Survival Benefit of Statins in Hemodialysis Patients Awaiting Renal Transplantation

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Abstract

End-stage renal disease (ESRD) patients have extraordinarily high cardiovascular risk and mortality, yet the benefit of statins in this population remains unclear based on the randomized trials. We investigated the prognostic value of statins in a large, pure cohort of prospectively recruited patients with ESRD awaiting renal transplantation, and being followed up in a dedicated cardiac clinic.

We prospectively collected demographic, clinical, laboratory, and pharmacological data on 423 consecutive ESRD patients on hemodialysis awaiting renal transplantation. Survival analysis was performed as a function of statin therapy.

The baseline characteristics were as follows: age 57 ± 11 years, males 64%, diabetes mellitus in 68%, known coronary artery disease in 30%, left ventricular (LV) ejection fraction $61 \pm 11\%$. Over a mean follow-up of 2 years, there were 43 deaths. Adjusted for age, gender, hypertension, body mass index, diabetes mellitus, coronary artery disease, smoking, and treatment with angiotensin converting enzyme inhibitor, β blocker, and antiplatelet medications, statin use was a predictor of lower mortality (hazard ratio 0.30, 95% confidence interval 0.11–0.79, $p = 0.01$). This beneficial effect of statin was supported by propensity score analysis ($p = 0.02$) and was consistent across all clinical subgroups. The benefit of statins seemed to be greater in those with LV hypertrophy and smoking.

Statin therapy in hemodialysis patients awaiting renal transplant is independently associated with better survival supporting its use in this high-risk population.

Keywords

- end-stage renal disease
- statin
- survival
- hemodialysis
- diabetes

Patients with end-stage renal disease (ESRD) have one of the highest cardiovascular (CV) mortalities, being approximately 15 to 30 times an age-matched general population.¹ They have a high prevalence of coronary artery disease (CAD) and diabetes mellitus and have a systemic inflammatory state, making statin therapy an attractive option.^{2–5} Even milder forms of renal disease result in higher CV mortality, which is ameliorated with statin therapy.^{6–9} Yet, the randomized trials in ESRD population have failed to show a consistent mortality benefit with statins.^{10–12} Though the 4D (Deutsche Diabetes Dialyse Studie), AURORA (A Study to Evaluate the Use of

Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events), and SHARP (Study of Heart and Renal Protection) trials were negative for statin benefit in those with renal dysfunction, posthoc analyses of these trials in subsets with diabetes and increased low-density lipoproteins (LDLs) have shown potential benefit with statins.^{13,14} But none of these included a pure group of hemodialysis (HD) patients awaiting renal transplantation. Keeping these patients free of CV morbidity and mortality will not only increase renal transplant rates but also reduce perioperative morbidity and improve posttransplant survival.

We hypothesized that statins would be beneficial in these patients. Hence, we investigated the value of statins in a large, pure cohort of prospectively recruited patients with ESRD awaiting renal transplantation, and being followed up in a dedicated cardiac clinic.

Patients and Methods

Patient Population

We prospectively evaluated 423 consecutive HD patients from our ongoing prospective registry of kidney transplant candidates at our dedicated cardiology clinic from October 2008 to October 2010. The clinic was set up for aggressive risk identification and reduction for ESRD patients. The study was approved by our institutional review board. Informed consents were obtained from the patients.

Clinical Evaluations

Adult patients with ESRD on HD age 18 or older who had at least one clinical evaluation at our dedicated clinic were enrolled in the present study. The comprehensive clinical evaluation of patients included review of previous records, detailed history, and physical examination by one of the attending cardiologists followed by 12 lead electrocardiograms and a base line echocardiogram. The majority of patients were risk stratified with a subsequent stress test and/or a coronary angiogram as clinically appropriate. Fasting lipid panel, liver function tests, and C-reactive protein was obtained either in the first or subsequent visits. Dyslipidemia was defined according to the risk level of the patient outlined in NCEP (National Cholesterol Education Program)/ATP III (Adult Treatment Panel III) guidelines.¹⁵ In general, patients were considered to be dyslipidemic if they were on prior statin or other lipid lowering therapy, the pretreatment fasting cholesterol was > 200 mg/dL, LDL level was > 100 mg/dL, or serum triglycerides (TG) were > 150 mg/dL if patients did not have diabetes mellitus or vascular disease. For patients with diabetes mellitus or vascular disease, a diagnosis of dyslipidemia was extended to those who had LDL of > 70 mg/dL. Hypertension was defined as systolic blood pressure of 140 mm Hg or more and diastolic blood pressure of 90 mm Hg or more or treatment with antihypertensive medications. Diabetes was defined as fasting blood glucose of 126 mg/dL or more or being on treatment with an antidiabetic medication.

