renal Protection) trial, in which the statin combined therapy (ie, simvastatin plus ezetimibe), compared with placebo, reduced...
Statins and Post-ESRD Outcomes  Soohoo et al

### Clinical Perspective

**What Is New?**

- Although the SHARP (Study of Heart and Renal Protection), AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), and 4D (Deutsche Diabetes Dialyse Studie) clinical trials showed the relationship of statin therapy with cardiovascular outcomes across different stages of chronic kidney disease, the association of statin use in late-stage chronic kidney disease with post-end-stage renal disease transition outcomes has not previously been demonstrated.

- Herein, we demonstrate, among a cohort of US veterans transitioning to end-stage renal disease, the benefit of statin therapy before transition with posttransition mortality and hospitalization outcomes.

**What Are the Clinical Implications?**

- This analysis supports current guidelines, which indicate treatment of statin therapy for patients with late-stage kidney disease and potentially transitioning to end-stage renal disease.

### Demographics and Clinical Measurements

Baseline characteristics were developed from the combination of 3 national databases: USRDS, VA, and Centers for Medicare and Medicaid Services (CMS). Data on marital and smoking status were obtained from VA records only. Initial dialysis characteristics, including modality and access type, were obtained from USRDS files only. Preexisting comorbidity information at the time of transition was extracted from VA and CMS databases using *International Classification of Diseases, Ninth Revision (ICD-9)*, Diagnostic and Procedural codes and Current Procedural Terminology codes as guided by those listed in the Deyo Charlson Comorbidity Index and CMS Chronic Conditions. The presence of comorbidities was determined using a 1 inpatient or 2 outpatient visit algorithm. The Charlson Comorbidity Index was calculated without renal disease. The presence of cardiovascular disease (CVD) was determined as the presence of any prior atrial fibrillation, ischemic heart disease, myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease, or cerebrovascular disease.

Data on most pre-ESRD (prelude) laboratory measurements were sourced from VA databases. Serum creatinine data and, thus, estimated glomerular filtration rate within the past 90 days before transition were obtained from the VA Corporate Data Warehouse LabChem file and the USRDS CMS 2728 Medical Evidence form. Other serum laboratory measurements, including lipid panel, were obtained from the VA

The risk of major atherosclerotic events by 22% among 6247 patients with NDD-CKD. The SHARP trial also included 3023 maintenance dialysis patients, but the cardiovascular benefit of the statin combined therapy was not clearly observed in this dialysis patient subgroup. Given these observations, along with the results from the other clinical trials, the current guidelines do not recommend initiating statin therapy in patients already receiving maintenance dialysis.

In the SHARP trial, however, patients with NDD-CKD who transitioned to dialysis during the follow-up period were analyzed as part of the NDD-CKD group rather than separately. Therefore, it remains unclear whether the benefits of statin therapy observed in the NDD-CKD group persisted after transition to end-stage renal disease (ESRD) (ie, benefits of pre-ESRD statin use on post-ESRD outcomes). Thus, in a large cohort of US veteran patients transitioning to ESRD, we examined the associations of statin therapy in the year before transition with posttransition 12-month mortality risk and hospitalization rate.

### Methods

**Study Population and Data Source**

We retrospectively examined data from the Transition of Care in Chronic Kidney Disease US Renal Data System (USRDS) Special Study Center, which is focused on investigating the transition to renal replacement therapy among patients with incident ESRD. The USRDS identified the source cohort of 85,505 veterans who transitioned to renal replacement therapy from October 1, 2007, to March 30, 2014. We excluded 1958 patients for missing censor information; 25,792 patients for missing prescription medication information in the 1 year before ESRD transition; and 10,035 patients for receiving less than half of a year of statin prescription. The final cohort was composed of 47,720 veterans with incident ESRD, of whom 22,151 were not prescribed pre-ESRD statin therapy and 25,569 were prescribed pre-ESRD statin therapy (Figure S1).

This study was approved by the Tibor Rubin and Memphis Veterans Affairs Medical Centers’ Institutional Review Boards. The written consent requirement was waived given the large sample size, patient anonymity, and nonintrusive nature of this study. The data and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure given that data are provided under contract with the US Department of Veterans Affairs (VA) and are at its disposal. Hence, this center may not override the contractual agreements. Additional details about the analytical methods can be provided on request.

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Decision Support System National Data Extracts Laboratory Results file, whereas body mass index and blood pressures were obtained from the VA Corporate Data Warehouse Vital Signs file. With the exception of estimated glomerular filtration rate, for which a single measurement was used, laboratory measurements within the baseline 1 year prelude period were averaged.

**Exposure Measurement**

Both inpatient and outpatient medication data were sourced from CMS Medicare Part D and VA pharmacy dispensation records. Lipid-lowering drugs, including statins, were extracted using specific VA drug class codes and names. Patients covered with prescriptions for at least half of the 1 year before transition to ESRD were characterized as receiving statin therapy. Patients with medication prescriptions for other treatments in the 1 year prelude period, yet not prescribed statin therapy during the same time period, were categorized as not receiving statin therapy. Patients covered with prescriptions for statin therapy for less than half of the year were excluded from our main analyses.

**Outcome Assessment**

The primary outcomes were all-cause and cardiovascular mortality in the first 12 months after transition to ESRD. The secondary outcome was hospitalization incidence in the first 12 months after transition to ESRD.

All data on all outcomes and censoring events were obtained from USRDS, VA, and CMS data sets. Follow-up started at ESRD initiation until death, kidney transplantation, lost to follow-up, end of the 12-month follow-up period, or date of administrative censoring, whichever occurred first. The last date of follow-up was September 2, 2014, or June 30, 2014, for all-cause events or cardiovascular mortality, respectively.

Cardiovascular causes of death, including MI, cardiac arrest, CHF, valvular heart disease, cardiac arrhythmia, cardiomyopathy, pericarditis, cerebrovascular event, pulmonary embolus, and atherosclerotic heart disease, were obtained from USRDS records only.

Cardiovascular mortality was examined in a subset of patients with an available and known cause of death from USRDS files. The subset cohort included 42,771 and 37,729 patients for 12-month and 7-year cardiovascular mortality, respectively.

**Statistical Analysis**

Baseline patient characteristics were presented as mean±SD or median (25th–75th percentile) for continuous variables and proportions for categorical variables, as appropriate. Standardized differences were used to compare characteristics between statin therapy groups.

For all analyses, nonreceipt of statin therapy served as the referent group. Cox proportional hazard models were used to examine the association of statin therapy with 12-month posttransition all-cause mortality and cardiovascular mortality. Moreover, we examined the association of statin therapy with 12-month posttransition hospitalization incidence rate using a negative binomial regression model.

