ORIGINAL RESEARCH

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,[1] 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,[2] and current guidelines recommend treatment with statins irrespective of cholesterol levels and kidney function among adult patients with non–dialysis-dependent (NDD) CKD.[1,3,4] 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,[5] in which the statin combined therapy (ie, simvastatin plus ezetimibe), compared with placebo, reduced

From the Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, CA (M.S., H.M., Y.O., C.M.R., K.K.-Z., E.S.); Nephrology Section, Tibor Rubin Veterans Affairs Medical Center, Long Beach, CA (M.S., H.M., K.K.-Z., E.S.); Nephrology Section, Stratton Veterans Affairs Medical Center, Albany, NY (E.O.G.); Division of Nephrology, Department of Medicine, Albany Medical College, Albany, NY (E.O.G.); Division of Transplant Surgery, Methodist University Hospital Transplant Institute, Memphis, TN (M.Z.M.); Division of Nephrology (C.P.K.), Departments of Surgery (M.Z.M.), and Medicine (M.Z.M.), University of Tennessee Health Science Center, Memphis, TN; Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary (M.Z.M.); Atherosclerosis Research Center, Gerontology Section, Geriatric, Rehabilitation Medicine and Extended Care Health Care Group, Veterans Affairs Medical Center, Long Beach, CA (M.L.K.); Department of Medicine, University of California, Irvine, CA (D.L.G.); and Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN (C.P.K.).

Accompanying Tables S1 through S8 and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011869

Correspondence to: Elani Streja, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine, 101 The City Dr S, City Tower, Ste 400, Orange, CA 92868. E-mail: estreja@uci.edu

Received December 24, 2018; accepted February 20, 2019.

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.

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,[5–7] the current guidelines do not recommend initiating statin therapy in patients already receiving maintenance dialysis.[1,3,4]

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.[2,8,9] 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.

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[10] 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

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.[11] 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.[12]

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.[13]

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 were prescribed 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 prelude low-density lipoprotein level did not modify the association of statin therapy with outcomes.

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 m^2	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

Table 1. Continued

Characteristics	Total (N=47 720)	Statin Therapy (n=25 569, 53.6%)	No Statin Therapy (n=22 151, 46.4%)	Standardized Difference
Initial dialysis modality, %				
Hemodialysis	82	83	81	0.06
Peritoneal dialysis	5	5	5	
Other/unknown	12	12	13	
Initial access type, %				
Arteriovenous fistula/arteriovenous graft	21	23	19	0.10
CVC	70	68	72	
Other	9	9	10	
Pre-ESRD nephrology visits				
Any VA or CMS physician nephrology visits in the year before transition, %	69	72	66	0.14
No. of VA or CMS physician nephrology visits in the year before transition	3 (0–8)	4 (0–8)	3 (0–7)	0.07
Any VA nephrology visits in the year before transition, %	33	39	28	0.24
No. of VA nephrology visits in the year before transition	0 (0–2)	0 (0–3)	0 (0–1)	0.23
Any CMS physician nephrology visits in the year before transition, %	43	42	44	−0.05
No. of CMS physician nephrology visits in the year before transition	0 (0–5)	0 (0–5)	0 (0–5)	−0.04

Data are presented as proportion, mean±SD, or median (25th–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. CCI indicates Charlson Comorbidity Index; CHF, congestive heart failure; CMS, Centers for Medicare and Medicaid Services; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; ISHD, ischemic heart disease; MI, myocardial infarction; LDL, low-density lipoprotein; PVD, peripheral vascular disease; VA, Veterans Affairs.

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

Table 2. Association of Pre-ESRD Statin Therapy (vs No Statin Therapy) With Posttransition 12-Month Mortality and Hospitalizations

Variable	No. of Patients			Unadjusted		Adjusted	
		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							
Total	47 720	79 144	208.0 (206.6–209.5)	0.077	0.98 (0.95–1.00)	<0.0001	0.89 (0.87–0.92)
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.[14] 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.[15] Older patients receiving dialysis have a marked excess of noncardiovascular mortality risk.[16] Appropriate lipid management in elderly patients, including those transitioning to dialysis, is a complex issue that merits further investigation.[17]

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.[18] 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.[19–23] In addition, statins are involved in stabilizing plaques with soft lipid cores.[24] 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.[25,26] 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[27] and in transplant patients.[28] Moreover, our group has also shown that blacks have better nutritional status at the transition to dialysis and, consequently, better survival.[29] We have also shown that black US veterans were found to have better survival across stages of kidney disease.[30–32] One potential explanation was related to the fact that black patients have less calcified atherosclerotic lesions, potentially allowing them to be more responsive to statin therapy.[33–35] Additional studies will be needed to establish whether the survival advantage of statin therapy in blacks is related to a racial difference in response to this treatment versus better overall nutritional

