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HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients

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HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients.

Background. Patients with end-stage renal disease (ESRD) suffer from markedly higher rates of cardiovascular disease than the general population. Although therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") has been demonstrated to reduce the mortality from cardiovascular disease in patients without ESRD, only 10% of patients on dialysis are treated with these medications by day 60 of ESRD. We determined whether the use of statins is associated with a reduction in cardiovascular-specific death and total mortality in ESRD patients.

Methods. Data were analyzed from the U.S. Renal Data System Dialysis Morbidity and Mortality Wave-2 study, a cohort of randomly selected patients who were initiating dialysis in 1996. Information about the use of statins as well as other baseline characteristics was abstracted from the patients' dialysis records by dialysis personnel. Cox proportional hazards models were developed to determine the association between use of statins at baseline and subsequent risk of mortality, with adjustment for known mortality risk factors.

Results. Follow-up data were available for 3716 patients through July 1998. At baseline, 362 (9.7%) of patients were using statins. These patients had a mortality rate of 143/1000 person-years, compared with a rate of 202/1000 person-years for patients not using statins. Statin use was independently associated with a reduced risk of total mortality [relative risk (RR) = 0.68, 95% confidence interval (CI) = 0.54, 0.87] as well as cardiovascular-specific mortality (RR = 0.64, 95% CI = 0.45, 0.91). In contrast, the use of fibrates was not associated with reduced mortality (RR = 1.29).

Conclusions. Statin use was associated with a reduction in cardiovascular-specific death and total mortality in patients on dialysis.

Key words: hypercholesterolemia, cardiovascular disease, end-stage renal disease, USRDS Wave 2, dialysis, blood pressure, lipoprotein.

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Over 25 years ago, it was recognized that patients with end-stage renal disease (ESRD) had markedly elevated rates of cardiovascular disease (CVD) [1]. Despite advances in the prevention and treatment of CVD, the increased risk associated with ESRD persists [2].

Although hypercholesterolemia is a risk factor for CVD in the general population, the association between lipid abnormalities and CVD is less clear among ESRD patients. While certain atherogenic lipid abnormalities are present in ESRD patients, including elevations in serum triglyceride, very-low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) cholesterol and reductions in high density lipoprotein (HDL) cholesterol, levels of total cholesterol and low-density lipoprotein (LDL) cholesterol are actually lower than those of persons without renal failure [3–5].

Treatment of hypercholesterolemia with HMG-CoA reductase inhibitors ("statins") has been shown to reduce both total mortality and cardiovascular mortality in patients without ESRD [6–8], both in patients with [6, 7] and without [8, 9] documented CVD. Because lipid abnormalities in ESRD patients differ from patients without ESRD, the beneficial effects of statins shown in large randomized control trials of non-ESRD patients may not be applicable to patients with ESRD.

Although fewer than 10% of dialysis patients are prescribed statins by day 60 of ESRD, several small short-term trials of statins in patients with ESRD have shown that they can be used safely in this patient population, and that they cause potentially beneficial changes in lipoprotein profiles [10–16]. To date, however, there have been no studies specifically examining the association between use of statins and mortality from cardiovascular disease in the ESRD population. We utilized data from the United States Renal Data System Dialysis Morbidity and Mortality Study Wave 2 (USRDS DMMS-2) to assess the association between the use of statins and mortality from cardiovascular disease.

METHODS

Subjects

A secondary analysis of data from the USRDS DMMS Wave 2 was performed; details of the studies performed by the USRDS are described elsewhere [17]. Briefly, the USRDS collects demographic and clinical data on patients who have survived more than 90 days on dialysis. DMMS Wave 2 was a prospective cohort study that included all eligible patients initiating peritoneal dialysis and a 20% random sample of patients initiating hemodialysis in 1996 and early 1997. Patients were sampled from among 25% of the dialysis units listed in the December 1993 Master List in addition to all new dialysis units opening after January 1, 1994. The USRDS excluded patients from DMMS Wave 2 if they were younger than 18 years, were home dialysis patients, or if they had previously received a kidney transplant. Dialysis modality was determined on day 60 of renal replacement therapy. For the purposes of this study, data from all patients who participated in DMMS Wave 2 were included in our analysis.