All associations were examined in unadjusted and adjusted models, which included adjustment for demographics (age, sex, race, and ethnicity) and the following comorbidities: Charlson Comorbidity Index, diabetes mellitus, atherosclerotic CVD (defined as the presence of MI, peripheral vascular disease, or ischemic heart disease), atrial fibrillation, CHF, and cerebrovascular disease. Moreover, we performed separate adjustments for indicators of pre-ESRD care, including initial access type and VA or CMS nephrology outpatient visits in the year before ESRD transition (use of nephrology services). Furthermore, we examined associations of statin therapy with all outcomes across a priori selected subgroups. Formal tests of interactions were performed using Wald’s test under the adjusted model. Among all patients with any statin therapy in the pre-ESRD period (n=35,604), we modeled statin therapy exposure as the total number of days in association with mortality outcomes using restricted cubic splines with best placed knots at the 5th, 35th, 65th, and 95th percentiles of exposure.

In sensitivity analyses, we also examined associations in patients with available and complete laboratory information in the past 1 year before transition. Models were additionally adjusted for smoking status, last estimated glomerular filtration rate before transition, and the following averaged laboratory variables: body mass index, serum hemoglobin, albumin, calcium, white blood cell count, bicarbonate, and blood urea nitrogen. We also examined associations for all outcomes for up to 7 years of follow-up. Finally, we calculated propensity scores (PS) for bias reduction as well as to account for patient differences between groups. The PS was calculated as the probability of statin therapy given by the covariates from our adjusted model. We then used the PS for our mortality analyses, including PS matching (n=19,364 patients in each arm), PS adjustment in the overall cohort, and PS stratification in the overall cohort using a doubly robust estimation approach.

The proportionality assumption was checked using plots of log (−log[survival rate]) against log(survival time). Data on demographic and comorbid conditions used in analyses were missing for <0.40% of the cohort and imputed using means or missing categories. All analyses were conducted using SAS Enterprise Guide (7.1) (Cary, NC) and Stata 15 (College Station, TX).
Results
The study cohort comprised 47,720 patients, and their mean ± SD age was 71 ± 11 years (Table 1). The cohort also included 4% women, 23% blacks, 66% diabetics, and 78% patients with CVD. Overall, 54% of the cohort was prescribed statin therapy before ESRD initiation. Patients who received statin therapy for an average of 277 ± 45 (median [25th–75th percentile], 278 [247–314]) days in the year before transition to ESRD. Patients receiving statin therapy were more likely to have diabetes mellitus; have CVD history, including ischemic heart disease, MI, CHF, peripheral vascular disease, and cerebrovascular disease; use an arteriovenous fistula during initial dialysis treatment; and have greater use of VA nephrology services in the year before transition. They were also less likely to be black and had a lower prevalence of liver disease.

Association of Statin Therapy With All-Cause and Cardiovascular Mortality
Over 12 months of follow-up, there were 13,411 all-cause deaths, with an incidence rate (95% CI) of 35.3 (34.7–35.8) deaths per 100 person-years. Patients who received statin therapy in the year before transition had a lower crude all-cause mortality rate over the 12-month follow-up period compared with those who did not receive statin therapy (33.1 [95% CI, 32.3–33.8] versus 37.9 [95% CI, 37.0–38.8] per 100 person-years, respectively). In survival analyses, patients who received statin therapy had a 12% lower all-cause mortality risk in the unadjusted model (hazard ratio (HR), 0.88 [95% CI, 0.85–0.91]), which was slightly strengthened after adjustment for demographics and comorbidities (HR [95% CI], 0.79 [0.76–0.82]) (Table 2). Moreover, there were no differences observed in the comparison of crude cardiovascular mortality rates and in the unadjusted Cox model. However, in adjusted models, patients receiving statin therapy had a 17% lower risk of cardiovascular death (HR [95% CI], 0.83 [0.78–0.88]) (Table 2).

Association of Statin Therapy With Hospitalization Rate
Over the first 12 months post-ESRD transition, patients who received statin therapy in the 1 year before ESRD transition had a lower overall rate of hospitalizations compared with patients who did not receive statin therapy (rate [95% CI], 206.8 [204.8–208.8] versus 209.5 [207.4–211.7] hospitalizations per 100 patient-years, respectively). Patients receiving statin therapy had a lower hospitalization rate, persisting in all models (adjusted incidence rate ratio [95% CI]), 0.89 [0.87–0.92]) (Table 2).

Subgroup Analyses
Across all strata, receipt of statin therapy compared with no receipt of statin therapy was associated with a lower risk of all outcomes (Figure, Table S1). For both all-cause and cardiovascular mortality, lower HRs with statin therapy were observed for younger patients (P-interaction=0.0001 for all-cause mortality; P-interaction=0.03 for cardiovascular mortality) and nondiabetic patients (P-interaction=0.02 for all-cause mortality; P-interaction=0.011 for cardiovascular mortality). A similar effect of younger age was observed for hospitalization incidence rate (P-interaction=0.0003). Moreover, effect modification by black race was observed for mortality outcomes, whereby black patients compared with non-black patients had a lower death HR for statin therapy versus no statin therapy. There was also effect modification by CVD, for which a lower death HR and a lower incidence rate ratio were observed in patients without CVD for those who received statin therapy. Subgroup analyses by decomposed CVD are presented in Figure S2 and showed similar results; within all subgroups, patients who received statin therapy had a lower estimate of event, compared with that of those who did not receive statin therapy. However, with the exception of atrial fibrillation, for both outcomes of all-cause mortality and hospitalization rate, we observed effect modification by all individual CVDs where a lower risk was observed for patients without the CVD comorbidity. Effect modification was present for CHF, peripheral vascular disease, and atherosclerotic CVD for the cardiovascular mortality outcome only. Presence of liver disease also impacted the all-cause mortality risk and hospitalization incidence rates, whereby the HR and incidence rate ratio, respectively, for patients who received statin therapy were lower in those with versus without liver disease. Smoking and 1-year averaged pre-ESRD statin therapy had a lower risk of cardiovascular death (HR [95% CI], 0.83 [0.78–0.88]) (Table 2).

Sensitivity Analyses
Associations of statin therapy with a longer follow-up for 7-year outcomes were similar to findings in the main analyses (Figure S3), including hospitalization incidence rate ratio (0.90 [95% CI, 0.88–0.92]). Similar associations were observed after additional adjustment for pre-ESRD care indexes, including initial vascular access type and nephrology use for both all-cause and cardiovascular mortality outcomes, as well as hospitalization rate (Table S2). When modeled as a continuous variable, the number of days of statin therapy exposure showed a graded and inverse association with mortality outcomes (reference, 182 days), among a larger cohort of patients with any receipt of statin therapy in the pre-ESRD period. A longer amount of time receiving pre-ESRD statin therapy (more than
Table 1. Baseline Characteristics of 47,720 Patients Stratified by Use of Statin Therapy Before ESRD Transition