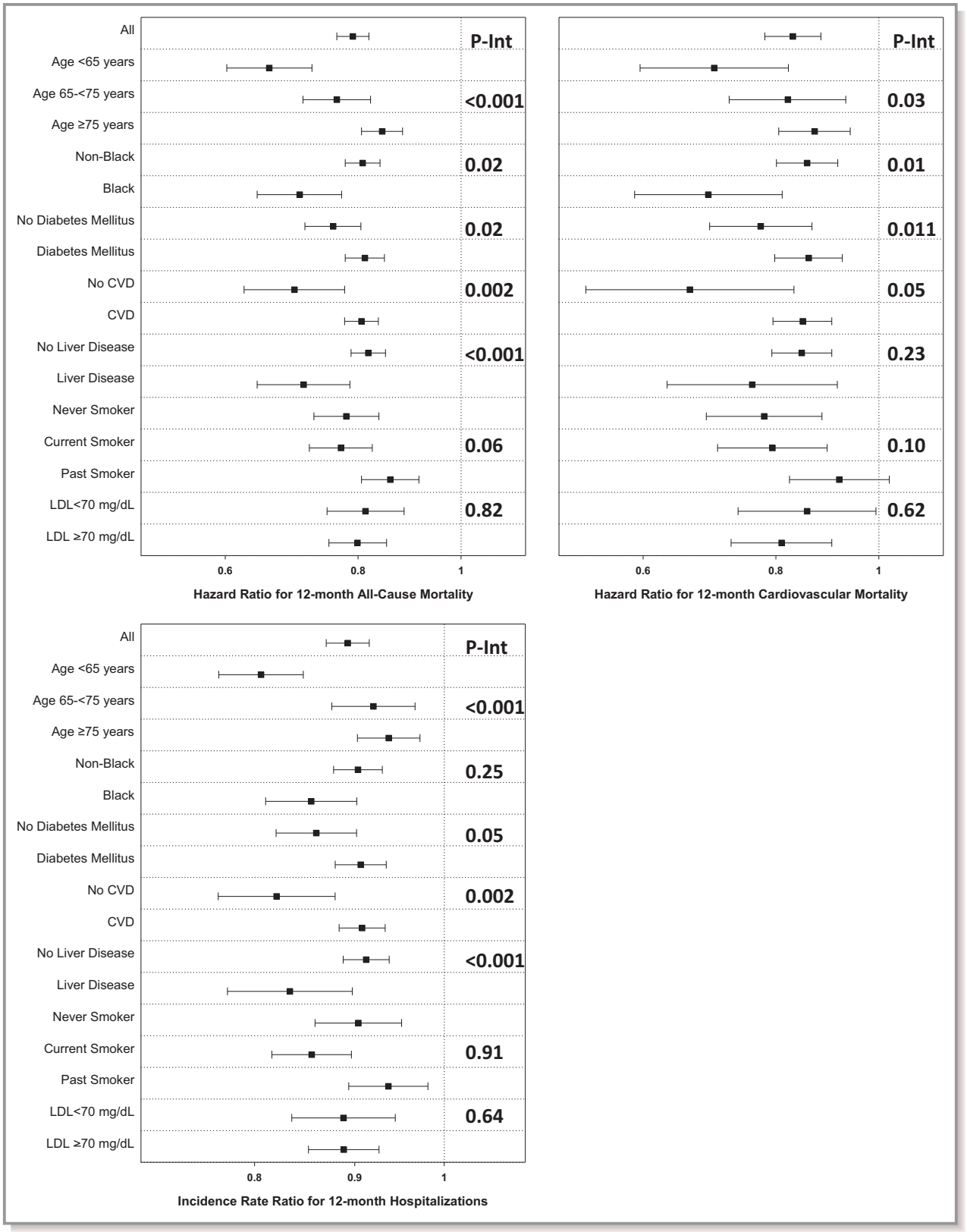


Figure. Associations of pre–end-stage renal disease statin therapy vs no statin therapy with 12-month all-cause mortality, cardiovascular mortality, and hospitalization incidence rate in a priori selected subgroups. Adjusted covariates included age, sex, race, and ethnicity as well as the following comorbidities: 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.

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 failure[41] 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 examined differences in septicemia in dialysis patients.[44] Previous studies have speculated that statins may also exhibit anti-inflammatory and antioxidant properties, which may explain differences in these noncardiovascular outcomes.[42,45,46] Associations of statin treatment before ESRD transition and its impact on the risk of individual cardiovascular and noncardiovascular events after transition should be further examined.

Our study finding that treatment with a statin before the transition to ESRD is associated with a lower risk of adverse outcomes supports the recommendations by the Kidney Disease: Improving Global Outcomes guidelines[3] and the American College of Cardiology guidelines.[4,40] Kidney Disease: Improving Global Outcomes recommendations for statin therapy have been mostly based on the results of the SHARP trial,[5] which included men and women aged ≥40 years with a history of CKD or of receiving dialysis and excluded patients with a history of MI or coronary revascularization or a definite history of chronic liver disease. As opposed to the SHARP trial, our cohort did include patients with prior MI or liver disease, and we separately analyzed patients who transitioned to ESRD. Our study should be noted for its large sample size and event numbers and for its use of both CMS and VA data to ascertain medication use, comorbidities, and outcomes.

However, there are several potential limitations to this study. We adjusted for only known and available confounders in our analyses; however, residual confounding cannot be completely eliminated, and a causal relationship cannot be inferred because of the observational study design. Patients categorized as not receiving statin therapy may have had medication compliance or adherence problems, which are associated with higher mortality risk in this cohort.[47] In addition, we excluded patients without medication data in the 1 year before ESRD transition, which may be a source of selection bias. Our analysis used a prevalent-user design, and we were unable to evaluate if patients not receiving statin therapy discontinued medications because of intolerance or other adverse effects. Because of a high level of missing lipid and other laboratory measurements, we were unable to include 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 fistula[55] 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 a recommendation of treatment with 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.

Acknowledgments

The data reported herein have been supplied by the US Renal Data System. Support for Veterans Affairs (VA)/Centers for Medicare and Medicaid Services data is provided by the US Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Nos. SDR 02-237 and 98-004). E.S., H.M., E.O.G., C.P.K., and K.K.Z. are employees of the US Department of Veterans Affairs. Opinions expressed herein are those of the authors and do not represent the official opinion of the US Department of Veterans Affairs.

Sources of Funding

This study was supported by grant U01-DK102163 from the National Institutes of Health (NIH) to Kovesdy and Kalantar-Zadeh, and by resources from the US Department of Veterans Affairs. Kalantar-Zadeh has been supported by the NIH/National Institute of Diabetes and Digestive and Kidney Diseases midcareer award K24-DK091419. Streja and Moradi are supported by career development awards from the Office of Research and Development of the US Department of Veterans Affairs (Streja, IK2-CX 001266-01; Moradi, 1IK CX 001043-01).

Disclosures

Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition and Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma. The remaining authors have no disclosures to report.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1–S45.

2. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, Balkrishnan R, Dietrich X, Eckard A, Eggers PW, Gaipov A, Gillen D, Gipson D, Hailpern SM, Hall YN, Han Y, He K, Herman W, Heung M, Hirth RA, Hutton D, Jacobsen SJ, Jin Y, Kalantar-Zadeh K, Kapke A, Kovesdy CP, Lavallee D, Leslie J, McCullough K, Modi Z, Molnar MZ, Montez-Rath M, Moradi H, Morgenstern H, Mukhopadhyay P, Nallamothu B, Nguyen DV, Norris KC, O'Hare AM, Obi Y, Park C, Pearson J, Pisoni R, Potukuchi PK, Rao P, Repeck K, Rhee CM, Schrager J, Schaubel DE, Selewski DT, Shaw SF, Shi JM, Shieu M, Sim JJ, Soohoo M, Steffick D, Streja E, Sumida K, Tamura MK, Tilea A, Tong L, Wang D, Wang M, Woodside KJ, Xin X, Yin M, You AS, Zhou H, Shahinian V. US Renal Data System 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2018;71:A7.

3. Tonelli M, Wanner C; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid management in chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2013 clinical practice guideline. *Ann Intern Med*. 2014;160:182.

4. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol*. 2016;68:92–125.

5. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin AA, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators. 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.

6. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248.

7. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395–1407.

8. Obi Y, Park C, Soohoo M, Sumida K, Hamano T, Rhee CM, Kovesdy CP, Kalantar-Zadeh K, Streja E. Association of pre-ESRD serum calcium with post-ESRD mortality among incident ESRD patients: a cohort study. *J Bone Miner Res*. 2018;33:1027–1036.

9. Soohoo M, Streja E, Obi Y, Rhee CM, Gillen DL, Sumida K, Nguyen DV, Kovesdy CP, Kalantar-Zadeh K. Predialysis kidney function and its rate of decline predict mortality and hospitalizations after starting dialysis. *Mayo Clin Proc*. 2018;93:1074–1085.

10. McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, Brown ST, Freiberg MS, Gibert CL, Goetz MB, Kim JW, Pisani MA, Rimland D, Rodriguez-Barradas MC, Sico JJ, Tindle HA, Crothers K. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res*. 2011;13:1233–1239.

