Association of Statin and Its Lipophilicity With Cardiovascular Events in Patients Receiving Chronic Dialysis

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Lipophilicity of statins has been linked to extrahepatic cell penetration and inhibition of isoprenoid synthesis and coenzyme Q10, which may affect myocardial contraction. Whether statins' lipophilicity affects the risk of cardiovascular disease development in patients under dialysis is unclear. This population-based study included 114,929 patients undergoing chronic dialysis, retrieved from the Registry for Catastrophic Illness Patients from the National Health Insurance Research Database in Taiwan from 2000 to 2013. Statins were initiated after dialysis and classified into hydrophilic and lipophilic by the duration of use. In total, 17,015 statin users and match controls were identified by using propensity score matching in 1:1 ratio. New statin use was associated with higher cardiovascular disease risk (adjusted hazard ratio (aHR): 1.2, 95% confidence interval (CI), 1.13–1.28) but lower all-cause mortality (aHR: 0.93, 95% CI, 0.89–0.96). Hydrophilic statins were significantly associated with lower risk of cardiovascular disease compared with lipophilic statins (aHR: 0.91, 95% CI, 0.85–0.97).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Cardiovascular disease is a leading cause of death in patients with advanced kidney disease. The role of statins in cardiovascular disease in patients under maintenance dialysis is still controversial.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the association between newly introduced statin treatment and later incidence of cardiovascular disease among adult patients undergoing chronic dialysis? What is the role of statin lipophilicity on cardiovascular disease risk reduction?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ New introduction of statin treatment may reduce mortality but increase cardiovascular events among patients undergoing dialysis. Hydrophilic statins may decrease the risk of cardiovascular disease more than lipophilic statins.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Initiation and choice of hydrophilic statins may be important to reduce cardiovascular mortality and morbidity, particularly for patients under maintenance dialysis. If statin initiation is considered, hydrophilic statin may be a preferable choice for lower risk of cardiovascular disease and any causes of mortality.

Cardiovascular disease (CVD) is a leading cause of morbidity as well as mortality in patients with end stage renal disease (ESRD). CVD-related mortality is reported to be 10-fold to 30-fold higher in dialysis patients than in the general population.[1] However, according to the 2014 Kidney Disease Improving Global Outcomes Lipid Work Group, statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, were not recommended to be initiated for patients undergoing chronic dialysis,[2] because statins showed little or no benefit on CVD prevention and mortality from any cause among patients who had just started dialysis, based on several large randomized controlled trials[3–5] and a systematic review.[6] The inconsistent evidence may be explained by the findings that statins may be beneficial only for a group of patients with elevated low-density lipoprotein (LDL)[7] or, specifically, atherosclerotic cardiac events.[8]

A recent indirect meta-analysis in patients with heart failure concluded that lipophilic statins (atorvastatin, simvastatin, and

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pitavastatin) showed greater effects on cardiac function, downregulating inflammation, and all-cause and cardiovascular mortality, than hydrophilic statins (rosuvastatin);[9,10] however, hydrophilic and lipophilic statins did not differ with respect to major adverse cardiovascular outcomes, cardiovascular death, or all-cause mortality among patients with preexisting CVD.[11] These differences in treatment effects between lipophilic and hydrophilic statins on cardiac functions may be related to the pharmacological properties of statins. Lipophilic statins can more easily penetrate extrahepatic cells and inhibit synthesis of essential substances such as isoprenoid and coenzyme Q10 via an HMG-CoA reductase reaction. Hence, lipophilic statins may worsen myocardial contractile dysfunction, which is associated with reduction of myocardial concentration of coenzyme Q10 and adenosine triphosphate (ATP).[12] In addition, hydrophilic statins have several pleotropic effects in atherosclerotic cardiovascular diseases.[13]

Whether statin initiation is beneficial for CVD primary prevention and which type of statin is preferable for patients on maintenance dialysis remain unknown. Focusing on the atherosclerotic events,[5,8] this population-based cohort study of patients on maintenance dialysis sought to better assess the associations between statin initiation and incident CVD as well as all-cause mortality.

METHODS

Data sources

This retrospective cohort study was conducted using a longitudinal nationwide database on the Registry for Catastrophic Illness Patients from National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Insurance program in Taiwan is a single-payer compulsory program launched in 1995 and covers over 99% of the population of 23 million in Taiwan.[14] The details of NHIRD have been described elsewhere;[15] briefly, it contains patient-level information, including inpatient and outpatient care claims, prescriptions, disease diagnosis, procedures, and registry for catastrophic illnesses for public research purposes. In the Registry for Catastrophic Illness Patients database, copayments were waived when patients met explicit criteria of a "severe illness" diagnosis, such as ESRD,[16] ischemic stroke, or acute myocardial infarction.[17,18] This database contains information on patients who received renal replacement therapy for ESRD, including dialysis and kidney transplantation from 2000 to 2013 in Taiwan. The study was approved by the Institutional Review Board of the Chang Gung Medical Foundation at Taoyuan, Taiwan (permitted number: 201800314B0C501).

Study cohort

Under the NHI program coverage, patients with dialysis are designated as those having a "catastrophic illness" and are issued a catastrophic illness certificate.[16] Patients with ESRD (International Classification of Diseases, ninth revision, Clinical Modification, ICD-9-CM code 585) who had received hemodialysis or peritoneal dialysis continuously for 3 months, with at least one dialysis procedure per month, were identified in the Registry for Catastrophic Illness Patients data set. Patients were defined by ICD-9-CM codes and Taiwan NHI billing codes for hemodialysis or peritoneal dialysis (**Table S3**).

In order to investigate the primary prevention effect of lipophilic statin initiation (in the new user cohort) on CVD incidence, patients were excluded if they had ever undergone any of the following prior to the first date of maintenance dialysis: (i) received any statin within 3 months (prior users); (ii) received coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) procedures for myocardial infarction; (iii) ever been diagnosed with cardiovascular disease, such as myocardial infarction (MI), unstable angina, or ischemic stroke caused by cerebral artery occlusion, which is more prevalent in Asians;[17–19] or (iv) received kidney transplantation that carries immunosuppression-related cardiovascular risks (**Table S3**). The prior CVD outcomes were obtained using a validated algorithm applied to NHIRD to minimize potential confounding (**Table S3**). To avoid possible treatment and outcomes misclassification, patients were further excluded if there was a lack of baseline period (< 365 days) prior to the first date of chronic dialysis to ensure the definitions of new statin user cohort and incident CVD events in the follow-up period.