Statin Therapy

The decision to start statin therapy or to modify was taken according to the lipid profile, risk assessment, and outcome of stress test or coronary angiogram. A goal LDL of < 70 mg/dL was established for patients with diabetes mellitus or vascular disease; whereas for other slightly lower risk group, a goal LDL of 70 to 100 mg/dL was established. Statin therapy was also offered to all patients with stroke and CAD regardless of the LDL levels. As part of the treatment, lifestyle changes and dietary advice were offered. Statin treatment was however not delayed in high-risk patients and in those who had previously tried lifestyle changes and dietary modifications

but had not resulted in goal LDL levels. Lipid panel and liver function tests were repeated after 8 to 12 weeks of continuous therapy and dose adjustments were made according to the LDL reductions. In general, we started treatment of dyslipidemia either with simvastatin or pravastatin avoiding highest dosage of both the medications. In high-risk patients with CAD or stroke and in those where goal LDL was either not achieved or was perceived to be unachievable with moderate dose simvastatin or pravastatin, a change was made to atorvastatin or rosuvastatin. In patients with adequate initial treatment of high LDL, attention was given to risk reduction from control of non-high-density lipoprotein (HDL). In these patients with high TG levels, non-HDL goal was established to be < 100 mg/dL and in all others to be < 130 mg/dL. To improve compliance with therapy, close collaboration was established with patient families, primary care providers, dialysis centers, and referring nephrologists.

Statistical Analysis

Statistical analysis was performed using Statview 2005 (SAS Institute Inc., Cary, NC) software. Group comparisons were made using Student *t*-test or Chi-square test. Patients were censored at the date of kidney transplant. Survival analysis was performed using Cox regression model and survival curves were generated by Kaplan–Meier analysis. The important univariable predictors of survival with *p*-value 0.1 or less were studied in multivariable regression analysis. Further, this regression analysis was modified by entering clinically significant variables and other CV risk factors into it. Propensity score analysis was used to adjust for the effect of group differences between treated and untreated groups on survival. The probability of receiving a statin (propensity score) for each patient was modeled by using logistic regression conditioned on the covariate values for that individual, including age, diabetes, LDL levels, hypertension, left ventricular (LV) hypertrophy, concomitant angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), and antiplatelet therapies.

Results

Patient Characteristics

► **Table 1** shows the general characteristics of the cohort and group differences between those on statin and those not on statin therapy. General characteristics of the patients on HD were as follows: age 57 ± 11 years, male gender 64%, hypertension 96%, diabetes mellitus 68%, smoking or history of smoking 41%, history of CAD 30%, history of stroke 8%, history of peripheral vascular disease 4%, a baseline ejection fraction (EF) of $61 \pm 11\%$. Total 24% of the patients with type II diabetes had neuropathy and 56% had retinopathy. Lipid profile of the cohort showed average total cholesterol (TC) of 152 ± 38 mg/dL, TG of 146 ± 83 mg/dL, HDL of 48 ± 15 mg/dL, and LDL of 81 ± 33 mg/dL. In 39% of the patients, statin treatment was started by primary care physicians or treating nephrologists. In these patients, lipid profiles on first clinical evaluation were as follows: TC 146 ± 38 mg/dL, TG 148 ± 83 mg/dL, HDL 48 ± 18 mg/dL and LDL of 78 ± 32 mg/dL. Additional 36% of the patients