| Characteristics                          | Total (N=47,720) | Statin Therapy (n=25,569, 53.6%) | No Statin Therapy (n=22,151, 46.4%) | Standardized Difference |
|------------------------------------------|------------------|----------------------------------|------------------------------------|-------------------------|
| Cardiovascular disease, %                |                  |                                  |                                    |                         |
| No                                       | 22               | 14                               | 30                                 | 0.38                    |
| Yes                                      | 78               | 86                               | 70                                 | 0.09                    |
| Atrial fibrillation                      | 17               | 18                               | 15                                 | 0.07                    |
| ISHD                                     | 59               | 68                               | 48                                 | 0.41                    |
| MI                                        | 26               | 31                               | 20                                 | 0.26                    |
| CHF                                      | 55               | 61                               | 49                                 | 0.24                    |
| PVD                                      | 38               | 44                               | 32                                 | 0.25                    |
| Cerebrovascular disease                  | 31               | 36                               | 26                                 | 0.23                    |
| Age, y                                   | 71±11            | 72±10                            | 71±12                              | 0.14                    |
| Aged <65 y, %                            | 29               | 25                               | 33                                 | −0.16                   |
| Aged 65–<75 y, %                         | 27               | 29                               | 25                                 | 0.09                    |
| Aged ≥75 y, %                            | 44               | 46                               | 43                                 | 0.07                    |
| Female sex, %                            | 4                | 3                                | 5                                  | −0.09                   |
| Race, %                                  |                  |                                  |                                    |                         |
| White                                    | 73               | 76                               | 69                                 | 0.16                    |
| Black                                    | 23               | 20                               | 27                                 | −0.16                   |
| Other                                    | 4                | 4                                | 5                                  | −0.01                   |
| Hispanic ethnicity, %                    | 6                | 6                                | 6                                  | 0.01                    |
| Married status, %                        | 60               | 62                               | 58                                 | 0.08                    |
| CCI                                       | 4 (2–6)          | 4 (3–6)                         | 3 (2–5)                           | 0.24                    |
| Comorbidities, %                         |                  |                                  |                                    |                         |
| Diabetes mellitus                        | 66               | 74                               | 57                                 | 0.37                    |
| Anemia                                   | 72               | 74                               | 69                                 | 0.12                    |
| Depression                               | 22               | 23                               | 22                                 | 0.04                    |
| Hyperlipidemia                           | 78               | 91                               | 63                                 | 0.71                    |
| COPD                                     | 42               | 45                               | 39                                 | 0.12                    |
| Peptic ulcer disease                     | 7                | 7                                | 7                                  | −0.02                   |
| Liver disease                            | 11               | 8                                | 15                                 | −0.22                   |
| Cancer                                   | 24               | 24                               | 25                                 | −0.02                   |
| Smoking status, %                        |                  |                                  |                                    |                         |
| Never                                    | 30               | 30                               | 30                                 | 0.11                    |
| Current                                  | 35               | 33                               | 37                                 |                         |
| Past                                     | 35               | 37                               | 32                                 |                         |
| eGFR at initiation, mL/min per 1.73 m²   | 10.1 (7.3–13.8)  | 10.3 (7.6–13.9)                  | 9.8 (7.0–13.6)                    | 0.00                    |
| 1 year Averaged lipids, mg/dL            |                  |                                  |                                    |                         |
| HDL                                      | 40±14            | 39±13                            | 41±15                              | −0.10                   |
| LDL                                      | 85±35            | 80±32                            | 94±38                              | −0.40                   |
| Cholesterol                              | 155±46           | 149±42                           | 165±50                             | −0.35                   |
| Triglycerides                            | 124 (87–181)     | 127 (89–182)                     | 120 (84–181)                       | 0.01                    |

Continued
half a year) was associated with a lower risk of all-cause and cardiovascular mortality (Figure S4A and S4B).

Furthermore, although data on laboratory measurements were limited, serum levels of albumin, white blood cell count, blood urea nitrogen, and hemoglobin were comparable between the statin therapy and no statin therapy groups (Table S3). However, for patients receiving statin therapy, body mass index and serum bicarbonate and calcium levels were higher, compared with patients receiving no statin therapy. Nonetheless, associations were similar and only slightly attenuated after additional adjustment for these markers (Table S4) in analysis restricted to patients with complete laboratory and smoking information. Patients included in this sensitivity analysis had similar characteristics to those excluded, with the exception that they had a greater use of nephrology services, in particular within the VA, and hence also had more of these VA-drawn laboratory measurements available (Table S5).

Finally, we observed similar associations between statin therapy compared to no statin therapy and mortality outcomes across a series of PS analyses. In matched analyses, both statin therapy and no statin therapy groups were similar in baseline patient characteristics (Table S6). After adjustment, statin therapy was associated with a 20% lower risk of both all-cause and cardiovascular mortality compared with no statin therapy, in matched analyses (Table S7). Moreover, this relationship of statin therapy and lower risk of all-cause and cardiovascular mortality was similar in PS adjustment models and stratification by PS tertiles.

**Discussion**

In a contemporary cohort of 47 720 veterans with incident ESRD, patients prescribed statin therapy for at least half of the year before ESRD transition had a lower risk of both all-cause and cardiovascular mortality and a lower hospitalization incidence rate in the first 12 months after ESRD initiation. This relationship was consistent across strata of clinical characteristics.
Table 2. Association of Pre-ESRD Statin Therapy (vs No Statin Therapy) With Posttransition 12-Month Mortality and Hospitalizations

| Variable            | No. of Patients | No. of Events | Rate per 100 Person-Years (95% CI) | P Value | Ratio (95% CI) | P Value | Ratio (95% CI) |
|---------------------|-----------------|---------------|------------------------------------|---------|----------------|---------|----------------|
| **All-cause mortality** |                 |               |                                    |         |                |         |                |
| Total               | 47 720          | 13 411        | 35.3 (34.7–35.8)                   | <0.0001 | 0.88 (0.85–0.91) | <0.0001 | 0.79 (0.76–0.82) |
| No                  | 22 151          | 6541          | 37.9 (37.0–38.8)                   |         |                |         |                |
| Yes                 | 25 569          | 6870          | 33.1 (32.3–33.8)                   |         |                |         |                |
| **Cardiovascular mortality** |             |               |                                    |         |                |         |                |
| Total               | 42 771          | 4373          | 12.3 (11.9–12.7)                   | 0.7069  | 0.99 (0.93–1.05) | <0.0001 | 0.83 (0.78–0.88) |
| No                  | 19 696          | 1994          | 12.4 (11.9–12.9)                   |         |                |         |                |
| Yes                 | 23 075          | 2379          | 12.2 (11.7–12.7)                   |         |                |         |                |
| **Hospitalization incidence** |             |               |                                    | 0.077   | 0.98 (0.95–1.00) | <0.0001 | 0.89 (0.87–0.92) |
| Total               | 47 720          | 79 144        | 208.0 (206.6–209.5)                |         |                |         |                |
| No                  | 22 151          | 36 167        | 209.5 (207.4–211.7)                |         |                |         |                |
| Yes                 | 25 569          | 42 977        | 206.8 (204.8–208.8)                |         |                |         |                |

Adjusted covariates included age, sex, race, and ethnicity as well as the following comorbidities: Charlson Comorbidity Index, diabetes mellitus, atherosclerotic cardiovascular disease (defined as the presence of myocardial infarction, peripheral vascular disease, or ischemic heart disease), atrial fibrillation, congestive heart failure, and cerebrovascular disease. Hazard ratios (HR) and incidence rate ratios (IRR) are presented for mortality and hospitalization outcomes, respectively. ESRD indicates end-stage renal disease.

characteristics, during longer periods of follow-up, after further adjustment for laboratory measures, pre-ESRD care indexes, and PS analyses.