Medication exposure

To prevent healthy users effect bias,[19] a new users design was employed to dialysis patients who were first-time treated with statin therapy. Among new users of statins, only those with at least 28 days of supply for statin therapy during the follow-up were included. The study index date for a statin user was the first date of statin prescription following the initiation of chronic dialysis. The hydrophilic statins included in the study were pravastatin and rosuvastatin; and lipophilic statins were atorvastatin, simvastatin, pitavastatin, fluvastatin, and lovastatin.

Considering that medication may be switched or overlapping during follow-up time, proportion of days covered was calculated to categorize the patterns of exposure intensity. In addition, statin adherence is associated with all-cause mortality in patients with atherosclerotic CVD.[20] Three types of exposures based on the proportion of sum of days for each property and sum of days of any statin use and property of statin were employed: lipophilic statin (≥ 60% of overall days for lipophilic statin use), hydrophilic statin (≥ 60% of overall days for hydrophilic statin use), and other group (< 60% of overall days of lipophilic or hydrophilic statin use).

Outcome assessment

According to statin lipophilicity, treatment outcomes were compared between lipophilic and hydrophilic statin users. The primary outcome was a composite of MI, unstable angina, ischemic stroke, or undergoing CABG/PCI. The onset of outcome event during follow-up was identified by the ICD-9-CM code at hospital discharge (**Table S3**). The secondary outcomes included all-cause mortality, or MI, or unstable angina, or ischemic stroke, or receiving CABG/PCI, separately. All patients were followed from the study index date (date of first statin prescription) until the outcome event of interest, or the latest date in the data set (December 31, 2013), or censored at switching to different types of statin, or receiving kidney transplantation, whichever came first. For nonstatin users, the index date at random corresponded to the index date of matched statin users.

Covariates

Because the risk of underlying comorbid conditions could influence both statin initiation and treatment outcomes, this study controlled for 26 baseline covariates by clinical knowledge and literature reviewed, including demographics (age, sex), dialysis (year of dialysis initiation and initial dialysis modality), clinical conditions (Charlson comorbidity index disease conditions, hypertension, hyperlipidemia, and atrial fibrillation, but except for renal disease and acute myocardial infarction (AMI)), and prior medication uses (nonstatin lipid-lowering agent (LLA), antihypertensive agents, digoxin, and anti-thrombotic agents) which were assessed within 365 days prior to the study index date (**Table S3**).

Time-varying covariates, including concomitant use of nonstatin LLAs, antihypertensive agents, digoxin, antithrombotic agents, and glucose-lowering agents during the follow-up and before the onset of CVD event were categorized and controlled in treatment effect regression models.

Statistical methods

Because this is not a random treatment allocation design, 1:1 propensity score matching without replacement with greedy matching algorithm was employed to establish comparisons between treatment and nontreatment of statin groups to minimize confounding by indication.[21] A logistic regression model based on potential confounding covariates (26 baseline covariates listed above) was employed to calculate propensity

score of statin initiation for participants. The differences in baseline characteristics between the statin and nonstatin groups were assessed using standardized mean differences, with value < 0.1 considered well balanced between the two comparison groups.[22]

To mitigate the effect of immortal time bias, it was ensured that the index date for a nonstatin user coincided with the date they were followed up in the study plus the time between their matched counterpart's entry date and first statin prescription.[23]

Kaplan-Meier curves were employed to generate cumulative incident CVD events and mortality between the comparison groups. The Cox proportional hazards model was employed to evaluate the associations between statin use and CVD risk, adjusting for time-varying confounders (e.g., ≥ 28 days concomitant use of nonstatin LLAs, antihypertensive agents, digoxin, antithrombotic agents, and glucose-lowering agents during the follow-up). The impacts of the competitive risk between death and kidney transplantations were assessed using the Fine and Gray subdistribution hazard approach.[24,25]

Stratified analyses were performed to assess the heterogenetic effects in different groups by age, sex, comorbidity, and concomitant medication. Additional sensitivity analyses for rigorous definition of patients without use of digoxin or nonstatin LLA before the index date were conducted. *P* values were two-sided and considered significant if $P < 0.05$. All data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

The population source comprised 114,929 patients with ESRD who were undergoing maintenance dialysis; of them 80,946 who met the study inclusion and exclusion criteria were analyzed (statin group: 17,973; nonstatin group: 62,973; **Figure 1**). The statin group was younger (mean age: 57.21 ± 13.49 vs. 62.14 ± 15.31 years) and had more females than the nonstatin group (63.23% vs. 46.51%). Hypertension (> 80%) and diabetes/diabetes complications (30-38%) were the most prevalent comorbid conditions in the study cohort (**Table S1**).

In the matched cohort, baseline characteristics were well balanced between 17,015 statin users and nonusers (**Table S1**). Of matched statin new users, 12,739 were in the lipophilic group, 3,510 were in the hydrophilic group, and the remaining 766 were in the other group.