Data collection

Baseline and follow-up patient data were abstracted by dialysis facility personnel from the patients' medical records. For the purposes of this analysis, the following demographic characteristics were included: age, race (black, white, other), and gender. Clinical characteristics included: dialysis modality (hemodialysis, peritoneal dialysis, transplant), cause of ESRD (diabetes, hypertension, glomerulonephritis, and "other"), history of diabetes, history of cardiovascular disease (coronary artery disease, myocardial infarction, coronary angioplasty, coronary artery bypass surgery, cardiac arrest, congestive heart failure, or stroke) and history of smoking (current, former, or never). These clinical characteristics, including cardiac history, were determined by dialysis personnel through review of notations in the patients' medical charts and through interviews with the patients themselves. Dialysis personnel also recorded whether the patient was believed to be "undernourished or cachectic" (a subjective impression). In addition, a maximum of 15 medications prescribed to each patient at the study start date (day 60 of dialysis) were recorded. From this list, the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibrates, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers was determined. Relevant laboratory data for each patient at the start of the study included serum albumin, triglycerides, and cholesterol. Triglyceride and cholesterol were abstracted from the USRDS database for descriptive purposes only. They were not assessed as independent predictors of mortality in this analysis because they likely mediate the relationship between statins and cardiovascular death. Although DMMS Wave 2 also recorded LDL and HDL cholesterol levels on some patients, they were not included in our analysis due to the high percentage (83%) of missing values.

Outcome measurements

Survival status and cause of death were linked to the DMMS Wave 2 data from the USRDS Patients Standard Analysis File (SAF) via unique patient identifiers assigned by the USRDS. The date and cause of death listed in a patient's SAF was obtained from a form submitted to the USRDS by the patient's nephrologist (form HCFA 2746). Patient survival status was complete through July 1998. For the purposes of this analysis, cardiovascular death was defined a priori as death from one of the following causes: myocardial infarction, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, or cardiac arrest.

Statistical analysis

The Cox proportional hazards model for censored survival data was used to assess the association between baseline statin use and mortality, independent of other predictors of survival. Adjustment variables were chosen for the multivariate regression model based on the possibility that the covariate of interest may be associated with or may confound the relationship between statin use and the risk of CV mortality. Formal tests as well as graphic methods were used to verify the existence of proportional hazards. Further, residual diagnostics were used to identify outlying points and to model the correct functional form of adjustment variables. Estimated relative risks (RR) along with corresponding 95% confidence intervals (CI) and P values for two-sided tests of association are reported for all regression covariates.

To improve the generalizability of these results the patients were not censored at the time of transplantation. Patients selected to receive a renal transplant are generally healthier when compared to typical dialysis patients; by excluding these patients, our study results would only be applicable to a less healthy group of individuals. Further, censoring patients at the time of transplantation would introduce informative censoring into the analysis, leading to potentially biased results. Hence transplantation, along with hemodialysis and peritoneal dialysis, were included as valid treatment modalities during statistical analyses. To adjust for changes in treatment modality during the follow-up period, the modality variable was entered into the presented models as a time-dependent covariate. With the use of this time-dependent covariate, patients were not censored as they changed modality, but instead continued to contribute time at risk for a given modality for the amount of time they underwent that particular modality.

Table 1. Patient characteristics at the time of initial data collection ($N = 3716$)

Characteristic	Statin users ($N = 362$)	Non-users ($N = 3354$)
Age *years*	59.6 (13.2)	58.9 (16.0)
Female sex	183 (50.6%)	1564 (46.6%)
Race		
White	250 (69.3%)	2107 (63.4%)
Black	79 (21.9%)	939 (28.3%)
Other	32 (8.9%)	275 (8.3%)
History of coronary artery disease	153 (43.3%)	1022 (31.6%)
History of CVD[a]	170 (52.5%)	1460 (48.5%)
Undernourished	52 (14.7%)	651 (20.2%)
History of diabetes	210 (59.0%)	1615 (49.1%)
Smoking status		
Never	196 (58.3%)	1755 (56.3%)
Former	98 (29.2%)	921 (29.6%)
Current	42 (12.5%)	440 (14.1%)
Cholesterol *mmol/L*	5.46 (1.64) [211.1 (63.4) mg/dL]	4.97 (1.42) [191.7 (54.7) mg/dl]
Triglycerides *mmol/L*	2.92 (2.22)	2.16 (1.52)
Albumin *g/L*	35 (6.0)	35 (6.0)

Data are mean (SD) or *N* (%).