Associations of pre-ESRD statin therapy compared with no statin therapy with clinical outcomes in the first year after transition to ESRD exhibited heterogeneous protective effects across a priori selected subgroups. There was a progressive decline in favorable outcomes observed with statin therapy with advancing age, particularly among patients aged ≥75 years. This is supported by previous randomized trials that reported similar data. Furthermore, a meta-regression of randomized controlled statin trials showed that statins may have a decreased to null effect on all-cause mortality and cardiovascular events in populations with higher noncardiovascular mortality risk. Older patients receiving dialysis have a marked excess of noncardiovascular mortality risk. Appropriate lipid management in elderly patients, including those transitioning to dialysis, is a complex issue that merits further investigation.

Paradoxically, despite the fact that in the general population, diabetes mellitus and CVD are strong risk factors indicating a recommendation for statin treatment, in this cohort of patients transitioning to ESRD, the statin benefit was stronger in patients without these comorbidities. This observation is consistent with a meta-analysis of randomized clinical trials showing a trend toward diminished benefit of statins in patients with diabetes mellitus compared with those without diabetes mellitus in terms of coronary death. One potential explanation for these findings may be that patients with advanced CKD and preexisting CVD or diabetes mellitus have more advanced vascular disease, which renders statin therapy to be less effective in altering outcomes. Diabetes mellitus and CVD have both been associated with reduced endothelial function, and statin-mediated vascular responsiveness may be lower in more advanced disease. In addition, statins are involved in stabilizing plaques with soft lipid cores. Patients with diabetes mellitus and CVD comorbidity may have more fibrous plaques and medial calcification that are less vulnerable and may benefit less from statin-induced plaque stabilization. However, future studies will need to evaluate these findings in more detail. Our data also show a stronger impact of statin therapy on outcomes in blacks compared with nonblacks. Previous studies have shown similar results in hypertensive patients and in transplant patients. Moreover, our group has also shown that blacks have better nutritional status at the transition to dialysis and, consequently, better survival. We have also shown that black US veterans were found to have better survival across stages of kidney disease.
Figure. Associations of pre–end-stage renal disease statin therapy vs no statin therapy with 12-month all-cause mortality, cardiovascular mortality, and hospitalization incidence rate in a priori selected subgroups. Adjusted covariates included age, sex, race, and ethnicity as well as the following comorbidities: Charlson Comorbidity Index, diabetes mellitus, atherosclerotic cardiovascular disease (CVD; defined as the presence of myocardial infarction, peripheral vascular disease, or ischemic heart disease), atrial fibrillation, congestive heart failure, and cerebrovascular disease. LDL, low-density lipoprotein; P-Int, p-value for interaction.

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Statins and Post-ESRD Outcomes Soohoo et al

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status given that malnourished patients are less responsive to statin therapy.17

Patients with liver disease in our cohort had a greater benefit from statin therapy. This is supported by clinical trials in the general population reporting comparable findings.36,37 Older guidelines state that chronic liver disease is an absolute contraindication for statin therapy.38 However, a recent analysis found statins to be effective and safe in patients with chronic liver disease.39 Our findings suggest that pre-ESRD statin therapy may be beneficial among patients with liver disease and transitioning to ESRD.

Last, we have also found that the results of our associations are similar whether the patients achieved a target low-density lipoprotein cholesterol level of 70 mg/dL or not. These findings support the “fire and forget” strategy of some of the guidelines, in which patients at high risk for cardiovascular outcomes are prescribed statins without further testing or dose adjustment for achievement of lipid-lowering goals.3,40

In our cohort, patients who received statins also had a lower incidence rate of hospitalization in the 12 months after transition. Data on veterans transitioning to ESRD showed that the top 2 causes of hospitalization after transition for dialysis patients are septicemia and complications of arteriovenous grafts.2 Previous studies have also shown that treatment with statins was associated with a lower risk of both arteriovenous graft failure41 and hospitalization for sepsis in dialysis patients.42 The former has also been observed in post hoc analyses of SHARP trial patients, but when combined with another clinical trial, this was not shown to be statistically significant.43 Hospitalizations for cardiovascular events and revascularization in dialysis patients may be comparatively overshadowed by the frequency of hospitalizations attributable to septicemia or graft complications, particularly in the first months after transition. In our cohort, equally for patients receiving statin therapy and not receiving statin therapy, septicemia was the second most frequently listed primary cause of hospitalization admission in the first 12 months post-ESRD transition (Table S8). Although a post hoc analysis of the SHARP trial showed no difference in adverse events between study arms, there was no analysis that included these factors in our main multivariable model and we could not examine other potential confounder laboratory markers. However, in subgroup analyses among patients with low-density lipoprotein measurements, we did not observe effect modification in the statin-outcome relationship; and in sensitivity analysis models that included laboratory variables, similar results were also observed. Finally, these findings were limited by the source population of mostly older male veterans, thus potentially limiting generalizability to women.

Our study is clinically relevant because it directly supports the recommendation of treatment with statin therapy in all patients with NDD-CKD in the pre-ESRD stage and shows that the benefit of statins is extended after the initiation of dialysis therapy. Management of pre-ESRD patients by nephrologists is an essential factor in patient survival after initiation of dialysis.48–51 Use of renin-angiotensin-aldosterone system blockade,52 recombinant human erythropoietin,53 predialysis care by dietitians,54 and a functioning arteriovenous fistula55 have been shown to decrease mortality after the initiation of dialysis and are recommended. In our study, we additionally adjusted for factors related to pre-ESRD care, such as vascular access at initiation and use of nephrology services, which showed similar associations to those of our main results. This suggests that our observations were independent.
of these pre-ESRD care markers and further supports the use of statin therapy in patients with NDD-CKD. Consequently, slightly less than half of our cohort did not receive adequate statin therapy, according to guideline recommendations. Thus, in concordance with current guidelines that support treatment with statin therapy in patients with NDD-CKD, the results of this study support the value of statin therapy as it applies to predialysis management.

In conclusion, our study provides support for guideline recommendation of statin therapy for all adult patients with NDD-CKD and specifically identifies the benefit of statin therapy in pre-ESRD patients. Further studies are needed to identify methods for better implementation of the current guidelines.