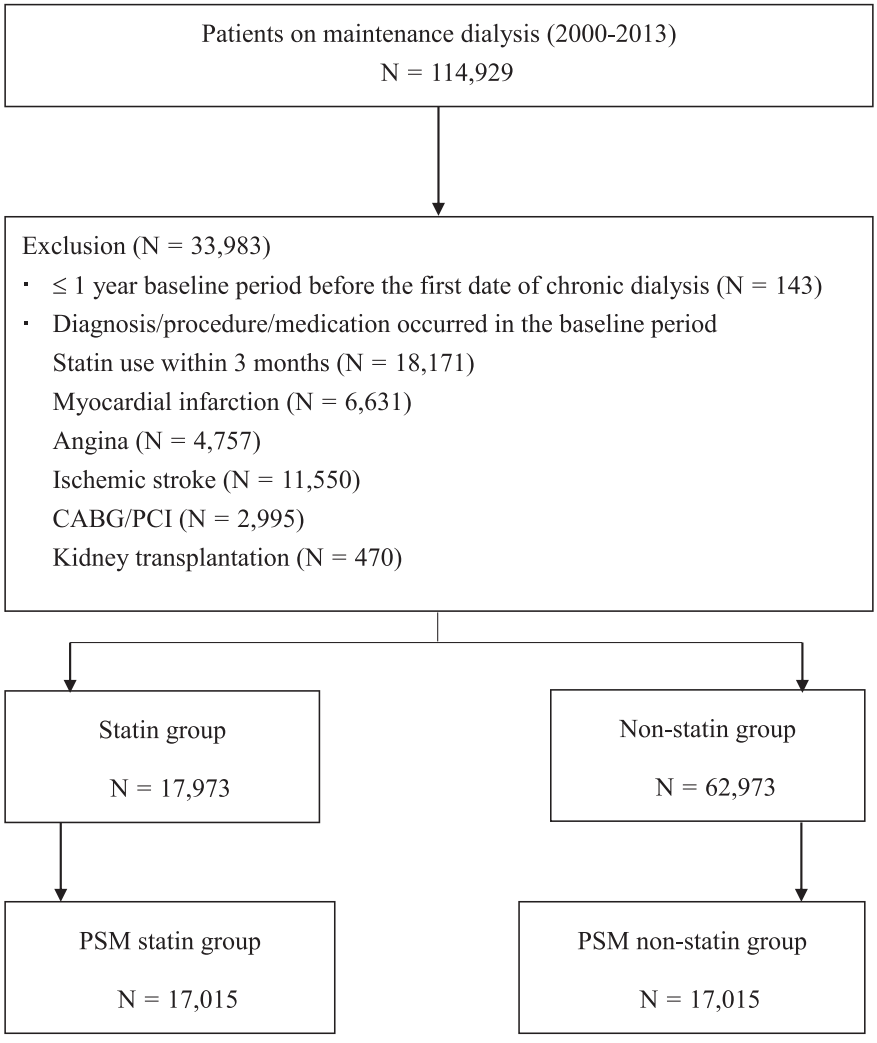

Figure 1 Flowchart showing the inclusion and matching of study participants. Statin and nonstatin groups with 1:1 PSM by age, sex, individual Charlson comorbid index disease conditions (except for renal disease and myocardial infarction), hypertension, hyperlipidemia, atrial fibrillation, year of dialysis initiation, initial dialysis modality, and prior medication of nonstatin lipid-lowering agent (nonstatin LLA), antihypertensive agents, digoxin, and antithrombotic agents. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PSM, propensity score matching.

Table 1 Characteristics of matched patients on chronic dialysis with or without statin initiation

	Statin group (*n* = 17,015)	Statin new users				Nonstatin group (*n* = 17,015)	
		Lipophilic statin (*n* = 12,739)	Hydrophilic statin (*n* = 3,510)	Others (*n* = 766)			
	n (%)	*n* (%)	*n* (%)	*n* (%)	*P* value[b]	*n* (%)	*P* value[c]
Age group							
< 55	7,093 (41.69)	5,253 (41.24)	1,489 (42.42)	351 (45.82)	0.0268	7,747 (45.53)	< 0.0001
55+	9,922 (58.31)	7,486 (58.76)	2,021 (57.58)	415 (54.18)		9,268 (54.47)	
Sex							
Male	6,504 (38.23)	4,871 (38.24)	1,359 (38.72)	274 (35.77)	0.3140	6,693 (39.34)	0.0355
Female	10,511 (61.77)	7,868 (61.76)	2,151 (61.28)	492 (64.23)		10,322 (60.66)	
High risk baseline group[a]							
No	12,682 (74.53)	9,508 (74.64)	2,590 (73.79)	584 (76.24)	0.3211	13,166 (77.38)	< 0.0001
Yes	4,333 (25.47)	3,231 (25.36)	920 (26.21)	182 (23.76)		3,849 (22.62)	
Baseline comorbidity							
Congestive heart failure	3,241 (19.05)	2,411 (18.93)	701 (19.97)	129 (16.84)	0.1062	2,963 (17.41)	0.0001
Peripheral vascular diseases	297 (1.75)	226 (1.77)	54 (1.54)	17 (2.22)	0.3790	284 (1.67)	0.5864
Cerebral vascular accident	1,139 (6.69)	869 (6.82)	221 (6.30)	49 (6.40)	0.5145	1,006 (5.91)	0.0030
Dementia	122 (0.72)	90 (0.71)	26 (0.74)	6 (0.78)	0.9537	90 (0.53)	0.0275
Pulmonary disease	1,668 (9.80)	1,245 (9.77)	352 (10.03)	71 (9.27)	0.7938	1,584 (9.31)	0.1214
Connective tissue disorder	423 (2.49)	312 (2.45)	92 (2.62)	19 (2.48)	0.8455	437 (2.57)	0.6287
Peptic ulcer	3,395 (19.95)	2,518 (19.77)	724 (20.63)	153 (19.97)	0.5282	3,204 (18.83)	0.0088
Liver diseases	892 (5.24)	687 (5.39)	163 (4.64)	42 (5.48)	0.2018	934 (5.49)	0.3123
Diabetes	6,572 (38.62)	4,946 (38.83)	1,364 (38.86)	262 (34.20)	0.0366	5,942 (34.92)	< 0.0001
Diabetes complications	6,121 (35.97)	4,665 (36.62)	1,232 (35.10)	224 (29.24)	0.0001	5,643 (33.16)	< 0.0001
Paraplegia	84 (0.49)	67 (0.53)	15 (0.43)	2 (0.26)	0.4897	79 (0.46)	0.6946
Cancer	959 (5.64)	715 (5.61)	210 (5.98)	34 (4.44)	0.2379	865 (5.08)	0.0237
Severe liver diseases	29 (0.17)	23 (0.18)	5 (0.14)	1 (0.13)	0.8565	26 (0.15)	0.6856
Metastatic cancer	61 (0.36)	46 (0.36)	14 (0.40)	1 (0.13)	0.5282	46 (0.27)	0.1464
HIV	2 (0.01)	1 (0.01)	0 (0.00)	1 (0.13)	0.0075	3 (0.02)	0.6547
Hypertension	14,154 (83.19)	10,550 (82.82)	2,982 (84.96)	622 (81.20)	0.0036	13,795 (81.08)	< 0.0001
Hyperlipidemia	4,332 (25.46)	3,200 (25.12)	930 (26.50)	202 (26.37)	0.2127	3,939 (23.15)	< 0.0001
Atrial fibrillation	297 (1.75)	235 (1.84)	55 (1.57)	7 (0.91)	0.1068	241 (1.42)	0.0149