[a] Defined as prior diagnosis of coronary artery disease, myocardial infarction, coronary artery bypass, angioplasty, cardiac arrest, congestive heart failure, or stroke

RESULTS

A total of 4065 patients were included in the DMMS Wave 2 cohort. Of these, follow-up data were available for 3716 patients. The remaining 349 patients were excluded from our analysis because they were not appropriately assigned a unique USRDS identifier code, and thus their survival status could not be determined. Compared to the patients for whom follow-up data were available, the excluded patients were less likely to be using statins (3 vs. 9.7%), less likely to have CVD (36.9 vs. 43.9%), were younger (mean age, 52 vs. 59 years), and had higher total cholesterol levels (224 vs. 193 mg/dL).

Characteristics of the study population are summarized in Table 1. Of the 3716 patients in the cohort, 362 (9.7%) were being prescribed statins as of day 60 after starting dialysis. Only 78 (2.1%) patients were prescribed fibrates at the study start. Patients who were prescribed statins were relatively more likely to be white (69.3 vs. 63.5%), to have coronary disease (43.3 vs. 31.6%) and diabetes (59.0 vs. 49.1%), and to have higher levels of serum cholesterol (211 vs. 192 mg/dL) and triglyceride (2.92 vs. 2.16 mmol/L). Of the 3716 patients, 223 (6%) were taking 15 or more medications at baseline.

There were 1232 total deaths in the cohort through July 1998. The mortality rate for patients using statins was 143/1000 person-years; the mortality rate for non-users was 202/1000 person-years. The adjusted and unadjusted relative risk estimates for all-cause mortality associated with various baseline demographic and clinical characteristics are presented in Table 2. The use of statins was associated with a 32% lower adjusted relative risk (aRR) of death (aRR = 0.68; 95% CI = 0.53, 0.86; $P = 0.002$). This lower risk was independent of other baseline risk factors. In contrast, the use of fibrates was not associated with a lower risk of death (aRR = 1.29; 95% CI = 0.85, 1.95). Figure 1 presents the adjusted cumulative survival functions for statin users and non-users. The lower mortality among patients using statins compared to patients not using these medications appears to have begun approximately two months after entry into the cohort. The association between statin use and reduced mortality was similar for hemodialysis and peritoneal dialysis patients ($P = 0.52$ for test of interaction between dialysis modality and statin use).

A higher risk of total mortality was associated with a history of diabetes, a history of CVD, increasing age, white race, low serum albumin, undernourishment, and not receiving a renal transplant during the follow-up period (Table 2). Neither gender, dialysis modality, nor cigarette smoking were associated with effects on total mortality.

A total of 560 cardiovascular deaths occurred by the end of the follow-up period. Among statin users, the cardiovascular-specific mortality rate was 61/1000 person-years; the corresponding rate for non-users was 88/1000 person-years. The adjusted and unadjusted relative risk estimates of cardiovascular-specific death are presented in Table 3. The use of statins was independently associated with a 37% lower risk of cardiovascular mortality (aRR = 0.63; 95% CI = 0.44, 0.91; $P = 0.014$). In contrast, the use of fibrates was not associated with a lower risk of cardiovascular death (aRR = 1.41; 95% CI = 0.79, 2.51). Among patients with pre-existing CVD, statin use was strongly associated with lower cardiovascular mortality (aRR = 0.50; 95% CI = 0.32, 0.79). In contrast, in patients with no history of CVD, there was no association between statin use and cardiovascular mortality (aRR = 1.21, 95% CI = 0.67, 2.17). The association between statin use and reduced cardiovascular mortality did not differ between hemodialysis and peritoneal dialysis patients ($P = 0.87$).

A higher risk of cardiovascular death was associated with a history of CVD, older age, white race, low serum albumin, a history of diabetes, and treatment with peritoneal dialysis (compared to hemodialysis; Table 3). Gender, cigarette smoking, and malnourishment were not significantly associated with risk of cardiovascular death.