Table 1 Showing base line characteristics and group differences between those on statin treatment and those not on statin

Groups	All patients (n = 423)	On statin (n = 317)	Not on statin (n = 106)	p-Value
Age (y)	57 ± 11	58 ± 12	53 ± 13	< 0.0001
Female gender	36%	35%	40%	0.24
Smoking	41%	43%	35%	0.13
Hypertension	96%	98%	92%	0.02
Diabetes mellitus	68%	77%	46%	< 0.0001
LV hypertrophy	85%	89%	79%	0.006
LV ejection fraction (%)	61 ± 11	60 ± 12	61 ± 12	0.53
CAD	30%	61%	42%	0.01
Peripheral vascular disease	4%	4%	2.0%	0.28
History of stroke	8%	8%	6%	0.41
Serum total cholesterol level (mg/dL)	153 ± 40	153 ± 40	143 ± 35	0.07
Serum triglyceride level (mg/dL)	146 ± 83	144 ± 77	150 ± 103	0.63
LDL level (mg/dL)	81 ± 33	84 ± 34	69 ± 29	0.002
HDL level (mg/dL)	48 ± 15	49 ± 14	48 ± 15	0.42
CRP level (mg/dL)	9.9 ± 23	10.58 ± 24	7.58 ± 13	0.43
Antiplatelet therapy	64%	75%	36%	< 0.0001
Niacin, omega 3 or fibrate therapy	10%	13%	9%	0.23
Sevelamer treatment				
Beta blocker therapy	71%	74%	63%	0.02
ACEI/ARB therapy	59%	60%	55%	0.33

Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular.

were started on statin therapy in our clinic, improving the overall treatment rate to 75% ($n = 317$) over a period of 2 years. In those 33% patients, baseline TC was 160 ± 40 mg/dL, TG was 142 ± 72 mg/dL, HDL was 47 ± 13 mg/dL, and mean LDL was 90 ± 34 mg/dL.

Correlates of Statin Therapy and Compliance to Therapy

Table 1 also shows the patient characteristics overall and as a function of statin therapy. Patients receiving statin were older in age ($p < 0.0001$), had a higher prevalence of diabetes ($p < 0.0001$), and LV hypertrophy ($p = 0.006$), higher LDL levels ($p = 0.002$), and higher prevalence of concomitant therapy with antiplatelet medications ($p < 0.0001$) or β blockers ($p = 0.02$). The duration of dialysis did not impact the decision to start or modify statin therapy.

Survival Analysis

Over a mean follow-up of 2 years, there were 43 deaths. Out of these, 42 events were in the patients on the transplant waiting list and only 1 was among the 46 patients who received a renal transplant during follow-up. All patients were censored at renal transplant in view of the potential salutary effect of renal transplant on survival. Using Cox regression analysis, statin treatment was a significant predictor of better survival on univariate analysis (hazard ratio [HR] 0.52, 95% confidence

interval [CI] 0.28–0.95, $p = 0.03$, Fig. 1) as well as on multi-variable analysis after adjusting for age, gender, smoking, diabetes, hypertension, CAD, LV ejection fraction, LV hypertrophy, therapy with niacin, fenofibrates, omega-3 fatty acids, antiplatelet agents, β blockers, and angiotensin converting enzyme inhibitors (HR 0.30, 95% CI 0.11–0.79, $p = 0.01$). This class effect

Fig. 1 Survival as function of statin therapy in hemodialysis patients awaiting renal transplantation.

of statin was also supported by propensity analysis using adjustment for propensity score for statin therapy ($p = 0.02$).

Statin Therapy and Survival in Clinical Subgroups

► **Table 2** shows frequency of statin use in different clinically important subgroups and its effect on survival. The survival benefit of statin was consistent across different clinical subgroups though the benefit seemed to be greater in those with LV hypertrophy and smoking. In patients with LV hypertrophy as well as in those with a history of smoking, statin therapy was independently associated with better survival ($p = 0.01$ and 0.0004 , respectively) after adjusting for age, gender, diabetes mellitus, CAD, LV ejection fraction, and therapy with β blockers, ACEI inhibitors, and aspirin.