(Continued)

Table 1 (Continued)

	Statin group (*n* = 17,015)	Statin new users				Nonstatin group (*n* = 17,015)	
		Lipophilic statin (*n* = 12,739)	Hydrophilic statin (*n* = 3,510)	Others (*n* = 766)			
	n (%)	*n* (%)	*n* (%)	*n* (%)	*P* value[b]	*n* (%)	*P* value[c]
Prior medications[d]							
Nonstatin LLA	2,393 (14.06)	1,781 (13.98)	484 (13.79)	128 (16.71)	0.0939	1,249 (7.34)	< 0.0001
Antihypertensive agents	14,017 (82.38)	10,460 (82.11)	2,941 (83.79)	616 (80.42)	0.0238	13,578 (79.80)	< 0.0001
Digoxin	354 (2.08)	269 (2.11)	71 (2.02)	14 (1.83)	0.8360	316 (1.86)	0.1381
Antithrombotic agents	6,574 (38.64)	5,011 (39.34)	1,287 (36.67)	276 (36.03)	0.0051	6,236 (36.65)	0.0002
Concomitant medications[e]							
Nonstatin LLA	4,833 (28.40)	3567 (28.00)	960 (27.35)	306 (39.95)	< 0.0001	1,839 (10.81)	< 0.0001
Antihypertensive agents	14,067 (82.67)	10,417 (81.77)	2,970 (84.62)	680 (88.77)	< 0.0001	11,622 (68.30)	< 0.0001
Digoxin	691 (4.06)	531 (4.17)	132 (3.76)	28 (3.66)	0.4694	576 (3.39)	0.001
Antithrombotic agents	9,297 (54.64)	7,037 (55.24)	1,822 (51.91)	438 (57.18)	0.0007	6,395 (37.58)	< 0.0001
Glucose-lowering agents	6,954 (40.87)	5,215 (40.94)	1,436 (40.91)	303 (39.56)	0.7507	4,594 (27.00)	< 0.0001

LLA, lipid-lowering agent.
[a]Patients had ≧ 3 comorbidities (congestive heart failure/peripheral vascular diseases/cerebral vascular accident/diabetes/hypertension/hyperlipidemia) and any prior medication (antihypertensive agents/antithrombotic agents). [b]Comparison of lipophilic, hydrophilic, and others group among statin initiators. [c]Comparison between statin and nonstatin groups. [d]Prior medication use: ≦ 365 days before the index date and use ≧ 28 days. [e]Concomitant medication use: use ≧ 28 days during the follow-up period.

The median duration of overall statin use was 252 days. Patients in the other group had longer duration of treatment (median 407 days) than those in the lipophilic (median 239 days) and hydrophilic groups (median 264 days). Additional baseline characteristics are listed in **Table 1**.

CVD events

The mean follow-up time was 4.7 years. The composite CVD incidence was higher in the statin group (16.91%) than in the nonstatin group (13.09%) ($P < 0.0001$; **Table S2**). The cumulative incidence of CVD events is shown in **Figure 2a**.

Overall, the adjusted hazard ratio (HR) for any CVD was 1.2 (95% confidence interval (CI), 1.13–1.28, $P < 0.0001$; **Table 2**). Exposure to lipophilic statins was significantly associated with higher CVD risk compared with nonstatin use (adjusted HR: 1.24, 95% CI, 1.17–1.32, $P < 0.0001$). However, the association did not hold in both groups of hydrophilic and other statin users. The subdistribution hazard competing risk of CVD regression revealed the similar effect of any statin use (**Table 3**).

Among statin initiators, compared with lipophilic statin initiators, hydrophilic statin initiators had significantly lower risk