Additional analyses were performed with adjustments for use of aspirin, ACE inhibitors, beta-blockers and calcium channel blockers. The addition of these covariates did not appreciably change the associations between statin use and total and cardiovascular mortality (RR = 0.69 and RR = 0.63, respectively); thus, these covariates

Table 2. All-cause mortality rates by statin use at baseline and other characteristics

Covariate	Deaths ($N = 1232$)	Person-years	Unadjusted RR (95% CI)	*P* value	Adjusted RR (95% CI)	*P* value
Statin use						
No	1142	5650	Referent		Referent	
Yes	90	628	0.70 (0.57, 0.87)	0.001	0.68 (0.53, 0.86)	0.002
Fibrate use						
No	1200	6156	Referent		Referent	
Yes	32	123	1.33 (0.94, 1.89)	0.112	1.29 (0.85, 1.95)	0.238
Sex						
Male	632	3334	Referent		Referent	
Female	600	2944	1.09 (0.97, 1.21)	0.147	1.08 (0.95, 1.24)	0.241
Race						
White	897	3803	Referent		Referent	
Black	267	1853	0.62 (0.54, 0.71)	<0.001	0.72 (0.61, 0.85)	<0.001
Other	63	560	0.48 (0.37, 0.62)	<0.001	0.55 (0.41, 0.74)	<0.001
Modality						
HD	720	3414	Referent		Referent	
PD	468	2302	0.96 (0.86, 1.08)	0.55	1.09 (0.95, 1.26)	0.220
Transplant	15	397	0.17 (0.10, 0.28)	<0.001	0.30 (0.16, 0.59)	<0.001
History of CVD[a]						
No	338	3114	Referent		Referent	
Yes	750	2502	2.79 (2.45, 3.17)	<0.001	1.65 (1.42, 1.93)	<0.001
Smoking status						
Never	608	3323	Referent		Referent	
Former	387	1648	1.28 (1.13, 1.46)	<0.001	0.99 (0.85, 1.15)	0.926
Current	142	838	0.96 (0.80, 1.15)	0.652	1.18 (0.96, 1.46)	0.110
Undernourished						
No	832	5032	Referent		Referent	
Yes	360	989	2.19 (1.93, 2.48)	<0.001	1.49 (1.28, 1.73)	<0.001
Prior Dx of diabetes						
No	502	3194	Referent		Referent	
Yes	712	2959	1.52 (1.36, 1.70)	<0.001	1.28 (1.11, 1.47)	0.001
Age *per decade increase*	1225		1.48 (1.42, 1.55)	<0.001	1.33 (1.26, 1.40)	<0.001
Albumin *1 g/dL decrease*	1126		1.82 (1.67, 2.00)	<0.001	1.50 (1.33, 1.70)	<0.001

[a] Defined as prior diagnosis of coronary artery disease, myocardial infarction, coronary artery bypass, angioplasty, cardiac arrest, congestive heart failure, or stroke

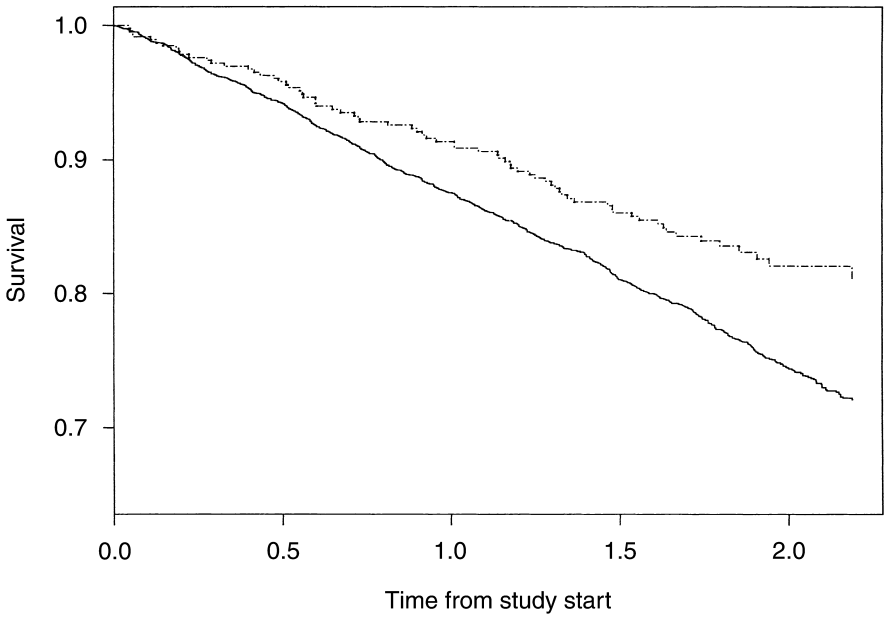

Fig. 1. Adjusted Kaplan-Meier survival curves modeling time to all-cause mortality. Solid line refers to no statin use reported. Dashed line refers to statin users.