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Disclosures

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Supplemental Material
Table S1. Subgroup analyses, N and P-interaction by outcome.

| Subgroup                        | All-Cause Mortality | Cardiovascular Mortality | Hospitalization Rate | P-Int | P-Int | P-Int |
|---------------------------------|---------------------|--------------------------|----------------------|-------|-------|-------|
|                                 | N Event/N Group     | Yes Statin               | No Statin            | N Event/N Group     | Yes Statin* | No Statin* | P-Int |
|                                 |                     |                          |                      |                   |              |            |       |
| Age<65                          | 2114/13689          | 893/6473                 | 1221/7216            | <.0001           | 2034/12768   | 1081/6744   | 1235/7216 |
| Age65-<75                       | 3068/12799          | 1643/7331                | 1425/5468            | .03              | 2034/12768   | 1081/6744   | 1235/7216 |
| Age≥75                          | 8229/21232          | 4334/11765               | 3895/9467            | .002             | 2034/12768   | 1081/6744   | 1235/7216 |
| Non-African American            | 11362/36738         | 6010/20501               | 5352/16237           | 0.02             | 2034/12768   | 1081/6744   | 1235/7216 |
| African American                | 2044/10976          | 860/5068                 | 1184/5908            | .0002            | 2034/12768   | 1081/6744   | 1235/7216 |
| No Diabetes                     | 4611/16074          | 1856/6578                | 2755/9496            | .02              | 2034/12768   | 1081/6744   | 1235/7216 |
| Diabetes                        | 8765/31465          | 5002/18907               | 3763/12585           | .11              | 2034/12768   | 1081/6744   | 1235/7216 |
| No CVD                          | 1670/10278          | 486/3672                 | 1184/6606            | .002             | 2034/12768   | 1081/6744   | 1235/7216 |
| CVD                             | 11706/37261         | 6372/21813               | 5334/15448           | .0002            | 2034/12768   | 1081/6744   | 1235/7216 |
| No Liver Disease                | 11587/42282         | 6231/23481               | 5356/18801           | .23              | 2034/12768   | 1081/6744   | 1235/7216 |
| Liver Disease                   | 1789/5257           | 627/2004                 | 1162/3253            | .11              | 2034/12768   | 1081/6744   | 1235/7216 |
| Never Smoker                    | 3192/12142          | 1662/6701                | 1530/5441            | .06              | 2034/12768   | 1081/6744   | 1235/7216 |
| Current Smoker                  | 3623/14025          | 1861/7381                | 1762/6644            | .0003            | 2034/12768   | 1081/6744   | 1235/7216 |
| Past Smoker                     | 4228/14194          | 2422/8407                | 1806/5791            | .82              | 2034/12768   | 1081/6744   | 1235/7216 |
| LDL<70 mg/dL                    | 2769/9990           | 1946/7041                | 823/2949             | .11              | 2034/12768   | 1081/6744   | 1235/7216 |
| LDL≥70 mg/dL                    | 4066/17758          | 2149/9713                | 1917/8665            | .11              | 2034/12768   | 1081/6744   | 1235/7216 |
| No Afib                         | 9896/39592          | 4989/20920               | 4907/18672           | .11              | 2034/12768   | 1081/6744   | 1235/7216 |
| A fib                           | 3480/7947           | 1869/4565                | 1611/3382            | .003             | 2034/12768   | 1081/6744   | 1235/7216 |
| No ISHD                         | 3941/19635          | 1426/8189                | 2515/11446           | .003             | 2034/12768   | 1081/6744   | 1235/7216 |
| ISHD                            | 9435/27904          | 5432/17296               | 4003/10608           | .003             | 2034/12768   | 1081/6744   | 1235/7216 |
| No MI                           | 8646/35163          | 3978/17542               | 4668/17621           | .02              | 2034/12768   | 1081/6744   | 1235/7216 |
| MI                              | 4730/12376          | 2880/9794                | 1850/4433            | .06              | 2034/12768   | 1081/6744   | 1235/7216 |
| No CHF                          | 4157/21340          | 1753/10023               | 2404/11317           | .002             | 2034/12768   | 1081/6744   | 1235/7216 |
| CHF                             | 9219/26199          | 5105/15462               | 4114/10737           | .002             | 2034/12768   | 1081/6744   | 1235/7216 |
| No PVD                          | 6924/29325          | 3111/14319               | 3813/15006           | .03              | 2034/12768   | 1081/6744   | 1235/7216 |
| PVD                             | 6452/18214          | 3747/11166               | 2705/7048            | .001             | 2034/12768   | 1081/6744   | 1235/7216 |
| No Cerebrovascular              | 8061/32711          | 3751/16307               | 4310/16404           | .001             | 2034/12768   | 1081/6744   | 1235/7216 |
| Cerebrovascular                 | 5315/14828          | 3107/9178                | 2208/5650            | .11              | 2034/12768   | 1081/6744   | 1235/7216 |
| No ASCVD                        | 3006/15991          | 990/6315                 | 2016/9676            | .01              | 2034/12768   | 1081/6744   | 1235/7216 |
| ASCVD                           | 10370/31548         | 5868/19170               | 4502/12378           | .0002            | 2034/12768   | 1081/6744   | 1235/7216 |
Hospitalization N Event is the total number of Hospitalizations during the follow-up period. Numerator is larger than the denominator because patients may experience multiple hospitalization events.

CVD; Cardiovascular Disease, LDL; low-density lipoprotein, Afib; Atrial Fibrillation, ISHD; Ischemic Heart Disease; MI; myocardial infarction, CHF; congestive heart failure, PVD; peripheral vascular disease, ASCVD; Atherosclerotic Cardiovascular Disease.
Table S2. Association of pre-ESRD statin therapy (vs. no statin therapy) with post-transition 12-month outcomes with additional adjustment for pre-ESRD care indices.

| Level                  | 12-Month All-Cause Mortality | 12-Month Cardiovascular Mortality | 12-Month Hospitalization Incidence Rate |
|------------------------|------------------------------|-----------------------------------|-----------------------------------------|
|                        | P               | HR [95% CI]                          | P               | HR [95% CI]                          | P               | IRR [95% CI]                          |
| Adjusted               | <.0001          | 0.79[0.76,0.82]                       | <.0001          | 0.83[0.78,0.88]                       | <.0001          | 0.89[0.87,0.92]                       |
| Adjusted+Access Type   | <.0001          | 0.81[0.79,0.84]                       | <.0001          | 0.85[0.80,0.91]                       | <.0001          | 0.92[0.89,0.94]                       |
| Adjusted+Any VA Nephrology Visit | <.0001 | 0.83[0.80,0.86]                       | <.0001          | 0.86[0.81,0.92]                       | <.0001          | 0.90[0.88,0.92]                       |
| Adjusted+Any CMS Nephrology Visit | <.0001 | 0.78[0.76,0.81]                       | <.0001          | 0.82[0.77,0.87]                       | <.0001          | 0.90[0.87,0.92]                       |
| Adjusted+Any Nephrology Visit | <.0001 | 0.80[0.77,0.82]                       | <.0001          | 0.83[0.78,0.89]                       | <.0001          | 0.89[0.87,0.92]                       |
| Adjusted+ # of VA Nephrology Visits | <.0001 | 0.83[0.80,0.86]                       | <.0001          | 0.87[0.82,0.92]                       | <.0001          | 0.91[0.89,0.93]                       |
| Adjusted+ # of CMS Nephrology Visits | <.0001 | 0.79[0.76,0.82]                       | <.0001          | 0.83[0.78,0.88]                       | <.0001          | 0.89[0.87,0.92]                       |
| Adjusted+# of Any Nephrology Visits | <.0001 | 0.79[0.76,0.82]                       | <.0001          | 0.83[0.78,0.88]                       | <.0001          | 0.89[0.87,0.92]                       |