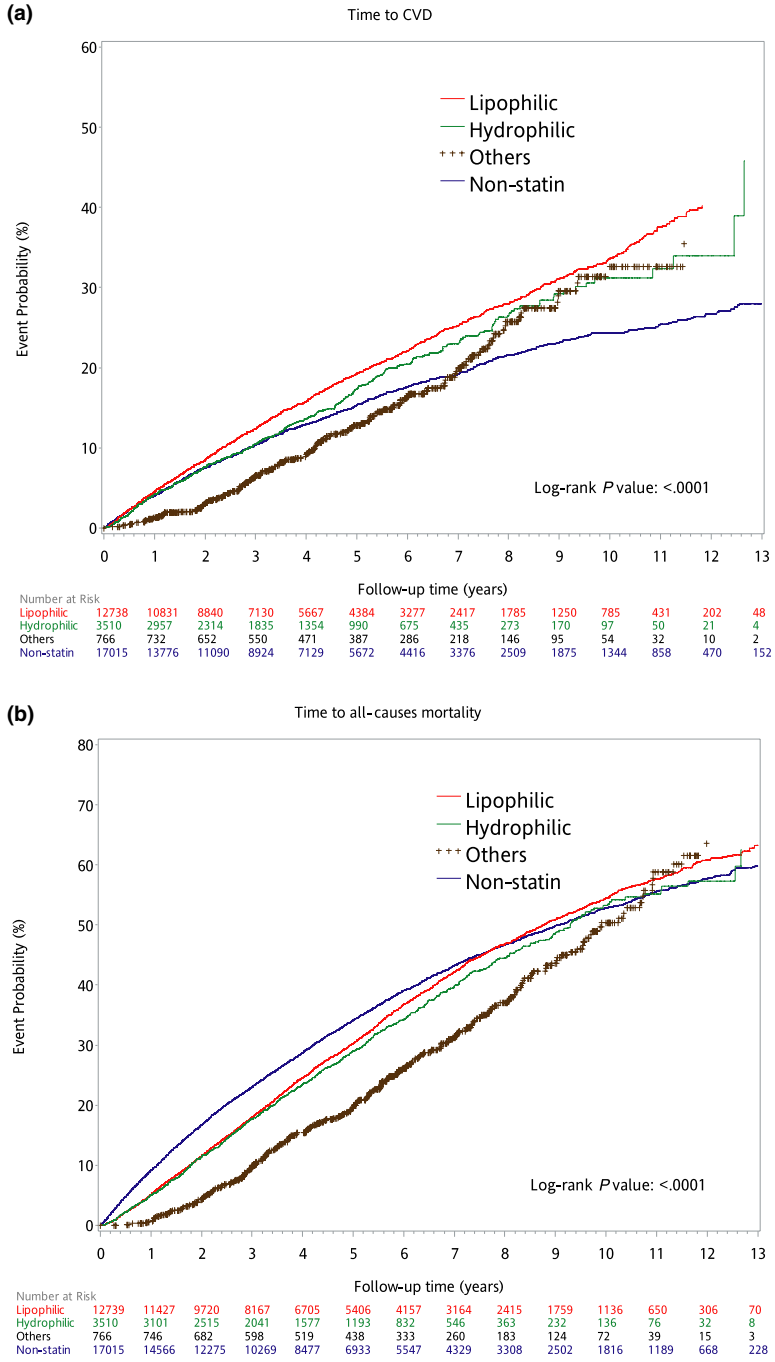

Figure 2 Kaplan–Meier curve of risk for (**a**) CVD (cardiovascular disease) and (**b**) all-cause mortality. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2 Multivariate analysis of the association between statin use and risk of CVD and mortality in the matched cohort

	Any CVD			All-cause mortality		
Variables	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Statin group						
Statin users	1.20	1.13, 1.28	< 0.0001	0.93	0.89, 0.96	< 0.0001
Nonstatin users	1.00	Reference		1.00	Reference	
Age group						
< 40	1.00	Reference		1.00	Reference	
40–54	2.42	2.09, 2.81	< 0.0001	2.08	1.89, 2.29	< 0.0001
55–69	3.41	2.94, 3.96	< 0.0001	3.88	3.54, 4.26	< 0.0001
70–84	4.12	3.53, 4.80	< 0.0001	6.55	5.96, 7.20	< 0.0001
85+	3.45	2.46, 4.84	< 0.0001	10.10	8.66, 11.77	< 0.0001
Sex						
Male	1.26	1.19, 1.33	< 0.0001	1.14	1.10, 1.18	< 0.0001
Female	1.00	Reference		1.00	Reference	
Initiated dialysis module						
HD	0.99	0.92, 1.07	0.8257	0.90	0.86, 0.95	< 0.0001
PD	1.00	Reference		1.00	Reference	
Comorbidities						
Congestive heart failure	1.23	1.15, 1.32	< 0.0001	1.26	1.21, 1.32	< 0.0001
Peripheral vascular diseases	0.85	0.70, 1.04	0.1202	1.12	0.99, 1.25	0.0659
Cerebral vascular accident	1.08	0.98, 1.20	0.1187	1.14	1.07, 1.22	< 0.0001
Diabetes	1.53	1.42, 1.65	< 0.0001	1.49	1.42, 1.56	< 0.0001
Hypertension	1.44	1.32, 1.58	< 0.0001	1.03	0.98, 1.09	0.2613
Hyperlipidemia	1.24	1.17, 1.32	< 0.0001	1.04	0.99, 1.08	0.0919
Concomitant medications						
Nonstatin LLA	0.93	0.85, 1.01	0.0872	0.84	0.79, 0.89	< 0.0001
Antihypertensive agents	0.91	0.84, 0.98	0.0121	0.79	0.76, 0.83	< 0.0001
Digoxin	1.03	0.90, 1.17	0.6920	1.32	1.22, 1.43	< 0.0001
Antithrombotic agents	1.07	1.01, 1.14	0.0238	0.84	0.81, 0.88	< 0.0001
Glucose-lowering agents	1.25	1.16, 1.35	< 0.0001	1.31	1.25, 1.37	< 0.0001

CI, confidence interval; CVD, cardiovascular disease; HD, hemodialysis; HR, hazard ratio; LLA, lipid-lowering agents; PD, peritoneal dialysis.

of CVD with (subdistribution HR: 0.84, 95% CI, 0.75–0.95, $P < 0.01$) and without (adjusted HR: 0.91, 95% CI, 0.85–0.97, $P < 0.01$) competing death adjustment (**Table 3**). Stratified analyses showed that hydrophilic statins were associated with a lower risk of CVD than lipophilic statins among patients aged < 55 years, females, those with lower baseline risk of CVD, those without concomitant medications of digoxin and antithrombotic and diabetes agents (glucose-lowering agents), and those with concomitant medications for hypertension (**Table 4**).

Sensitivity analyses showed similar findings after exclusion of prior users of digoxin or nonstatin LLA users; that is, lipophilic statin users had a higher risk of CVD incidence (subdistribution HR: 1.3, 95% CI, 1.22–1.39, $P < 0.0001$) than nonusers (**Table 5**). When restricting to patients who were treated with lipophilic or hydrophilic statins, a lower CVD risk was found in the hydrophilic group (subdistribution HR: 0.84, 95% CI, 0.73–0.96, $P = 0.0088$; **Table 5**).

All-cause mortality

All-cause mortality was significantly lower in statin users than in nonusers (33.98% vs. 37.88%, $P < 0.0001$; **Table S2**). The incidence of any-cause mortality in each statin group and nonusers is shown in **Figure 2b** (log-rank *P*-value < 0.0001). The adjusted HR for all-cause mortality was 0.93 (95% CI: 0.89–0.96, $P < 0.0001$) in the any statin group compared with the nonstatin group (**Table 2**); the beneficial effect was found in the lipophilic, hydrophilic, and other statin groups (**Table 3**).

There was no difference in the all-cause mortality rate between hydrophilic and lipophilic statin users (**Table 3**). Stratified analyses

Table 3 Multivariate analysis of the association between different lipophilicity statin groups and outcomes in the matched cohort

	Matched patients					Among statin initiators				
	Adjusted HR	95% CI	*P* value	Adjusted SHR[a]	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted SHR [a]	95% CI	*P* value
Any CVD												
Lipophilic	1.24	1.17, 1.32	< 0.0001	1.26	1.18, 1.34	< 0.0001	1.00	Reference		1.00	Reference	
Hydrophilic	1.10	1.00, 1.22	0.0560	1.08	0.98, 1.20	0.1193	0.91	0.85, 0.97	0.0068	0.84	0.75, 0.95	0.0059
Other	0.98	0.82, 1.18	0.8360	1.06	0.89, 1.26	0.5205	0.88	0.77, 1.00	0.0502	0.84	0.67, 1.04	0.1039
Nonstatin	1.00	Reference		1.00	Reference		–	–	–	–	–	–
All-cause mortality												
Lipophilic	0.93	0.89, 0.97	0.0003				1.00	Reference				
Hydrophilic	0.87	0.81, 0.93	< 0.0001				0.94	0.86, 1.02	0.1143			
Other	0.77	0.68, 0.88	< 0.0001				0.94	0.81, 1.10	0.4440			
Nonstatin	1.00	Reference					–	–	–			

CI, confidence interval; CVD, cardiovascular disease.
[a]SHR: subdistribution hazard ratio for competing risk adjustment: death and kidney transplantation.

showed that both lipophilic and hydrophilic statin groups were associated with a lower mortality rate than the nonstatin group in patients aged ≥ 55 years, females, those with lower baseline risk of CVD, those without concomitant medications of nonstatin LLAs and antithrombotic agents, and those with concomitant medications for hypertension/diabetes mellitus (**Table 4**).