Discussion

The results of our prospective registry shows a potential beneficial effect of statin therapy in ESRD patients waiting for renal transplant, an extremely high-risk population in terms of cardiac morbidity and mortality. Though these results are inconsistent with the overall results of major statin trials in patients with advanced renal disease, they are consistent with some of the posthoc analysis of these trials. We also show that it is possible to increase the rate of guideline-recommended statin therapy that improves CV outcomes in these patients. These results have important practical applications in the roughly 1 million patients with ESRD in United States where the rate of statin therapy can potentially be doubled leading to improved outcomes.^{1,2}

Dyslipidemias in ESRD patients on HD are common and are usually manifested by elevated TG levels, normal or elevated LDL levels, and decreased HDL levels. These abnormalities correspondingly are reflected by elevated apolipoprotein B (APOB) levels,¹⁶ increased very-LDL, elevated lipoprotein(a) (Lp[a]) levels,¹⁷ and decreased APOA1 and APOAII levels.¹⁸ Interestingly, these dyslipidemias remain during lifetime of a dialysis patient and depend upon a number of factors, including the use of sevelamer for hyperphosphatemia,¹⁹ thyroid

hormone levels, and nutrition. Quite often, HD patients carry over these dyslipidemias from early stages of chronic kidney disease (CKD). The underlying mechanism of abnormalities includes impaired metabolism of TG particles because of imbalance in levels of APOCII lipase and APOCIII lipase,²⁰ changes in LDL particle size²¹ to small, dense atherogenic particles, impaired activity of LCAT enzyme that plays crucial role in HDL generation²² and acquired abnormalities in LP(a) clearance with declining glomerular filtration rate.¹⁷ The type of HD modality, especially the use of high flux membrane may also affect lipid profiles in dialysis patients and may affect HDL particle levels, TG levels as well as oxidized LDL levels.^{23–25}

While some have implicated the link of elevated LDL as well as non-HDL cholesterol in this phenomenon directly or indirectly,^{26,27} others have argued against it, especially in light of the negative clinical evidence from trials of statin treatment. It is generally thought that atherosclerosis in these uremic patients is far more complex process than the general population and dyslipidemias are just a part of a very big and multiarrayed process.²⁸ Second, whether these dyslipidemias are associated with an increased overall or CV mortality as it is observed in the general population²⁹ has been a matter of debate. Interestingly, the authors of some epidemiological and observational studies have proposed an inverse relationship between total serum cholesterol levels and total mortality indicating the possible protective effect of hypercholesterolemia in these patients.^{30,31} Despite the lack of conclusive evidence, there is perhaps general consensus that statin treatment be given to such patients in acute coronary syndrome setting just as it would be to any other patient. The National Kidney Foundation (NKF) endorses this practice.³²

The use of statin treatment in these patients for primary prevention is currently viewed with somewhat pessimism as two well-designed randomized controlled clinical trials in recent past failed to show any survival benefits and a third trial showed mere benefit of nonstatistical significance.^{10–12} The results of our study support the broader use of intense treatment in these patients. The benefit of statin treatment in

Table 2 Rate of statin use in various subgroups and its impact on survival

Groups	Rate of statin treatment	HR	95% CI	p-Value
Male gender ($n = 271$)	76%	0.68	0.28–1.27	0.41
Female gender ($n = 152$)	74%	0.49	0.21–1.14	0.10
Smokers ($n = 173$)	76%	0.30	0.12–0.72	0.004
Nonsmokers ($n = 250$)	74%	0.68	0.29–1.59	0.37
Diabetics ($n = 288$)	80%	0.31	0.15–0.65	0.002
Patients with LV hypertrophy ($n = 355$)	75%	0.46	0.24–0.88	0.02
Patients with LV ejection fraction $\leq 40\%$ ($n = 28$)	76%	0.155	0.01–1.72	0.13
Patients with LV ejection fraction $> 40\%$ ($n = 395$)	74%	0.50	0.26–0.96	0.04
Patients with CAD ($n = 127$)	82%	0.64	0.18–2.33	0.50
Patients with CRP > 3	80%	0.56	0.15–2.13	0.40

Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; LV, left ventricular.

our study was seen across the whole cohort as well as in all important clinical subgroups. In general, our treatment strategies included treating high-risk individuals even when LDL levels were minimally or modestly elevated. The improved overall survival would thus suggest to some extent that statin therapy in high-risk dialysis patients may offer benefit even when TC or LDL is not markedly elevated.

