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# Does African American Race Impact Statin Efficacy in Renal Transplant Outcomes?

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**Abstract:** There is a lack of studies assessing if race impacts the efficacy of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) inhibitor ("statin") therapy on renal transplantation (RTx) outcomes. We examined the association between statin therapy and RTx outcomes, while concurrently quantifying the effect modification African American (AA) race has on statin efficacy.

This was a retrospective longitudinal cohort study of solitary adult RTx (n = 1176) between June 2005 and May 2013. The Cox proportional hazard model was used to examine the impact of statin therapy on graft loss, death, and acute rejection and determine if significant interactions exist between statin therapy and race. Models were adjusted for demographics, socioeconomic status, cardiovascular history, medication use, and transplant characteristics.

AAs (n = 624) and non-African Americans (n = 552) were equally likely to receive statin therapy ($P = 0.922$). Mean LDL and TGs in AA were 94 mg/dL and 133 mg/dL compared to 90 mg/dL and 163 mg/dL in non-AA, respectively. After adjusting for confounders, high statin users had 52% lower risk of developing graft loss (HR 0.48, 95% CI 0.29–0.80) and a nonstatistically significant reduction in death (HR 0.50, 95% CI 0.23–1.06) compared to low statin users. Acute rejection was not significantly influenced by statin use (HR 0.77 95% CI 0.46–1.27). There was a significant interaction between race and statin therapy for death ($P = 0.007$), but not for graft loss ($P = 0.121$) or rejection ($P = 0.605$). After stratifying by race, high statin use reduced the risk of death in AAs (HR 0.43, 95% CI 0.20–0.94), but not in non-AAs (HR 1.09, 95% CI 0.49–2.44).

High statin use reduces the risk of graft loss in RTx, with a mortality benefit in AAs compared to non-AA, despite similar LDL levels. These results suggest a compelling reason to optimize statin therapy in renal transplant recipients (RTR), especially in AAs.

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## INTRODUCTION

Dyslipidemia is a common finding in renal transplant recipients (RTR) and is a predominant risk factor for premature cardiovascular disease (CVD) and death.[1] The annual mortality associated with CVD in RTR may be up to 46 times higher than the general population in certain age groups.[2] Studies demonstrate cardiovascular (CV) events are the leading cause of graft loss with function [3,4] and that dyslipidemia is a risk factor for the development of chronic graft failure.[5,6]

Treatment of dyslipidemia in RTR results in a decrease in CV events.[7] 3-Hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) inhibitors ("statins") are the treatment of choice and the most common, safe, and efficient antilipemic agents used in RTR.[1,8] Several studies [9–12] have examined the effect of statin therapy in RTR outcomes (particularly acute rejection) and most found no effect on outcomes. On the contrary, a retrospective study on the benefits of statins on RTR outcomes demonstrated that statin therapy had beneficial effects on RTR outcomes—acute rejection, graft loss, and death.[13]

African Americans (AA) are less likely to receive statin therapy following renal transplantation [14] despite being more likely to die post-transplant compared to non-African Americans (non-AA).[15] The reason for this finding among African Americans remains unclear. Conversely, the disproportionate CVD risk and CVD risk treatment among AA in general renal transplant recipient populations is well established;[16] however, there is a lack of studies assessing if race impacts the efficacy of

statin therapy on RTR outcomes. Thus, the objective of this study was to examine the association between statin therapy and clinical outcomes in renal transplant recipients, while concurrently quantifying the effect modification AA race has on statin-associated efficacy. The study hypotheses are that statin therapy improves graft outcomes, and this effect is significantly modified by AA race.

## METHODS

### Study Design

This was a retrospective longitudinal cohort study of solitary adult renal transplantation (RTx) at a tertiary institution, which included recipients transplanted between June 2005 and May 2013. Patients were eligible if they were 18 years old or older and renal transplant recipients (RTR) with follow-up care at our facility. We excluded patients <18 years old, nonrenal transplant recipients, and those lost to follow-up. The study was approved by the institutional review committee (IRB)-PRO00022010. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the ''Declaration of Istanbul on Organ Trafficking and Transplant Tourism.''

## OUTCOMES

The primary outcomes for this study were incidence of acute rejection, graft loss, and time to death in ''high statin users'' and ''low statin users'' renal transplant recipients. We also sought to determine if the effect of statins on graft outcomes differed across AAs versus non-AAs by using interaction terms in multivariable models.

### Variable Definitions

Statin use: ''high statin use'' was defined as receiving statin therapy at least 50% of the post-transplant follow-up time, which was consistently documented in the medical record. ''Low statin use'' was defined as receiving statin therapy <50% of the post-transplant follow-up time. For ease of comparison, all statin doses were transformed to atorvastatin equivalence using standardized dose equivalent.[17]

Race: this was self-reported, captured at the time of kidney transplant. Race was dichotomized to AA and non-AA, as we have very low numbers of Asians and non-Black Hispanic recipients.

Acute rejection: this was defined as biopsy proven with a Banff score of at least 1A criteria.[18]

Graft loss: this was defined as return to chronic dialysis or death.