DISCUSSION

This study is one of the few large, population-based cohort studies that have evaluated the association of statin initiation with incident CVD in patients on maintenance dialysis. Although statin initiation was associated with the overall increased risk of CVD, the risk varied according to the property of the statin and adherence to treatment. For instance, hydrophilic statins were associated with decreased risk of CVD compared with lipophilic statin use. A decreased all-cause mortality rate was associated with statin initiation and there was no heterogeneity between types of statins used.

Statin use was significantly associated with lower all-cause mortality and cardiovascular mortality among patients who had undergone hemodialysis in different populations.[26–29] Our study, consistent with prior studies, suggests that initiating statin use for patients on dialysis was associated with a lower any-cause mortality risk. However, the concern about initiating statin use in patients receiving dialysis remains. Prior studies have shown that patients undergoing dialysis may have increased cholesterol absorption,[30] and low cholesterol absorption may benefit from atorvastatin use in reducing cardiovascular risk in hemodialysis patients.[31] In contrast, other evidence suggested that dialysis patients may have different pathogeneses of arterial lesions and the lesions are so severe that they are unlikely to be meaningfully reduced by statins.[32,33]

Statins have shown limited benefit in the primary prevention of CVD and mortality among patients receiving dialysis in the 4D, AURORA, and SHARP trials.[3–5] However, a systematic review has suggested that there was no difference between statin use and placebo in the risk of major adverse CVD in patients receiving dialysis (relative risk (RR): 0.95, 95% CI, 0.88–1.03).[6] In the present cohort, initiating use of statins in patients on maintenance dialysis was associated with a subsequent higher CVD risk, but the additional risk was observed to be lower in hydrophilic statin than lipophilic statin users. Lipophilic statins reduce ATP production, theoretically enhance myocardial stunning after ischemia, and result in the worsening of shortening in reperfusion.[34] In an animal study, it has been demonstrated that lipophilic statins worsened myocardial stunning and reduced tissue ATP after coronary reperfusion; but the effects were not found with hydrophilic statins.[35]

Several studies[13,36] have compared lipophilic and hydrophilic statins in clinical settings. One study showed that hydrophilic pravastatin could be superior to lipophilic statins for preventing new Q-wave appearance and reducing cardiovascular events in normocholesterolemic Japanese patients after AMI.[13] Another study revealed that the event rate of MI or death was not different between lipophilic and hydrophilic statin use in patients with AMI.[36] A meta-analysis concluded that lipophilic statins

Table 4 Stratified multivariable analysis for risk of all-cause mortality and any cardiovascular disease

	All-cause mortality									Any CVD								
	Matched patients						Among statin initiators			Matched patients						Among statin initiators		
	Lipophilic vs. nonstatin			Hydrophilic vs. nonstatin			Lipophilic vs. hydrophilic			Lipophilicity vs. nonstatin			Hydrophilic vs. nonstatin			Lipophilic vs. hydrophilic		
Subgroup	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Age group																		
< 55	1.04	0.96, 1.12	0.3393	1.00	0.87, 1.14	0.9664	0.97	0.84, 1.11	0.6269	1.46	1.32, 1.63	< 0.0001	1.15	0.96, 1.38	0.1204	0.75	0.62, 0.91	0.0038
55+	0.89	0.85, 0.94	< 0.0001	0.83	0.77, 0.90	< 0.0001	0.93	0.85, 1.01	0.1005	1.15	1.07, 1.24	0.0002	1.07	0.95, 1.21	0.2325	0.90	0.79, 1.03	0.1183
Sex																		
Male	0.98	0.93, 1.05	0.6186	0.96	0.86, 1.06	0.4127	0.97	0.86, 1.08	0.5581	1.47	1.34, 1.61	< 0.0001	1.32	1.13, 1.53	0.0003	0.86	0.74, 1.01	0.0682
Female	0.90	0.85, 0.94	< 0.0001	0.82	0.75, 0.89	< 0.0001	0.92	0.83, 1.01	0.0895	1.10	1.02, 1.19	0.0160	0.97	0.85, 1.10	0.6165	0.84	0.73, 0.98	0.0238
High risk baseline group[a]																		
Yes	0.89	0.83, 0.95	0.0005	0.91	0.82, 1.02	0.1081	1.01	0.90, 1.15	0.8188	1.12	1.02, 1.24	0.0243	1.10	0.94, 1.30	0.2204	0.92	0.77, 1.09	0.3275
No	0.95	0.91, 1.00	0.0404	0.84	0.77, 0.92	< 0.0001	0.90	0.81, 0.99	0.0264	1.31	1.22, 1.41	< 0.0001	1.09	0.96, 1.24	0.1637	0.82	0.71, 0.94	0.0045
Concomitant medications																		
Nonstatin LLA																		
Yes	1.01	0.92, 1.12	0.7663	0.89	0.77, 1.02	0.1004	0.87	0.75, 0.99	0.0415	1.01	0.88, 1.16	0.8662	0.85	0.70, 1.04	0.1226	0.80	0.66, 0.98	0.0279
No	0.91	0.87, 0.95	< 0.0001	0.88	0.81, 0.95	0.0009	0.97	0.88, 1.06	0.4481	1.31	1.22, 1.40	< 0.0001	1.18	1.05, 1.32	0.0047	0.87	0.76, 0.99	0.0414
Antihypertensive agents																		
Yes	0.91	0.87, 0.95	< 0.0001	0.84	0.78, 0.91	< 0.0001	0.93	0.85, 1.01	0.1009	1.23	1.15, 1.31	< 0.0001	1.11	0.99, 1.23	0.0629	0.87	0.76, 0.98	0.0225
No	1.00	0.93, 1.08	0.9549	0.97	0.83, 1.14	0.6894	0.97	0.82, 1.15	0.7448	1.31	1.15, 1.50	< 0.0001	1.04	0.79, 1.37	0.7971	0.76	0.57, 1.02	0.0686
Digoxin																		
Yes	0.95	0.81, 1.12	0.5482	0.97	0.74, 1.27	0.8361	0.99	0.76, 1.30	0.9674	1.05	0.81, 1.37	0.7073	0.73	0.45, 1.19	0.2120	0.64	0.40, 1.05	0.0776
No	0.93	0.89, 0.97	0.0004	0.86	0.80, 0.93	< 0.0001	0.93	0.86, 1.01	0.1014	1.25	1.18, 1.34	< 0.0001	1.12	1.02, 1.24	0.0245	0.86	0.77, 0.97	0.0162