11. *VIReC Research User Guide: VHA Pharmacy Prescription Data*. 2nd ed. 2008. https://www.virec.research.va.gov/Resources/RUGs.asp. Accessed June 8, 2017.
12. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107.
13. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
14. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
15. Kim CA, Kim DH. Statins provide less benefit in populations with high noncardiovascular mortality risk: meta-regression of randomized controlled trials. *J Am Geriatr Soc*. 2015;63:1413–1419.
16. Wakasugi M, Kazama JJ, Yamamoto S, Kawamura K, Narita I. Cause-specific excess mortality among dialysis patients: comparison with the general population in Japan. *Ther Apher Dial*. 2013;17:298–304.
17. Streja D, Streja E. Management of dyslipidemia in the elderly. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, eds. *Endotext* [Internet]. South Dartmouth, MA: MDText.com, Inc.; 2000.
18. Cholesterol Treatment Trialists (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117–125.
19. Howes LG. The effects of lipid-lowering drug therapy on cardiovascular responsiveness in type 2 diabetic patients. *Diabetes Obes Metab*. 2006;8:8–14.
20. Hadi HA, Carr CS, Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. *Vasc Health Risk Manag*. 2005;1:183–198.
21. Beishuizen ED, Jukema JW, Tamsma JT, van de Ree MA, van der Vijver JC, Putter H, Maan AC, Meinders AE, Huisman MV. No effect of statin therapy on silent myocardial ischemia in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care*. 2005;28:1675–1679.
22. Beishuizen ED, Tamsma JT, Jukema JW, van de Ree MA, van der Vijver JC, Meinders AE, Huisman MV. The effect of statin therapy on endothelial function in type 2 diabetes without manifest cardiovascular disease. *Diabetes Care*. 2005;28:1668–1674.
23. Beishuizen ED, van de Ree MA, Jukema JW, Tamsma JT, van der Vijver JC, Meinders AE, Putter H, Huisman MV. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care*. 2004;27:2887–2892.
24. Bittencourt MS, Cerci RJ. Statin effects on atherosclerotic plaques: regression or healing? *BMC Med*. 2015;13:260.
25. Nakanishi R, Ceponiene I, Osawa K, Luo Y, Kanisawa M, Megowan N, Nezarat N, Rahmani S, Broersen A, Kitslaar PH, Dailing C, Budoff MJ. Plaque progression assessed by a novel semi-automated quantitative plaque software on coronary computed tomography angiography between diabetes and non-diabetes patients: a propensity-score matching study. *Atherosclerosis*. 2016;255:73–79.
26. Al-Aly Z. Medial vascular calcification in diabetes mellitus and chronic kidney disease: the role of inflammation. *Cardiovasc Hematol Disord Drug Targets*. 2007;7:1–6.
27. Margolis KL, Dunn K, Simpson LM, Ford CE, Williamson JD, Gordon DJ, Einhorn PT, Probstfield JL; ALLHAT Collaborative Research Group. Coronary heart disease in moderately hypercholesterolemic, hypertensive black and non-black patients randomized to pravastatin versus usual care: the antihypertensive and lipid lowering to prevent heart attack trial (ALLHAT-LLT). *Am Heart J*. 2009;158:948–955.
28. Ozieh MN, Taber DJ, Egede LE. Does African American race impact statin efficacy in renal transplant outcomes? *Medicine*. 2015;94:e2283.
29. Streja E, Kovesdy CP, Molnar MZ, Norris KC, Greenland S, Nissenson AR, Kopple JD, Kalantar-Zadeh K. Role of nutritional status and inflammation in higher survival of African American and Hispanic hemodialysis patients. *Am J Kidney Dis*. 2011;57:883–893.
30. Kovesdy CP, Norris KC, Boulware LE, Lu JL, Ma JZ, Streja E, Molnar MZ, Kalantar-Zadeh K. Association of race with mortality and cardiovascular events in a large cohort of US veterans. *Circulation*. 2015;132:1538–1548.
31. Norris KC, Mensah GA, Boulware LE, Lu JL, Ma JZ, Streja E, Molnar MZ, Kalantar-Zadeh K, Kovesdy CP. Age, race and cardiovascular outcomes in African American veterans. *Ethn Dis*. 2016;26:305–314.
32. Kovesdy CP, Quarles LD, Lott EH, Lu JL, Ma JZ, Molnar MZ, Kalantar-Zadeh K. Survival advantage in black versus white men with CKD: effect of estimated GFR and case mix. *Am J Kidney Dis*. 2013;62:228–235.
33. Youssef G, Guo M, McClelland RL, Shavelle DM, Nasir K, Rivera J, Carr JJ, Wong ND, Budoff MJ. Risk factors for the development and progression of thoracic aorta calcification: the multi-ethnic study of atherosclerosis. *Acad Radiol*. 2015;22:1536–1545.
34. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2005;111:1313–1320.
35. Lee TC, O'Malley PG, Feuerstein I, Taylor AJ. The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects. *J Am Coll Cardiol*. 2003;41:39–44.
36. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelias ED, Theocharidou E, Karagiannis A, Mikhailidis DP; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet*. 2010;376:1916–1922.
37. Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, Kastelein JJ, Holme I, Pedersen TR; IDEAL Investigators. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. *Int J Cardiol*. 2013;168:3846–3852.
38. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
39. Tzefos M, Olin JL. 3-Hydroxyl-3-methylglutaryl coenzyme a reductase inhibitor use in chronic liver disease: a therapeutic controversy. *J Clin Lipidol*. 2011;5:450–459.
40. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation*. 2013;129:S1–S72.
41. Chang HH, Chang YK, Lu CW, Huang CT, Chien CT, Hung KY, Huang KC, Hsu CC. Statins improve long term patency of arteriovenous fistula for hemodialysis. *Sci Rep*. 2016;6:22197.
42. Gupta R, Plantinga LC, Fink NE, Melamed ML, Coresh J, Fox CS, Levin NW, Powe NR. Statin use and sepsis events [corrected] in patients with chronic kidney disease. *JAMA*. 2007;297:1455–1464.
43. Herrington W, Emberson J, Staplin N, Blackwell L, Fellström B, Walker R, Levin A, Hooi LS, Massy ZA, Tesar V, Reith C, Haynes R, Baigent C, Landray MJ; SHARP Investigators. The effect of lowering LDL cholesterol on vascular access patency: post hoc analysis of the Study of Heart and Renal Protection. *Clin J Am Soc Nephrol*. 2014;9:914–919.
44. Reith C, Staplin N, Herrington WG, Stevens W, Emberson J, Haynes R, Mafham M, Armitage J, Cass A, Craig JC, Jiang L, Pedersen T, Baigent C, Landray MJ; SHARP Collaborative Group. Effect on non-vascular outcomes of lowering LDL cholesterol in patients with chronic kidney disease: results from the Study of Heart and Renal Protection. *BMC Nephrol*. 2017;18:147.
45. Mason NA, Bailie GR, Satayathum S, Bragg-Gresham JL, Akiba T, Akizawa T, Combe C, Rayner HC, Saito A, Gillespie BW, Young EW. HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients. *Am J Kidney Dis*. 2005;45:119–126.
46. Seliger SL, Weiss NS, Gillen DL, Kestenbaum B, Ball A, Sherrard DJ, Stehman-Breen CO. HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. *Kidney Int*. 2002;61:297–304.
47. Molnar MZ, Gosmanova EO, Sumida K, Potukuchi PK, Lu JL, Jing J, Ravel VA, Soohoo M, Rhee CM, Streja E, Kalantar-Zadeh K, Kovesdy CP. Predialysis cardiovascular disease medication adherence and mortality after transition to dialysis. *Am J Kidney Dis*. 2016;68:609–618.
48. Khan SS, Xue JL, Kazmi WH, Gilbertson DT, Obrador GT, Pereira BJ, Collins AJ. Does predialysis nephrology care influence patient survival after initiation of dialysis? *Kidney Int*. 2005;67:1038–1046.
49. Singhal R, Hux JE, Alibhai SM, Oliver MJ. Inadequate predialysis care and mortality after initiation of renal replacement therapy. *Kidney Int*. 2014;86:399–406.
50. Fischer MJ, Stroupe KT, Kaufman JS, O'Hare AM, Browning MM, Sohn MW, Huo Z, Hynes DM. Predialysis nephrology care and dialysis-related health outcomes among older adults initiating dialysis. *BMC Nephrol*. 2016;17:103.

51. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. *Am J Med*. 2011;124:1073–1080.e2.
52. Hsu TW, Liu JS, Hung SC, Kuo KL, Chang YK, Chen YC, Hsu CC, Tarng DC. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. *JAMA Intern Med*. 2014;174:347–354.
53. Watanabe Y, Akizawa T, Saito A, Gejyo F, Suzuki M, Nishizawa Y, Tomino Y, Tsubakihara Y, Akiba T, Hirakata H, Kawanishi H, Bessho M, Udagawa Y, Aoki K, Uemura Y, Ohashi Y; Co-JET Study Group. Effect of predialysis recombinant human erythropoietin on early survival after hemodialysis initiation in patients with chronic kidney disease: Co-JET Study. *Ther Apher Dial*. 2016;20:598–607.
54. Slinin Y, Guo H, Gilbertson DT, Mau LW, Ensrud K, Collins AJ, Ishani A. Prehemodialysis care by dietitians and first-year mortality after initiation of hemodialysis. *Am J Kidney Dis*. 2011;58:583–590.
55. Lorenzo V, Martn M, Rufino M, Hernandez D, Torres A, Ayus JC. Predialysis nephrologic care and a functioning arteriovenous fistula at entry are associated with better survival in incident hemodialysis patients: an observational cohort study. *Am J Kidney Dis*. 2004;43:999–1007.