Table 3. Cardiovascular death rates by statin use at baseline and other characteristics

Covariate	Deaths ($N = 560$)	Person-years	Unadjusted RR (95% CI)	*P* value	Adjusted RR (95% CI)	*P* value
Statins						
No	522	5650	Referent		Referent	
Yes	38	628	0.65 (0.47, 0.90)	0.011	0.63 (0.44, 0.91)	0.014
Fibrates						
No	544	6156	Referent		Referent	
Yes	16	123	1.46 (0.89, 2.39)	0.138	1.41 (0.79, 2.51)	0.249
Sex						
Male	304	3334	Referent		Referent	
Female	256	2944	0.96 (0.81, 1.14)	0.650	0.98 (0.80, 1.20)	0.82
Race						
White	409	3803	Referent		Referent	
Black	117	1853	0.60 (0.49, 0.74)	<0.001	0.75 (0.59, 0.95)	0.02
Other	31	560	0.52 (0.36, 0.75)	<0.001	0.55 (0.36, 0.86)	0.008
Modality						
HD	321	3414	Referent		Referent	
PD	229	2302	1.03 (0.87, 1.22)	0.745	1.25 (1.02, 1.54)	0.034
Transplant	3	397	0.09 (0.03, 0.27)	<0.001	0.11 (0.02, 0.73)	0.022
History of CVD[a]						
No	127	3114	Referent		Referent	
Yes	366	2502	3.54 (2.89, 4.33)	<0.001	1.96 (1.55, 2.48)	<0.001
Smoking status						
Never	279	3323	Referent		Referent	
Former	185	1648	1.33 (1.10, 1.60)	0.003	0.97 (0.78, 1.21)	0.8
Current	51	838	0.73 (0.54, 0.98)	0.035	0.87 (0.61, 1.23)	0.426
Undernourished						
No	391	5032	Referent		Referent	
Yes	146	989	1.87 (1.55, 2.26)	<0.001	1.24 (0.98, 1.57)	0.072
Prior Dx of diabetes						
No	210	3194	Referent		Referent	
Yes	342	2959	1.73 (1.46, 2.06)	<0.001	1.58 (1.28, 1.95)	<0.001
Age *per decade increase*	555		1.56 (1.47, 1.67)	<0.001	1.41 (1.29, 1.53)	<0.001
Albumin *1 g/dL decrease*	515		1.64 (1.43, 1.89)	<0.001	1.29 (1.07, 1.57)	0.009

[a] Defined as prior diagnosis of coronary artery disease, myocardial infarction, coronary artery bypass, angioplasty, cardiac arrest, congestive heart failure, or stroke

are excluded from the final regression models presented in Tables 2 and 3.

DISCUSSION

Data from the USRDS DMMS Wave 2, a prospective cohort of incident dialysis patients, were analyzed to assess the association between use of HMG CoA-reductase inhibitors and risk of death. Statin use was associated with a 32% lower risk of total mortality, independent of the effects of other characteristics known to affect mortality, including diabetes, age, prior cardiovascular disease, and smoking. The use of statins was associated with a similar lower risk of cardiovascular-specific mortality (aRR = 0.63). In contrast, the use of fibrates was not associated with lower mortality (for total mortality, aRR = 1.29, 95% CI = 0.85, 1.95).

Although to our knowledge there have been no prior studies of the effect of HMG CoA-reductase inhibitors on cardiovascular outcomes among patients with ESRD, the association between use of statins and reduced risk of cardiovascular mortality seen in this study is similar to that found in large, randomized controlled trials in the general population. The Scandinavian Simvastatin Survival Study (4S) randomized hypercholesterolemic patients with known coronary heart disease to simvastatin and placebo. There was a 35% reduction in the risk of cardiovascular deaths, and a 30% reduction in the risk of all deaths [6]. The West of Scotland Coronary Prevention Study Group randomized hypercholesterolemic patients without CAD to pravastatin or placebo. After five years of follow-up, the relative risk of cardiovascular-related death was reduced by 32% [8]. The Cholesterol and Recurrent Events Trial Investigators randomized normocholesterolemic patients following myocardial infarction to pravastatin or placebo, and also found a reduction in the relative risk of coronary-related deaths (RR = 0.8) [7].