(Continued)

Table 4 (Continued)

	All-cause mortality									Any CVD								
	Matched patients					Among statin initiators				Matched patients					Among statin initiators			
	Lipophilic vs. nonstatin			Hydrophilic vs. nonstatin		Lipophilic vs. hydrophilic				Lipophilicity vs. nonstatin			Hydrophilic vs. nonstatin		Lipophilic vs. hydrophilic			
Subgroup	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Antithrombotic agents																		
Yes	0.91	0.86, 0.96	0.0009	0.91	0.83, 1.00	0.0404	1.00	0.91, 1.10	0.9701	1.22	1.12, 1.32	< 0.0001	1.17	1.04, 1.33	0.0115	0.93	0.82, 1.07	0.3260
No	0.95	0.90, 1.01	0.0966	0.81	0.73, 0.90	< 0.0001	0.85	0.76, 0.96	0.0084	1.29	1.18, 1.42	< 0.0001	0.97	0.82, 1.15	0.7427	0.71	0.59, 0.85	0.0003
Glucose-lowering agents																		
Yes	0.88	0.83, 0.94	< 0.0001	0.86	0.78, 0.94	0.0013	0.97	0.87, 1.08	0.5501	1.14	1.04, 1.24	0.0042	1.05	0.92, 1.20	0.4832	0.89	0.77, 1.04	0.1343
No	0.97	0.92, 1.02	0.2794	0.87	0.79, 0.96	0.0066	0.90	0.81, 1.01	0.0694	1.35	1.25, 1.47	< 0.0001	1.14	0.99, 1.32	0.0768	0.81	0.69, 0.95	0.0083

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LLA, lipid-lowering agents.
[a]Patients had ≥ 3 comorbidies (congestive heart failure/peripheral vascular diseases/cerebral vascular accident/diabetes/hypertension/hyperlipidemia) and any one of prior medication (antihypertensive agents/antithrombotic agents).

showed a comparable risk to hydrophilic statins for major adverse cardiovascular events (RR: 0.969, 95% CI, 0.835–1.125, $P = 0.682$), MI (RR: 0.880, 95% CI, 0.731–1.085, $P = 0.174$), and all-cause mortality (RR: 0.797, 95% CI, 0.590–1.075, $P = 0.137$).[11] One population-based cohort study in Taiwan provided the all-cause mortality for use of different kinds of statins in the predialysis chronic kidney disease cohort. The adjusted HR of hydrophilic rosuvastatin was 0.41 (0.35–0.49), lower than that of lipophilic statins, for which the adjusted HR was around 0.51–0.55.[33]

Guidelines suggested that for patients who do not achieve the targeted level of low-density lipoprotein cholesterol (LDL-C), a combination of nonstatin LLA with statin therapy is recommended as an alternative therapeutic option.[37,38] In our cohort, 28.4% of statin users and 10.81% of nonusers were treated with nonstatin LLAs at some time during the study period. Among them, the most common LLAs prescribed were fibrates (to reduce triglycerides and increase high-density lipoprotein). Prior clinical trials suggested that fibrate monotherapy was associated with cardiovascular risk reduction.[39,40] In the present study, in the subgroup of patients without nonstatin LLA use during the study period, hydrophilic statin use (adjusted HR: 0.87, 95% CI, 0.76–0.99) was associated with reduced CVD risk compared with lipophilic statin use, as well as in patients with nonstatin LLA use (adjusted HR: 0.80, 95% CI, 0.66–0.98). The insights generated from this study indicate an important role of statin lipophilicity in CVD prevention, in particular for patients who were on dialysis.

A recent national-representative observational study found that AMI with cardiogenic shock is associated with increased risk of AMI and mortality in the non-dialysis-dependent population.[41] In fact, AMI with or without cardiogenic shock was even higher in patients with dialysis dependency than nondialysis, and was also associated with poor long-term cardiovascular outcomes as well as survival.[42] Kidney function alters clinical presentation of AMI, such as chest pain or ST-segment elevation is lower in dialysis patients than nondialysis patients, which has been addressed in registry data and likely contributed a lower rate of AMI diagnosis.[43] These results suggested that accurate recognition of AMI and use of evidence-based pharmacological intervention in the dialysis population are warranted.

It is known that alteration in lipid-soluble drug distribution is the main concern for obese patients.[44] The blood flow to fat is poorer in obese individuals than in normal weight people, and it makes a large compartment of fat to increase volume of distribution for lipophilic drugs and increase their half-lives; although, the drug's disposition and its determinants in obesity have been reviewed in a number of drug classes.[44] Effects of different body weight on statin dosing and biological responses in obesity remain limited. Data from randomized trial settings have indicated that obesity should be taken into consideration for the variance in drug distribution. The Reversal of Atherosclerosis with Aggressive Lipid Lowering study found that obesity did not make a change in LDL-C from baseline between those at or above the median body mass index (29.6 kg/m^2) compared with those below the median body mass index for patients with pravastatin (hydrophilic) 40 mg/day therapy, but found a significantly greater reduction

Table 5 Sensitivity analysis of excluding patients with prior digoxin or nonstatin LLA use