Supplemental Material

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

	12-month											
	All-Cause Mortality				Cardiovascular Mortality				Hospitalization Rate			
	N Event/N Group				N Event/N Group				N Event/N Group*			
Subgroup	Total	Yes Statin	No Statin	P-Int	Total	Yes Statin	No Statin	P-Int	Total*	Yes Statin*	No Statin*	P-Int
Age<65	2114/13689	893/6473	1221/7216	<.0001	669/12849	6103/318	351/6746	0.03	23395/13689	6473/11060	12335/7216	0.0003
Age65-<75	3068/12799	1643/7331	1425/5468		1038/11665	6732/595	443/4933		21157/12799	7331/12426	8731/5468	
Age≥75	8229/21232	4334/11765	3895/9467		2666/18257	10240/1466	1200/8017		34592/21232	11765/19491	15101/9467	
Non-African American	11362/36738	6010/20501	5352/16237	0.02	3720/32667	18382/2096	1624/14285	0.01	60526/36738	20501/34397	26129/16237	0.25
African American	2044/10976	860/5068	1184/5908		653/10103	4693/283	370/5410		18618/10976	5068/8580	10038/5908	
No Diabetes	4611/16074	1856/6578	2755/9496	0.02	1345/14334	5877/579	766/8457	0.11	23837/16074	6578/9691	14146/9496	0.05
Diabetes	8765/31465	5002/18907	3763/12558		3013/28271	17119/1795	1218/11152		55172/31465	18907/33223	21949/12558	
No CVD	1670/10278	486/3672	1184/6606	0.002	385/9600	3460/114	271/6140	0.05	12198/10278	3672/3918	8280/6606	0.002
CVD	11706/37261	6372/21813	5334/15448		3973/33005	19536/2260	1713/13469		66811/37261	21813/38996	27815/15448	
No Liver Disease	11587/42282	6231/23481	5356/18801	0.0002	3860/38037	21241/2177	1683/16796	0.23	68355/42282	23481/38812	29543/18801	0.001
Liver Disease	1789/5257	627/2004	1162/3253		498/4568	1755/197	301/2813		10654/5257	2004/4102	6552/3253	
Never Smoker	3192/12142	1662/6701	1530/5441	0.06	1015/10952	6075/551	464/4877	0.10	18381/12142	6701/10363	8018/5441	0.91
Current Smoker	3623/14025	1861/7381	1762/6644		1170/12632	6681/643	527/5951		25218/14025	7381/13285	11933/6644	
Past Smoker	4228/14198	2422/8407	1806/5791		1426/12713	7569/861	565/5144		23194/14198	8407/13969	9225/5791	
LDL<70 mg/dL	2769/9990	1946/7041	823/2949	0.82	914/8949	6324/672	242/2625	0.62	17185/9990	7041/12199	4986/2949	0.64
LDL≥70 mg/dL	4066/17578	2149/9713	1917/7865		1353/16081	8915/745	608/7166		28761/17578	9713/16050	12711/7865	
No Afib	9896/39592	4989/20920	4907/18672	0.11	3114/35860	19047/1665	1449/16813	0.14	63467/39592	20920/33826	29641/18672	0.12
Afib	3480/7947	1869/4565	1611/3382		1244/6745	3949/709	535/2796		15542/7947	4565/9088	6454/3382	
No ISHD	3941/19635	1426/8189	2515/11446	0.003	1041/18079	7620/398	643/10459	0.07	27528/19635	8189/10980	16548/11446	0.001
ISHD	9435/27904	5432/17296	4003/10608		3317/24526	15376/1976	1341/9150		51481/27904	17296/31934	19547/10608	
No MI	8646/35163	3978/17542	4668/17621	0.002	2603/31896	16068/1275	1328/15828	0.06	54218/35163	17542/26838	27380/17621	0.004
MI	4730/12376	2880/7943	1850/4433		1755/10709	6928/1099	656/3781		24791/12376	7943/16076	8715/4433	
No CHF	4157/21340	1753/10023	2404/11317	0.0002	1100/19743	9338/486	614/10405	0.01	28978/21340	10023/13227	15751/11317	0.002
CHF	9219/26199	5105/15462	4114/10737		3258/22862	13658/1888	1370/9204		50031/26199	15462/29687	20344/10737	
No PVD	6924/29325	3111/14319	3813/15006	<.0001	2100/26685	13140/1019	1081/13545	0.03	43864/29325	14319/21306	22558/15006	0.01
PVD	6452/18214	3747/11166	2705/7048		2258/15920	9856/1355	903/6064		35145/18214	11166/21608	13537/7048	
No Cerebrovascular	8061/32711	3751/16307	4310/16404	0.001	2553/29744	14960/1291	1262/14784	0.33	50158/32711	16307/25077	25081/16404	0.02
Cerebrovascular	5315/14828	3107/9178	2208/5650		1805/12861	8036/1083	722/4825		28851/14828	9178/17837	11014/5650	
No ASCVD	3006/15991	990/6315	2016/9676	<.0001	750/14776	5899/256	494/8877	0.01	21270/15991	6315/7902	13368/9676	0.002
ASCVD	10370/31548	5868/19170	4502/12378		3608/27829	17097/2118	1490/10732		57739/31548	19170/35012	22727/12378	

*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.

	12-Month All-Cause Mortality		12-Month Cardiovascular Mortality		12-Month Hospitalization Incidence Rate	
Level	*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/m^2)	13072	29.9±6.5	30.7±6.4	28.9±6.5	0.27
White Blood Cell Count ($x10^3/\mu L$)	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*	HR [95% CI]
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*	HR [95% CI]
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*	IRR [95% CI]
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.

	Total	Excluded	Included in Labs Adjusted Model	Standardized difference
N,(%)	47720	23403	24317	
Cardiovascular Disease(%)				
No	22	19	24	-0.12
Yes	78	81	76	
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	74±11	69±11	-0.51
Age <65 (%)	29	18	39	0.49
Age 65-<75 (%)	27	26	27	0.02
Age≥75 (%)	44	56	34	-0.46
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 (%)	60	66	55	-0.22
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 (%)				0.19
Never	30	30	30	
Current	35	30	38	
Past	35	40	32	
eGFR at initiation (mL/min/1.73 m^2)	10.1[7.3,13.8]	10.4[7.6,14.4]	9.7[7.1,13.2]	-0.13
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	0.10
Peritoneal Dialysis	5	5	5	
Other/Unknown	12	14	11	
Initial Access Type (%)				
AV Fistula/AV Graft	21	19	23	0.10
CVC	70	72	68	
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 [25^{th} percentile, 75^{th} 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.