Another interesting observation of our study was benefit of statin therapy in subgroup of patients with LV hypertrophy diagnosed on echocardiography. HD patients have a higher prevalence of LV hypertrophy because of comorbidities such as hypertension, diabetes, anemia, and dynamic fluid shifts.³³ Presence of LV hypertrophy in these patients has been shown to increase CV mortality.³⁴ In animal studies, statins have been shown to reduce development of LV hypertrophy and transition of LV hypertrophy to heart failure.^{35,36} In human studies, there is evidence to suggest that statin therapy in those with established LV hypertrophy may attenuate myocardial fibrosis.³⁷ The clinical implications of this phenomenon are not clear and whether statins can prevent progression or reverse changes of LV hypertrophy is not known.³⁸ We speculate that statin use in these patients, which was obviously prescribed for other reasons, might have slowed the progression of many of these highly vulnerable patients in to overt heart failure and might have also reduced other cardiac events indirectly including arrhythmias and coronary events, thus reducing mortality.

The results of our study reconcile with prior large clinical trials of statin in general population with diabetes mellitus and other clinical trials where study population had significant number of diabetic participants. Generally, the results of these trials have advocated for intense lowering of LDL cholesterol levels.^{39–41} Based upon the results of these studies and other clinical evidence, NCEP/ATPIII in its updated 2004 guidelines recommended bringing LDL levels to < 100 mg/dL for these patients to offer maximum CV benefit.¹⁵ As ESRD patients on dialysis have highest oxidative stress and suffer from high inflammation and endothelial dysfunction, we speculate that statin treatment is beneficial in these patients not just because of their cholesterol lowering effects but also through pleiotropic effects. These results also reconcile with prior observational data of statin use in HD patients⁴² and suggest that patients on prior statin treatment reaching HD should not be taken off the statin therapy so as to continue on going reduction in overall cardiac risk achieved in early stages of CKD.

The results of our study, however, do not reconcile with the recent clinical trials of statin in HD patients. Out of these, the results of 4D trial of atorvastatin in type II diabetes mellitus on HD were more surprising and unexpected.¹⁰ In this trial, atorvastatin 20 mg did not significantly affect primary end points (CV death, nonfatal myocardial infarction, and stroke) over a period of 4 years despite adequate (median 42%) reductions in LDL levels easily achieved in first few weeks of the study. Several reasons have been cited for these negative results. First, this trial was not strictly a primary prevention trial since trial population also included patients with prior cardiac events. Second, the trial excluded diabetic patients who were > 2 years on HD treatment and those with LDL > 190 mg/dL or LDL < 80 mg/dL potentially depriving

very dyslipidemic diabetic and long-term dialysis patients. Third, more interestingly during trial duration, LDL reductions were observed in first few weeks in atorvastatin arm only. However, over the period of entire follow-up, placebo arm was also seen to have substantial reductions in LDL levels. The authors attributed it to malnutrition but study population maintained their body mass and albumin levels. If malnutrition was the responsible factor for decreased LDL levels in placebo arm of 4D trial, then we should have seen increased overall mortality in placebo group, giving an edge to atorvastatin group as malnutrition and elevated inflammation has long been postulated to increase short-term mortality in dialysis patients. We speculate that the rate of out of study use of statin in placebo group was higher than reported (15%) and this might have contributed to overall negative results of this trial along with other factors. It is interesting to note that though main published 4D trial was interpreted to be negative, a posthoc analysis of 4D trial patients with highest quartile of LDL > 145 mg/dL (145–269 mg/dL) ($n = 314$) showed a clear benefit in reducing primary end point by 31%, cardiac deaths by 42%, and all-cause mortality by approximately 28%.¹³ Contrary to the authors of the main trial, authors of posthoc analysis study argued in favor of treating the elevated LDL in these patients.