Adjusted covariates: age, sex, race, and ethnicity, as well as the following comorbidities: CCI, diabetes, atherosclerotic CV disease (defined as the presence of MI, PVD or ISHD), atrial fibrillation, CHF and cerebrovascular disease.
Table S3. Laboratory measurements of 47,720 patients stratified by receipt of statin therapy prior to ESRD transition.

|                      | N missing | Total   | Statin Therapy | No Statin Therapy | Standardized difference |
|----------------------|-----------|---------|----------------|-------------------|-------------------------|
|                      |           | 47720   | 25569(53.6)    | 22151(46.4)       |                         |
| 12-month Averaged Laboratory Markers |           |         |                |                   |                         |
| Albumin (g/dL)       | 18543     | 3.5±0.6 | 3.5±0.6        | 3.4±0.6           | 0.09                    |
| Bicarbonate(mEq/L)   | 17421     | 23.6±3.9| 24.0±3.7       | 23.0±4.0          | 0.25                    |
| Blood Urea Nitrogen (mg/dL) | 16838    | 56.9±22.0 | 57.3±20.7 | 56.3±23.7 | 0.05                    |
| Hemoglobin(g/dL)     | 18393     | 11.0±1.6| 11.0±1.6       | 10.9±1.7          | 0.07                    |
| Calcium (mg/dL)      | 17857     | 8.8±0.7 | 8.9±0.6        | 8.7±0.7           | 0.19                    |
| Body Mass Index (kg/m²) | 13072   | 29.9±6.5| 30.7±6.4       | 28.9±6.5          | 0.27                    |
| White Blood Cell Count (x10³/µL) | 18308  | 7.7±3.0 | 7.8±2.8        | 7.6±3.4           | 0.07                    |

Standardized differences of ≥0.2 are considered as a meaningful imbalance, where 0.8, 0.5 and 0.2 represent large, medium and small imbalances, respectively.
Table S4. Association of pre-ESRD statin therapy (vs. no statin therapy) with post-transition 12-month outcomes, among patients with complete laboratory and smoking information.

|                                      | All-Cause Mortality |                                      |                                      |                                      |
|--------------------------------------|---------------------|--------------------------------------|--------------------------------------|--------------------------------------|
|                                      | Unadjusted HR       | Adjusted HR                          | Adjusted+Lab HR                      |                                      |
|                                      | N patients          | P                                    | HR [95% CI]                          | P                                    | HR [95% CI]                          | P                                    |
| TOTAL                                | 24317               | 0.0183                               | 0.94[0.89,0.99]                      | <.0001                               | 0.81[0.77,0.85]                      | <.0001                               | 0.83[0.78,0.87]                      |
| NO                                   | 10005               |                                      |                                      |                                      |                                      |                                      |
| YES                                  | 14312               |                                      |                                      |                                      |                                      |                                      |

Cardiovascular Mortality

|                                      | Unadjusted HR       | Adjusted HR                          | Adjusted+Lab HR                      |                                      |
|                                      | N patients          | P                                    | HR [95% CI]                          | P                                    | HR [95% CI]                          | P                                    |
| TOTAL                                | 22165               | 0.2159                               | 1.06[0.97,1.17]                      | <.0001                               | 0.82[0.75,0.90]                      | 0.0002                               | 0.83[0.75,0.91]                      |
| NO                                   | 9095                |                                      |                                      |                                      |                                      |                                      |
| YES                                  | 13070               |                                      |                                      |                                      |                                      |                                      |

Hospitalization Incidence Rate

|                                      | Unadjusted IRR       | Adjusted IRR                          | Adjusted + Lab IRR                    |                                      |
|                                      | N patients          | P                                    | IRR [95% CI]                          | P                                    | IRR [95% CI]                          | P                                    |
| TOTAL                                | 24317               | 0.7646                               | 1.01[0.97,1.04]                      | <.0001                               | 0.89[0.86,0.93]                      | <.0001                               | 0.92[0.88,0.95]                      |
| NO                                   | 10005               |                                      |                                      |                                      |                                      |                                      |
| YES                                  | 14312               |                                      |                                      |                                      |                                      |                                      |

Adjusted covariates: age, sex, race, and ethnicity, as well as the following comorbidities: CCI, diabetes, atherosclerotic CV disease (defined as the presence of MI, PVD or ISHD), atrial fibrillation, CHF and cerebrovascular disease.

Adjusted+Lab covariates: age, sex, race, and ethnicity, as well as the following comorbidities: CCI, diabetes, atherosclerotic CV disease (defined as the presence of MI, PVD or ISHD), atrial fibrillation, CHF and cerebrovascular disease, as well as smoking status, last eGFR prior to transition, and the following averaged laboratory variables: BMI, hemoglobin, albumin, calcium, white blood cell count, bicarbonate and blood urea nitrogen.

Table S5. Comparison of patients excluded vs. included in laboratory adjusted complete case analyses.
| N. (%)  | Total | Excluded | Included in Labs Adjusted Model | Standardized difference |
|---------|-------|----------|--------------------------------|-------------------------|
| Cardiovascular Disease (%) |       |          |                                |                         |
| No      | 47720 | 23403    | 24317                          | -0.12                   |
| Yes     |       |          |                                |                         |
| Atrial Fibrillation | 17    | 19       | 15                             | -0.11                   |
| ISHD    | 59    | 63       | 54                             | -0.19                   |
| MI      | 26    | 29       | 23                             | -0.15                   |
| CHF     | 55    | 59       | 51                             | -0.16                   |
| PVD     | 38    | 42       | 35                             | -0.14                   |
| Cerebrovascular Disease | 31    | 34       | 28                             | -0.13                   |
| Age (years) |       |          |                                |                         |
| 71±11   | 29    | 18       | 39                             | 0.49                    |
| Age <65 (%) |       |          |                                |                         |
| 27      | 26    | 27       | 27                             | 0.02                    |
| Age 65-<75 (%) |       |          |                                |                         |
| 44      | 56    | 34       | 34                             | -0.46                   |
| Age≥75 (%) |       |          |                                |                         |
| Sex (%) |       |          |                                |                         |
| Female  | 4     | 7        | 2                              | -0.24                   |
| Race (%) |       |          |                                |                         |
| White   | 73    | 79       | 67                             | -0.27                   |
| African American | 23    | 17       | 29                             | 0.28                    |
| Other   | 4     | 4        | 5                              | 0.02                    |
| Ethnicity (%) |       |          |                                |                         |
| Hispanic | 6     | 5        | 7                              | 0.10                    |
| Married (%) |       |          |                                |                         |
| CCI     | 4[2,6]| 4[2,6]   | 4[2,5]                         | -0.12                   |
| Comorbidities (%) |       |          |                                |                         |
| Diabetes | 66    | 63       | 69                             | 0.11                    |
| Anemia  | 72    | 72       | 71                             | -0.03                   |
| Depression | 22    | 19       | 26                             | 0.16                    |
| Hyperlipidemia | 78    | 77       | 79                             | 0.04                    |
| COPD    | 42    | 46       | 39                             | -0.13                   |
| Peptic Ulcer Disease | 7     | 8        | 6                              | -0.07                   |
| Liver Disease | 11    | 10       | 12                             | 0.04                    |
| Cancer  | 24    | 26       | 23                             | -0.07                   |
| Smoking Status (%) |   |   |   |   |
|-------------------|---|---|---|---|
| Never             | 30| 30| 30| 0.19|
| Current           | 35| 30| 38|   |
| Past              | 35| 40| 32|   |