	Stain 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 (%)			0.09
Never	30	31	
Current	33	36	
Past	37	34	
eGFR at initiation (mL/min/1.73 m^2)	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

	All-Cause Mortality					Cardiovascular Mortality				
Propensity Score Analyses		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.

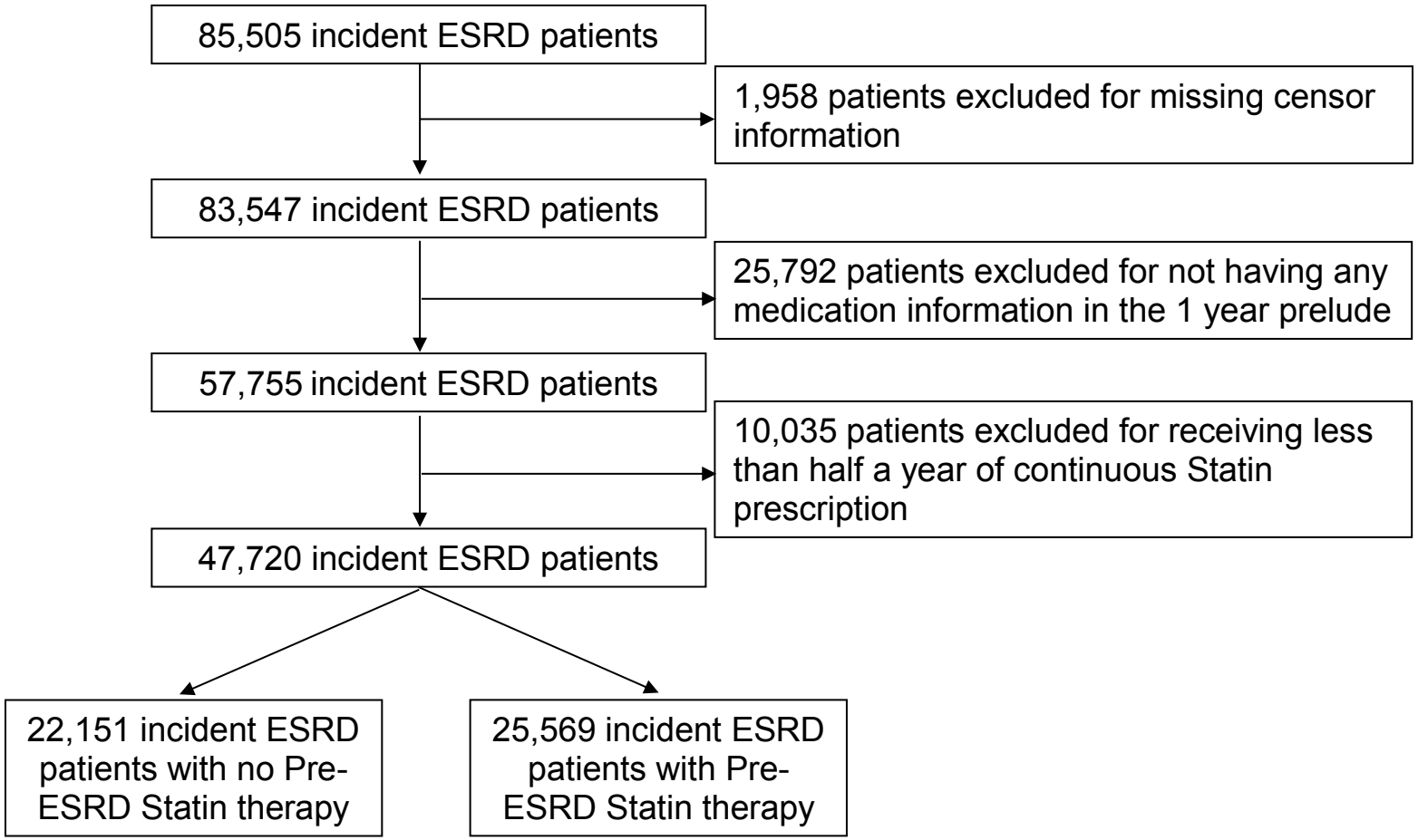
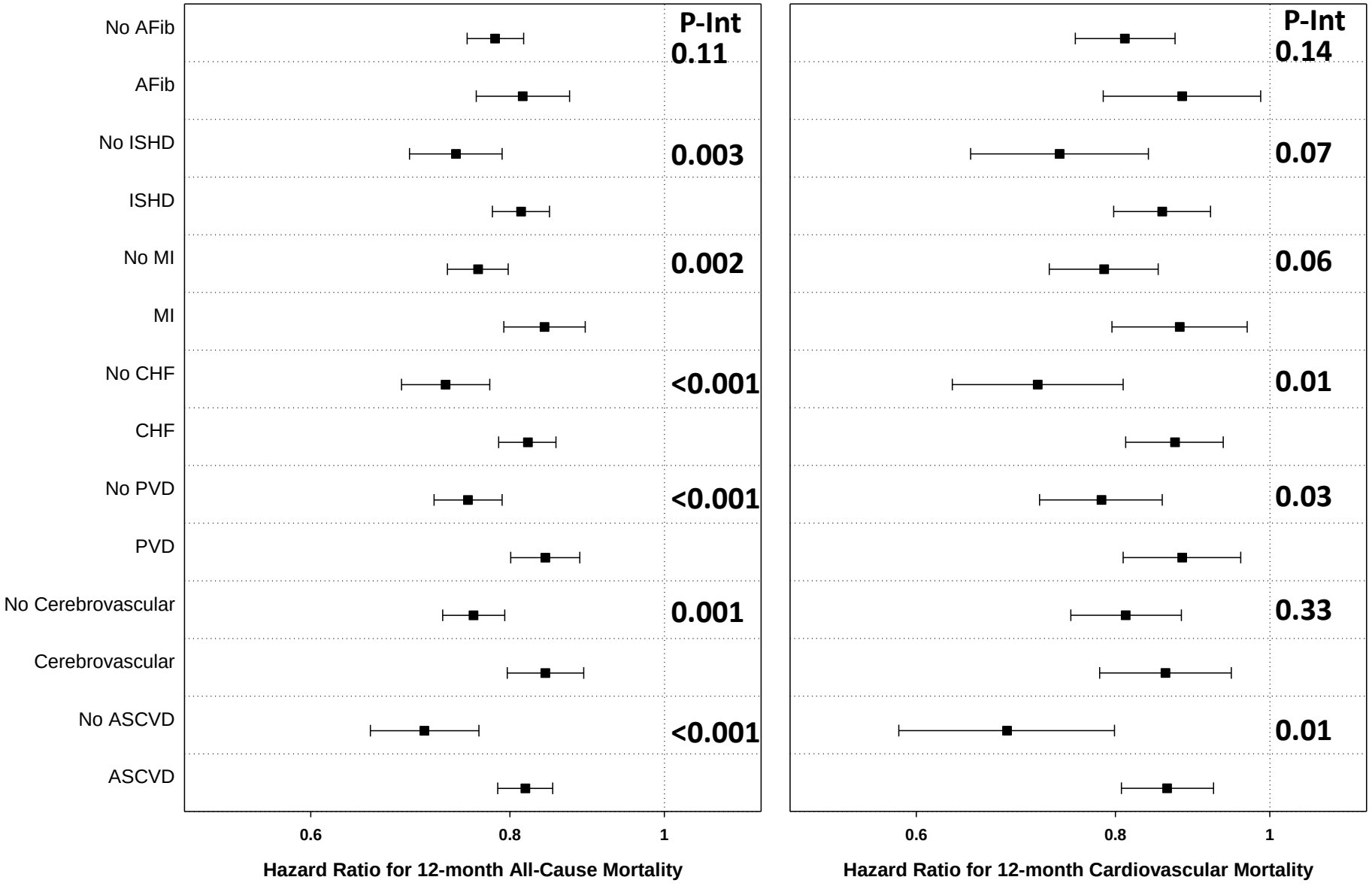