Another recent randomized control trial of statin therapy with whom our results did not reconcile was AURORA trial. In this trial, 2,776 HD patients were randomized to either rosuvastatin 10 mg orally daily or placebo. The majority of patients were nondiabetic. Patients were followed up for a period of 3.8 years and there was no significant effect of rosuvastatin treatment on composite primary end points (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) despite a 43% reduction in LDL levels. Further, in subgroup analysis of patients with diabetes mellitus or high C-reactive protein, no benefit of rosuvastatin therapy was observed. Interestingly, just like the 4D trial, in the posthoc analysis of 731 diabetic patients from AURORA trial, rosuvastatin was actually shown to reduce cardiac events by 32%.¹⁴ Thus, though the results of our study do not reconcile with the main trial populations, they do so with the posthoc analysis of those with high LDL levels and diabetes. In a strict sense, though posthoc analysis results should not be projected for clinical practice guidance and should only portray hypothetical expansion, we do feel that the potential beneficial effects of statins in this high-risk population should not be dismissed. In AURORA trial, approximately 600 patients who had been on statin treatment for 6 or more months before the start of dialysis were not included. This possibly excluded good number of patients who might have gained CV benefits from long-term statin treatment that might have been started early in their CKD. This shortcoming was addressed in the SHARP trial. In this study, 9,270 patients in various stages of CKD were randomized to either simvastatin 20 plus ezetimibe 10 mg daily versus placebo. The authors claimed that rosuvastatin reduced CV risk by 10% in HD patients and by 17% in those CKD patients who were not on HD. They argued that these differences were statistically nonsignificant and implied that benefit of statin therapy was available for both the groups. However, SHARP

had high prevalence of earlier stage CKD patients and beneficial effects of statin in this subgroup have been shown previously. Out of the 9,270 patients, 2,527 patients were on HD. In these patients, statin treatment did not show desired benefit and more importantly, SHARP was neither designed nor powered to show that. Thus, the results of this trial too do not provide satisfactory answer and despite a better prevention design it does not resolve the controversy surrounding use of statin in HD patients.

Conclusions

In conclusion, results of our observational study show survival benefit of statin in HD patients awaiting renal transplant. This effect is most notable in those with diabetes mellitus, LV hypertrophy, or smoking. Despite the limitations of observational study design and our findings being inconsistent with the main results of randomized trials, we feel that beneficial effects of statin therapy should not be dismissed in this high-risk population. Appropriate statin therapy rate can be increased through meticulous evaluation and follow-up in a dedicated cardiac clinic.

Study Limitations

The main limitation of our study is its observational nature and lacks randomization of statin therapy. However, we have used propensity score analysis, which is reported to remove approximately 80% of the treatment bias.^{43,44} This study addresses a specific group of patients awaiting renal transplant treated in a specialized cardiac clinic and may not be generalizable to all with ESRD. The study population belonged to the patients who had already been prescreened by the referring physicians for basic transplant eligibility. Thus, patients with severe clinical conditions and comorbidities were perhaps not referred to the clinic. Further, patients who were deemed extremely low risk were also not referred for a cardiac evaluation. These population characteristics might have impacted the results. Another limitation of our study is the data on follow-up levels of lipids and change in dosage of the medications. The lipid levels were monitored as appropriate as indicated during the course of follow-up and dose of statin therapy or switching between different statins was modified accordingly. The data on lipid levels on specific follow-up intervals and statin dosage were however not collected. Another limitation of our study is data on cause of death, which might have been helpful in further explaining results of our study. We also did not have dialysis-related data such as frequency of dialysis treatments, type of filter, constitution of dialysate, or markers of efficiency such as Kt/V. In addition, we do not have exact duration of statin therapy, which might have modified some of the results.

Note

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