| eGFR at initiation (mL/min/1.73 m²) |   |   |   |   |
|-------------------------------------|---|---|---|---|
| Never                              | 10.1[7.3,13.8] | 10.4[7.6,14.4] | 9.7[7.1,13.2] | -0.13 |
| Current                            |   |   |   |   |
| Past                               |   |   |   |   |

| 12-month Averaged Lipids |   |   |   |   |
|-------------------------|---|---|---|---|
| HDL (mg/dL)             | 40±14 | 40±13 | 40±14 | 0.01 |
| LDL (mg/dL)             | 85±35 | 85±34 | 86±35 | 0.02 |
| Cholesterol (mg/dL)     | 155±46 | 154±44 | 156±46 | 0.03 |
| Triglycerides (mg/dL)   | 124[87,181] | 121[85,178] | 125[88,182] | 0.05 |

| Initial Dialysis Modality (%) |   |   |   |   |
|-------------------------------|---|---|---|---|
| Hemodialysis                  | 82| 80| 84|   |
| Peritoneal Dialysis           | 5 | 5 | 5 | 0.10 |
| Other/Unknown                 | 12| 14| 11|   |

| Initial Access Type (%) |   |   |   |   |
|-------------------------|---|---|---|---|
| AV Fistula/AV Graft     | 21| 19| 23|   |
| CVC                     | 70| 72| 68| 0.10 |
| Other                   | 9 | 9 | 9 |   |

| Pre-ESRD Nephrology Visits |   |   |   |   |
|----------------------------|---|---|---|---|
| Any VA or CMS physician nephrology visits in the year prior to transition (%) | 69| 31| 77| 0.35 |
| # VA or CMS physician nephrology visits in the year prior to transition | 3[0.8] | 2[0.8] | 4[1.8] | 0.02 |
| Any VA nephrology visits in the year prior to transition (%) | 33| 9 | 57| 1.19 |
| # VA nephrology visits in the year prior to transition | 0[0.2] | 0[0.0] | 1[0.5] | 0.83 |
| Any CMS physician nephrology visits in the year prior to transition (%) | 43| 55| 32| -0.49 |
| # CMS physician nephrology visits in the year prior to transition | 0[0.5] | 1[0.7] | 0[0.2] | -0.37 |

eGFR: estimated glomerular filtration rate, CCI: Charlson Comorbidity Index, ISHD: Ischemic Heart Disease; MI: myocardial infarction, CHF: congestive heart failure, PVD: peripheral vascular disease, COPD: chronic obstructive pulmonary disease, AV: arteriovenous, CVC: central venous catheter, ESRD: end-stage renal disease, VA: Veterans Affairs, CMS: Centers for Medicare and Medicaid Services, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

Data presented as proportion, mean ± standard deviation or median [25th percentile, 75th percentile] where appropriate, and compared between groups using standardized differences.

Standardized differences of ≥0.2 are considered as a meaningful imbalance, where 0.8, 0.5 and 0.2 represent large, medium and small imbalances, respectively.
Table S6. Baseline characteristics of 38,728 patients matched by pre-ESRD statin therapy.

|                                | Statin Therapy | No Statin Therapy | Standardized difference |
|--------------------------------|----------------|-------------------|-------------------------|
| N, (%)                         | 19364 (50.0)   | 19364 (50.0)      |                         |
| Cardiovascular Disease (%)     |                |                   |                         |
| No                             | 19             | 23                | 0.10                    |
| Yes                            | 81             | 77                |                         |
| Atrial Fibrillation            | 17             | 17                | 0.02                    |
| ISHD                           | 60             | 55                | 0.12                    |
| MI                             | 28             | 23                | 0.12                    |
| CHF                            | 56             | 53                | 0.05                    |
| PVD                            | 40             | 36                | 0.08                    |
| Cerebrovascular Disease (%)    | 32             | 29                | 0.07                    |
| Age (years)                    | 72±11          | 71±12             | 0.06                    |
| Age <65 (%)                    | 26             | 30                | -0.08                   |
| Age 65-<75 (%)                 | 28             | 25                | 0.06                    |
| Age≥75 (%)                     | 46             | 45                | 0.02                    |
| Sex (%)                        |                |                   |                         |
| Female                         | 4              | 4                 | -0.01                   |
| Race (%)                       |                |                   |                         |
| White                          | 73             | 72                | 0.03                    |
| African American               | 23             | 24                | -0.03                   |
| Other                          | 4              | 5                 | -0.02                   |
| Ethnicity (%)                  |                |                   |                         |
| Hispanic                       | 6              | 6                 | -0.02                   |
| Married (%)                    | 61             | 60                | 0.02                    |
| CCI                            | 4[2,6]         | 4[2,6]            | 0.05                    |
| Comorbidities (%)              |                |                   |                         |
| Diabetes                       | 66             | 64                | 0.05                    |
| Anemia                         | 73             | 71                | 0.05                    |
| Depression                     | 22             | 22                | 0.01                    |
| Hyperlipidemia                 | 90             | 67                | 0.58                    |
| COPD                           | 44             | 42                | 0.04                    |
| Peptic Ulcer Disease           | 7              | 8                 | -0.03                   |
| Liver Disease                  | 8              | 14                | -0.20                   |
| Cancer                         | 26             | 25                | 0.02                    |
| Smoking Status (%)             |                |                   |                         |
| Never                          | 30             | 31                |                         |
| Current                        | 33             | 36                |                         |
| Past                           | 37             | 34                |                         |
| eGFR at initiation (mL/min/1.73 m²) | 10.1[7.4,13.7] | 10.0[7.2,13.9] | -0.03                   |
| 12-month Averaged Lipids      |                |                   |                         |
| HDL (mg/dL)                    | 40±13          | 40±15             | -0.03                   |
| LDL (mg/dL)                    | 81±32          | 94±38             | -0.36                   |
| Cholesterol (mg/dL)            | 150±42         | 165±50            | -0.31                   |
| Triglycerides (mg/dL)          | 125[89,180]    | 121[85,182]       | -0.02                   |
| Initial Dialysis Modality (%) |     |     |     |
|-------------------------------|-----|-----|-----|
| Hemodialysis                  | 83  | 82  | 0.03|
| Peritoneal Dialysis           | 6   | 5   |     |
| Other/Unknown                 | 12  | 13  |     |