Figure S2. Associations of pre-ESRD statin therapy vs no statin therapy with 12-month all-cause, cardiovascular mortality, and hospitalization incidence rate in individual cardiovascular disease subgroups after adjustment.



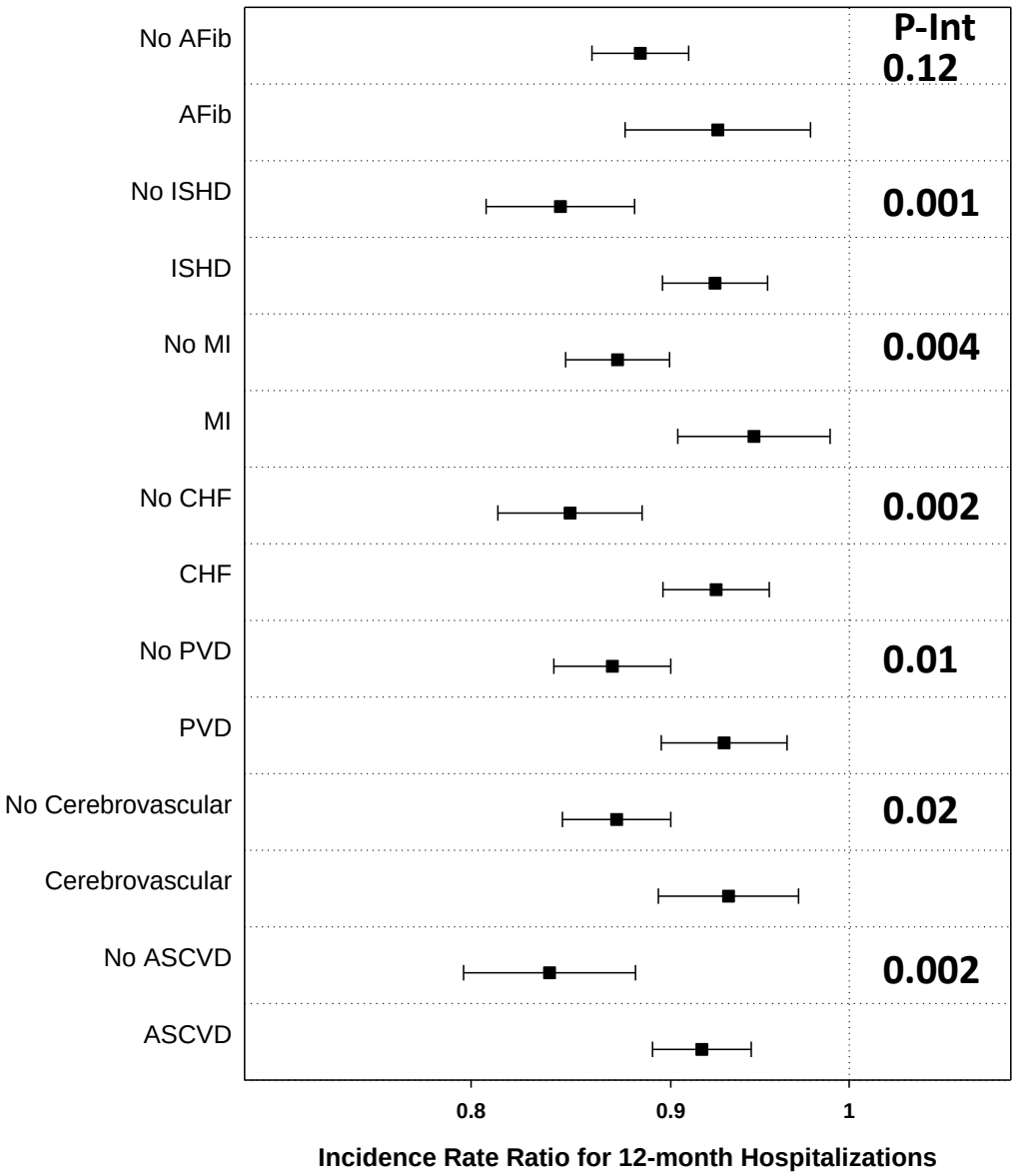
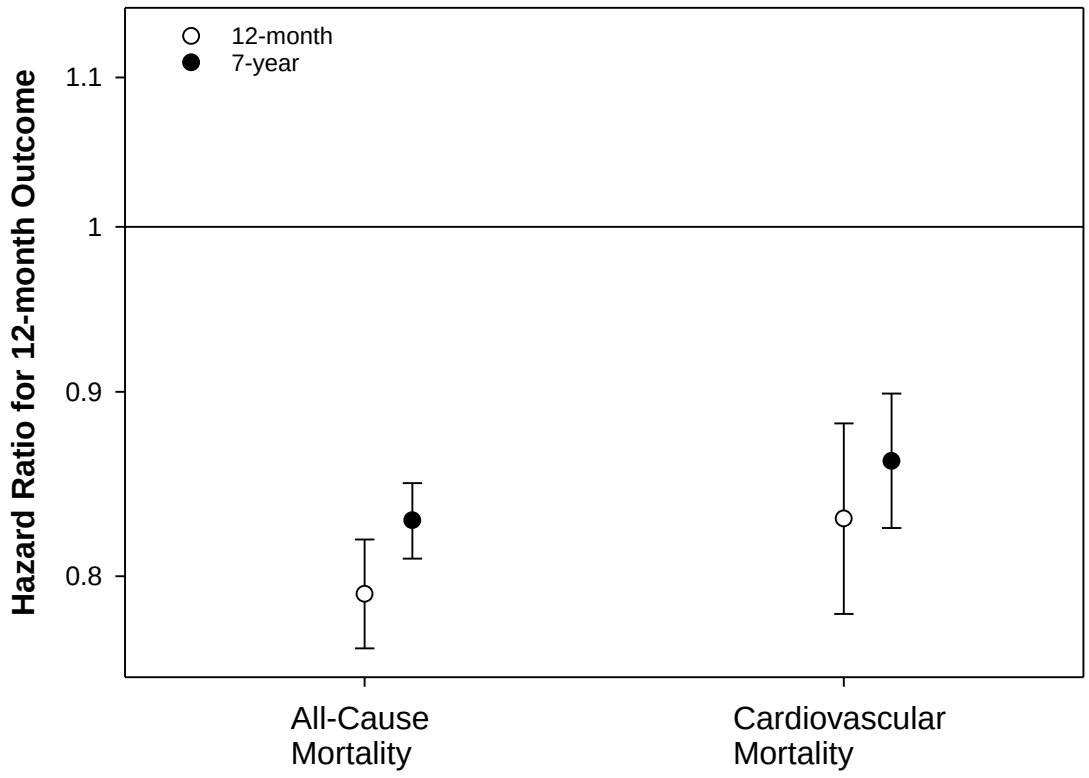