	Matched patients						Among statin initiators					
	Adjusted HR	95% CI	*P* value	Adjusted SHR[a]	95% CI	*P* value	Adjusted HR	95% CI	*P* value	Adjusted SHR[a]	95% CI	*P* value
Any CVD												
Lipophilic	1.30	1.22, 1.39	< 0.0001	1.31	1.22, 1.40	< 0.0001	1.00	Reference		1.00	Reference	
Hydrophilic	1.14	1.02, 1.27	0.0204	1.11	0.99, 1.24	0.0692	0.85	0.75, 0.97	0.0145	0.84	0.73, 0.96	0.0088
Other	1.08	0.88, 1.31	0.4749	1.15	0.95, 1.39	0.1612	0.86	0.68, 1.09	0.2136	0.86	0.68, 1.09	0.2131
Nonstatin	1.00	Reference		1.00	Reference		–	–	–	–	–	–
All-cause mortality												
Lipophilic	0.79	0.69, 0.91	0.0013	–	–	–	1.00	Reference		–	–	–
Hydrophilic	0.89	0.83, 0.96	0.0026	–	–	–	0.96	0.88, 1.05	0.3441	–	–	–
Other	0.79	0.69, 0.91	0.0013	–	–	–	0.99	0.83, 1.17	0.8676	–	–	–
Nonstatin	1.00	Reference		–	–	–	–	–	–	–	–	–

CI, confidence interval; CVD, cardiovascular disease.
[a]Competing risk: death and kidney transplantation.

(−43 ± 22% vs. −49 ± 21%, respectively) in percent change LDL-C in obese patients with 80 mg/day atorvastatin therapy (lipophilic).[45]

It is worth noting that the study was conducted in the Taiwanese population, and the study results may be not generalizable to other ethnicities. For instance, plasma exposure to rosuvastatin and its metabolites was observed significantly higher (twofold) in Asians (Chinese, Malay, and Asian-Indian) than white healthy volunteers.[46] Two polymorphisms in the organic anion-transporting polypeptide 1B1 (OATP1B1; encoded by *SLCO1B1*) and the intestinal breast cancer resistance protein (BCRP; encoded by *ABCG2*) genes contribute to the ethnicity-dependent variability in rosuvastatin exposure.[47]

Statin use was associated with adverse drug reactions such as myotoxicity, photosensitivity, neurotoxicity, hepatotoxicity, and renal toxicity in some patients.[48,49] Multiple factors contributed to statin-induced toxicity, involving mechanisms of statin-mediated oxidative stress in different organs, metabolism of statins (metabolic pathways, enzyme polymorphism), and toxicity due to combination with other medications, have been elaborated by Liu *et al.*[49] For instance, the most common statin-associated with myopathy and rhabdomyolysis, which is associated with statin-inducing oxidative stress, and the risk is higher when taking high-dose or in long-term use.[49] Pravastatin, rosuvastatin, and pitavastatin (hydrophilic type) were less likely to induce myotoxicity, hepatotoxicity, and nephrotoxicity than other lipophilic statins,[49] which indicated that the lipophilicity may be a partial mechanism of statin-induced toxicity. In order to avoid or manage statin-associated adverse effects, it is necessary for health professionals to educate patients to recognize early signs and symptoms of side effects, which must be handled properly; to provide tailored statin therapy and lipid-lowering alternatives; and to regularly monitor at-risk patients with multiple morbidities and polypharmacy in clinical practice.

Strengths and limitations

The study findings are relevant to making decisions about statin initiation for primary CVD prevention in patients on maintenance dialysis. Moreover, they provide empirical confirmation for the heterogeneity between the lipophilicity of statins in dialysis patients and suggest that hydrophilic statins, such as rosuvastatin and pravastatin, may be preferable for lowering CVD risk compared with lipophilic statins. Notably, patient adherence to statin therapy is the key toward CVD prevention in some nondialysis populations.[20,50] The treatment pattern is variable (due to early discontinuation, switching, etc.) in practice; thus, the per-protocol approach was employed for patients who were exposed to at least 60% of overall statin use time to lipophilic or hydrophilic statins to identify the best possible treatment effect in this large, real-world representative samples of dialysis patients. It is important that these factors are investigated in future research.

There are some limitations in the present study. Although the large population-based sample with the propensity score matching technique was employed in the statin new-user cohort to minimize usual confounding and potential biases in nonrandomized observational studies, unmeasured CVD risk

at baseline, such as obesity, smoking, social behavior, diet, and family history of diseases, cannot be completely ruled out. We suspected that a magnitude of risk may exist that the group of patients with multiple comorbid conditions (diabetes, hypertension, or hyperlipidemia), which are known as potential risk factors for cardiovascular events, might more easily develop CVD than others and adjusted this effect in the primary and stratified analyses.

Because statin prescriptions in our study cohort were covered by Taiwan NHI reimbursement program based on a patient's total cholesterol and LDL levels and risk factors of CVD, such as hypertension, treatment misclassification, although it is unlikely, might have occurred since we were unable to identify those patients who did not meet the reimbursement coverage and used self-paid statins, which might have led to misclassification of statin groups and potentially influenced the average treatment effect on CVD primary prevention. Similarly, without a controlled trial environment, systematic error in classification of outcomes (onset of cardiovascular events) in administrative data sets may impact the accuracy of diagnostic information using ICD-9-CM coding system. The new onset CVD event, defined using codes that have been validated for the diagnosis, occurred at hospital discharge in the present study, which is typically considered the gold standard for measuring final outcome. However, we acknowledge that the coding algorithm to identify CVD event could underestimate risks of intermediary or less severe CVD, resulting in decreased CVD incidence in the present study. In addition, the final coding algorithm based on discharge records could vary depending on hospital practice variations in different healthcare systems.

AUTHOR CONTRIBUTIONS

S.-W.W. and C.-N.H. wrote the manuscript; S.-W.W., L.-C.L., C.-H.S., Y.-H.Y., T.-W.H., and C.-N.H. designed the research; S.-W.W., L.-C.L., C.-H.S., Y.-H.Y., T.-W.H., and C.-N.H. performed the research; S.-W.W., L.-C.L., Y.-H.Y., and C.-N.H. analyzed the data.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Table S1. Codes and definition of disease condition and medication use.
Table S2. Patient characteristics with and without propensity score matching.
Table S3. Study outcomes in the statin, nonstatin, and subgroup statin groups.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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