| Initial Access Type (%)       |     |     |     |
|-------------------------------|-----|-----|-----|
| AV Fistula/AV Graft           | 23  | 18  | 0.13|
| CVC                           | 67  | 72  |     |
| Other                         | 9   | 9   |     |

| Pre-ESRD Nephrology Visits   |     |     |     |
|-------------------------------|-----|-----|-----|
| Any VA or CMS physician nephrology visits in the year prior to transition (%) | 72  | 67  | 0.10|
| # VA or CMS physician nephrology visits in the year prior to transition | 4[0,8] | 3[0,7] | 0.02|
| Any VA nephrology visits in the year prior to transition (%) | 39  | 26  | 0.27|
| # VA nephrology visits in the year prior to transition | 0[0,3] | 0[0,1] | 0.26|
| Any CMS physician nephrology visits in the year prior to transition (%) | 41  | 47  | -0.13|
| # CMS physician nephrology visits in the year prior to transition | 0[0,4] | 0[0,6] | -0.11|

eGFR; estimated glomerular filtration rate, CCI; Charlson Comorbidity Index, ISHD; Ischemic Heart Disease; MI; myocardial infarction, CHF; congestive heart failure, PVD; peripheral vascular disease, COPD; chronic obstructive pulmonary disease, AV; arteriovenous, CVC; central venous catheter, ESRD; end-stage renal disease, VA; Veterans Affairs, CMS; Centers for Medicare and Medicaid Services, LDL; low-density lipoprotein, HDL; high-density lipoprotein.

Data presented as proportion, mean ± standard deviation or median [25th percentile, 75th percentile] where appropriate, and compared between groups using standardized differences. Standardized differences of ≥0.2 are considered as a meaningful imbalance, where 0.8, 0.5 and 0.2 represent large, medium and small imbalances, respectively.
Table S7. Association of pre-ESRD statin therapy vs. no statin therapy with 12-month all-cause and cardiovascular mortality across propensity score analyses

| Propensity Score Analyses          | All-Cause Mortality | Cardiovascular Mortality |
|-----------------------------------|---------------------|--------------------------|
|                                   | Unadjusted          | Adjusted                 | Unadjusted          | Adjusted                 |
|                                   | N  | P   | HR[95%CI]   | P   | HR[95%CI]   | N  | P   | HR[95%CI]   | P   | HR[95%CI]   |
| Matched                           | 38728 | <.0001 | 0.81[0.78,0.85] | <.0001 | 0.79[0.76,0.82] | 34627 | <.0001 | 0.86[0.80,0.91] | <.0001 | 0.82[0.77,0.88] |
| Adjusted for Propensity Score     | 47720 | <.0001 | 0.79[0.76,0.81] | <.0001 | 0.79[0.76,0.82] | 42771 | <.0001 | 0.82[0.78,0.88] | <.0001 | 0.83[0.78,0.88] |
| Tertile 1                         | 15740 | <.0001 | 0.80[0.75,0.86] | <.0001 | 0.71[0.66,0.76] | 14113 | 0.08  | 0.88[0.77,1.01] | <.0001 | 0.73[0.63,0.84] |
| Tertile 2                         | 16239 | <.0001 | 0.77[0.73,0.82] | <.0001 | 0.78[0.74,0.83] | 14538 | <.0001 | 0.80[0.73,0.88] | <.0001 | 0.80[0.73,0.88] |
| Tertile 3                         | 15741 | <.0001 | 0.82[0.78,0.87] | <.0001 | 0.87[0.82,0.92] | 14120 | 0.004 | 0.87[0.79,0.96] | 0.05  | 0.91[0.83,1.00] |

Adjusted covariates: age, sex, race, and ethnicity, as well as the following comorbidities: CCI, diabetes, atherosclerotic CV disease (defined as the presence of MI, PVD or ISHD), atrial fibrillation, CHF and cerebrovascular disease.
Table S8. Top Ten Primary Admission Reasons for Hospitalizations in the First Year post-ESRD Transition by pre-ESRD Statin Therapy Use.

| Primary Hospitalization Reason                                      | Statin Therapy | No Statin Therapy |
|---------------------------------------------------------------------|----------------|-------------------|
| Complication of device; implant or graft                            | 1              | 1                 |
| Septicemia (except in labor)                                       | 2              | 2                 |
| Congestive heart failure; nonhypertensive                          | 3              | 4                 |
| Hypertension with complications and secondary hypertension         | 4              | 3                 |
| Diabetes mellitus with complications                              | 5              | 8                 |
| Pneumonia (except that caused by tuberculosis or sexually transmitted disease) | 6              | 6                 |
| Chronic kidney disease                                             | 7              | 5                 |
| Coronary atherosclerosis and other heart disease                   | 8              | 10                |
| Cardiac dysrhythmias                                               | 9              | 9                 |
| Fluid and electrolyte disorders                                    | 10             | 7                 |
Figure S1. Cohort Construction.

85,505 incident ESRD patients

1,958 patients excluded for missing censor information

83,547 incident ESRD patients

25,792 patients excluded for not having any medication information in the 1 year prelude

57,755 incident ESRD patients

10,035 patients excluded for receiving less than half a year of continuous Statin prescription

47,720 incident ESRD patients

22,151 incident ESRD patients with no Pre-ESRD Statin therapy

25,569 incident ESRD patients with Pre-ESRD Statin therapy
Figure S2. Associations of pre-ESRD statin therapy vs no statin therapy with 12-month all-cause, cardiovascular mortality, and hospitalization incidence rate in individual cardiovascular disease subgroups after adjustment.
Incidence Rate Ratio for 12-month Hospitalizations

| Condition          | P-Int |
|--------------------|-------|
| No AFib            | 0.12  |
| AFib               |       |
| No ISHD            | 0.001 |
| ISHD               |       |
| No MI              | 0.004 |
| MI                 |       |
| No CHF             | 0.002 |
| CHF                |       |
| No PVD             | 0.01  |
| PVD                |       |
| No Cerebrovascular| 0.02  |
| Cerebrovascular    |       |
| No ASCVD           | 0.002 |
| ASCVD              |       |

Incidence Rate Ratio for 12-month Hospitalizations
Figure S3. Associations of pre-ESRD statin therapy vs. no statin therapy comparing 12-month vs. seven-year follow-up in adjusted models.

Adjusted covariates: age, sex, race, and ethnicity, as well as the following comorbidities: CCI, diabetes, atherosclerotic CV disease (defined as the presence of MI, PVD or ISHD), atrial fibrillation, CHF and cerebrovascular disease.
Figure S4. Adjusted restricted cubic splines of the number of pre-ESRD statin therapy days with A) 12-month all-cause mortality in 35,604 patients and B) 12-month cardiovascular mortality in 32,076 patients with at least one day of pre-ESRD statin therapy (reference: 182 days).

Adjusted covariates: age, sex, race, and ethnicity, as well as the following comorbidities: CCI, diabetes, atherosclerotic CV disease (defined as the presence of MI, PVD or ISHD), atrial fibrillation, CHF and cerebrovascular disease.