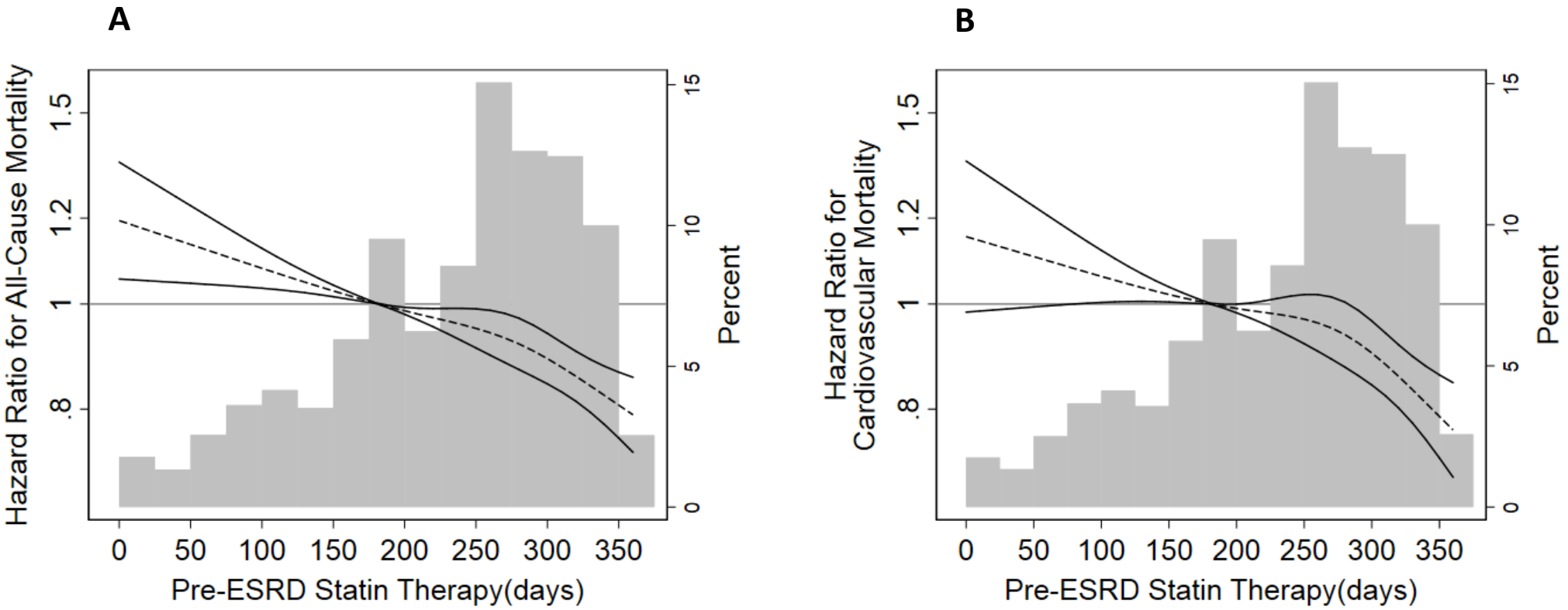

No AFib
AFib
No ISHD
ISHD
No MI
MI
No CHF
CHF
No PVD
PVD
No Cerebrovascular
Cerebrovascular
No ASCVD
ASCVD
P-Int
0.12
0.001
0.004
0.002
0.01
0.02
0.002
0.8
0.9
1
Incidence Rate Ratio for 12-month Hospitalizations

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.