The mechanisms by which statins could reduce the risk of cardiovascular mortality among ESRD patients are not fully understood. In the general population, elevated serum cholesterol, and in particular elevation of LDL cholesterol, is associated with higher cardiovascular mortality [18]. A similar association between elevated LDL and increased cardiovascular disease among dialysis patients has been reported [19], although other studies have not confirmed this observation [20]. It is well documented that statins cause significant reductions in

LDL cholesterol. In non-ESRD patients, even those with average cholesterol levels, statins can lower LDL cholesterol levels by 25 to 40% [7, 9]; similar results have been found in dialysis patients [10–12, 15, 16]. Reduction of LDL cholesterol with statins or other therapies can inhibit the development or progression of atherosclerosis in the general population; it is possible that a similar effect may occur in ESRD patients.

Although the lower mortality among ESRD patients using statins may be mediated in part by a reduction in LDL cholesterol, most ESRD patients actually have reduced total and LDL cholesterol levels when compared to patients without renal disease [3–5, 21]. However, these patients have other lipid abnormalities, including elevations of serum IDL cholesterol [4, 22]. This lipid component has been recognized as being highly atherogenic, and independently associated with progression of atherosclerosis in patients without ESRD [23, 24]. In the dialysis population, although its association with coronary disease has not been studied, elevated IDL cholesterol has been associated with generalized aortic atherosclerosis [5]. Statins have been demonstrated to lower IDL cholesterol in both non-ESRD patients [25, 26] and in patients on dialysis [12, 13]. Although previous studies have not determined if reductions in IDL are associated with a reduction in mortality, it is possible that the reduction in mortality associated with statin use in the general population is mediated, in part, by their ability to lower IDL. This effect on IDL cholesterol also may explain the lower mortality associated with statin use in the dialysis patients in this study

In addition to elevated IDL cholesterol, ESRD patients typically have reduced levels of HDL cholesterol. This abnormality is a well-described risk factor for atherosclerosis [27], and has been associated with an increased risk of cardiovascular death in the general population [18] and an increased risk of coronary artery disease among hemodialysis patients [20]. Many studies have shown that statins can increase HDL cholesterol levels in non-ESRD patients [6–8, 28]. In dialysis patients, some studies have shown an increase in HDL with statin therapy [16], although other studies have not confirmed this finding [12, 15]. These latter studies included relatively few subjects, and thus may have been underpowered to detect small improvements in HDL. Therefore, it is possible that statins may protect against cardiovascular mortality in dialysis patients by increasing HDL.

In addition to having quantitative abnormalities in lipid levels, dialysis patients often exhibit qualitative changes in lipids as a result of uremia or the dialysis itself. Some of these changes may promote the development of atherosclerosis, and may be modified by statin therapy. In particular, oxidative modification of LDL is thought to increase its atherogenic potential. In patients with ESRD, levels of oxidized LDL may be increased compared to patients without renal disease [reviewed in 29]. Statins have anti-oxidant properties in vitro, and may modulate atherosclerosis by preventing oxidation of LDL-cholesterol [30].

When studied in vitro, statins have yet other effects that in theory might mediate a cardioprotective effect in patients [reviewed in 30]. Statins can interfere with the uptake of LDL cholesterol into monocytes, thus inhibiting the formation of the foam cell, an important component of the atherosclerotic plaque. They also have been shown to inhibit smooth muscle cell proliferation, which is an important step in the progression of atherosclerosis. Statins may have direct antithrombotic properties, by up-regulating endothelial nitric oxide production, by up-regulating tissue plasminogen activator (tPA) activity, and by inhibiting platelet aggregation. Thus, there are a number of mechanisms that could explain the association between the use of statin and reduced cardiovascular death in the ESRD patients in this study.

In addition to finding that statins were associated with a reduced rate of cardiovascular death, we also found an association between statin use and reduced rates of cardiovascular death (RR = 0.72, 95% CI = 0.52, 0.99). There are several possible explanations for this finding. One explanation is that statins truly reduced the risk of non-cardiovascular death in this cohort. Although this has not been demonstrated in the general population [6–8], dialysis patients have increased levels of oxidative stress [29] that has been hypothesized to effect non-cardiac functions such as immune responses to infection. It is possible that the anti-oxidant properties of statins could cause beneficial changes in these non-cardiac functions and result in improved non-cardiac survival. Another explanation for our finding is that there is misclassification of the cause of death. In this study, the cause of death for a given patient was obtained from a form submitted to the USRDS by the patient's physician. A previous study has suggested that, for patients with ESRD, there is a poor correlation between cause of death reporting in the USRDS database and cause of death as reported in the patients' death certificates [31]. However, death certificates indicated that 40% of patients were classified as having died of renal disease, whereas the USRDS reporting system did not include renal disease as a possible cause of death. Since few ESRD patients die of renal failure per se, it is likely that the USRDS reporting system is more accurate in determining the true cause of death. Nevertheless, it is possible that some patients who died in our study were assigned an incorrect cause of death. Such misclassification might introduce a bias into our estimates of relative risk of cause-specific mortality, but it would not affect the observed association between statin use and reduced total mortality.

If patients who were prescribed statins were in better health than patients not taking statins, or had been re-

ceiving more aggressive pre-ESRD medical care, then the reduced mortality observed in statin users might simply be a result of their greater baseline health and/or superior pre-ESRD care, and not an effect of the medications themselves. However, there are several reasons why such a bias is unlikely to explain our findings. First, it could be expected that patients who were selected for treatment with statins would actually have more severe vascular disease than other patients, and thus be at higher risk of death for this reason than those not on statins. In this cohort, statin users were, in fact, more likely to have coronary disease than non-users (43 vs. 32%). Second, the associations between statin use and reduced mortality were not appreciably changed by adjusting for measures of pre-ESRD care, such as use of erythropoietin, duration of pre-ESRD nephrology care, and number of pre-ESRD nephrology visits (data not shown). Third, the use of statins was associated with a reduced mortality even after adjustment for the effects of known risk factors, suggesting that this association is independent of differences in baseline health. Finally, if healthier patients were preferentially selected for treatment with statins, one would expect the same bias to apply to the use of fibrates. However, we found no association between fibrate use and the risk of death (aRR = 1.29), providing further evidence that the observed improvement in mortality with statin use is not an effect due to confounding.

A potential limitation of this study is incorrect classification of patients as statin users or non-users. Such misclassification could occur if patients using statins at baseline subsequently discontinued the medication, or if non-users at baseline subsequently started to use statins. In addition, it is possible that statin use was not correctly recorded in the DMMS WAVE-2 database for patients who were truly using the medications at baseline. However, such a misclassification error (if it were non-selective) would actually be expected to result in an underestimation of the true relative risk of death associated with statin use.

Another limitation is the lack of information regarding the duration of statin use prior to the study start. In randomized controlled trials of non-ESRD patients, the reduction in cardiovascular mortality among statin users became evident after approximately one to two years of treatment [8, 28]. Whether a similar duration of treatment would be needed to produce a mortality benefit in ESRD patients is unknown. Nevertheless, if a patient in DMMS Wave 2 had been started on statin therapy only recently before the start of the study, one might not expect to see a mortality benefit within the follow-up period of this study.

Patients using statins at the start of WAVE-2 had lipid levels recorded only while on lipid-lowering therapy; no pre-treatment lipid levels were available. Thus, we were not able to assess the effect of statins on lipid levels in these patients, nor could we determine if the lower mortality among statin users was related to changes in lipid levels. We also could not assess whether the association between statin use and reduced mortality differed among patients with and without hyperlipidemia. However, given the clinical and in vitro properties of statins described above, it is possible that statins could have cardioprotective effects even in ESRD patients without elevated total cholesterol or elevated LDL cholesterol.

In conclusion, the use of HMG-CoA reductase inhibitors is associated with reduced mortality among a cohort of incident hemodialysis and peritoneal dialysis patients. This reduction in risk of death was independent of the effects of other known risk factors, and was observed in both hemodialysis and peritoneal dialysis patients. The results suggest that statins may be effective in improving survival in ESRD patients on dialysis.

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