Heart disease: this was defined as history of heart disease in medical record before transplant.

### Statistical Analysis

Baseline characteristics were compared across groups using Student's *t* test for continuous variables and chi square test for categorical variables. For univariate time to event analysis, Kaplan–Meier survival estimates were utilized with comparisons conducted using the log rank test. Cox regression model was used to examine the impact of statin therapy on graft loss, acute rejection, and death and determine if significant interactions exist between statin therapy and race. Models were adjusted for demographics, socioeconomic status, cardiovascular history, medication use, and transplant characteristics. Statistical significance was based on *P* value <0.05. SPSS

version 21.0 was used for statistical analysis (IBM, Armonk, NY).

## RESULTS

One thousand, one hundred and seventy-six renal transplant recipients (RTR) were included in the analysis, of which 53% were AA and 47%were non-AA; the majority of the RTR were males. The average age of AA and non-AA patients was 54 and 56 years old, respectively. The average dose and years on statin therapy was $19.4 \pm 13.3$ mg/day (atorvastatin equivalents) and $1.8 \pm 0.8$ years in AA, and $19.9 \pm 14.6$ mg/day and $1.7 \pm 1.0$ years in non-AA (Table 1). Duration of diabetes and donor age was similar in both racial groups. Mean LDL and triglycerides levels in AA were $94 \pm 29$ mg/dL and $133 \pm 118$ mg/dL compared to $90 \pm 38$ mg/dL and $163 \pm 83$ mg/dL in non-AA ($P = 0.053$ and <0.001, respectively).

High statin users were more likely to have Medicare/Medicaid insurance, diabetes, obesity, hyperlipidemia, heart disease, cardiac catheterization, coronary artery bypass grafting (CABG), and retransplant, which was independent of race (Table 1). AA reported less cigarette smoking and were more likely to receive pretransplant dialysis compared to non-AAs, regardless of statin therapy category; history of acute MI was more predominant in non-AA RTR.

The unadjusted incidence of acute rejection, graft loss, and death were higher (16.6%, 19.2% and 11.1% respectively) in AA low statin users compared to high statin users (see Table 2). The same trend was observed in non-AA except for the outcome of death. The incidence of new-onset diabetes in AA were 10.8% among low statin users and 12.8% among high statin users, which was not statistically significant, *P* value 0.43 (data not shown). New-onset diabetes was also not statistically significant (*P* value 0.17) in non-AA low statin users (7.2%) compared to high statin users (10.5%).

After adjusting for covariates (age, gender, insurance, cardiovascular risk factors, transplant characteristics, immunologic risk factors, and medications) high statin users had 52% lower risk of developing graft loss (HR 0.48, 95% CI 0.29–0.80) compared to low statin users. In the overall population, high statin use did not significantly reduce the risk of death (HR 0.50 95% CI 0.23–1.06) or influence the incidence of acute rejection (HR 0.77, 95% CI 0.46–1.27).

### Effect Modification of Statin Therapy by Race

Graft survival was improved by high statin use in both AA and non-AA to a similar magnitude and the effect of high statin therapy on improving graft survival was not appreciably modified by recipient's race (Fig. 1).

There was a statistically significant interaction between race and high statin use for death ($P = 0.007$), but not for graft loss ($P = 0.121$) or rejection ($P = 0.605$), data not shown. After stratifying the data by race (see Table 3 and Figure 2) the Cox regression analysis demonstrated high statin use reduced the risk of death in AA (HR 0.43, 95% CI 0.20–0.94), but not in non-AA (HR 1.09, 95% CI 0.49–2.44). In both AA (HR 0.32, 95% CI 0.14–0.76) and non-AA (HR 0.39, 95% CI 0.16–0.99), high statin use had a significant influence on graft loss. High statin use did not reduce the risk of acute rejection in either AA or non-AA.

## DISCUSSION

Overall, this study demonstrates that African Americans (AA) and non-AA were equally likely to receive statins; with graft survival being significantly better in patients receiving this

**TABLE 1.** Baseline Characteristics of Adult Renal Transplantation Recipients

| Baseline Statin Use | African Americans (n = 624) | | Non-African Americans (n = 552) | |
|---|---|---|---|---|
| | High Statin (n = 281) | Low Statin (n = 343) | High Statin (n = 247) | Low Statin (n = 305) |
| Female | 42.3 | 42.9 | 38.9 | 39.1 |
| Mean statin dose (mg/day) | 19.4 ± 13.3 | 16.4 ± 11.3 | 19.9 ± 14.6 | 17.3 ± 16.5 |
| Time on statin (years) | 1.8 ± 0.8** | 0.3 ± 0.6 | 1.7 ± 1.0** | 0.2 ± 0.6 |
| Time on statin | 70 ± 30** | 10 ± 20 | 70 ± 30** | 10 ± 20 |
| LDL (mg/dL) | 96 ± 29 | 92 ± 30 | 95 ± 45** | 85 ± 28 |
| TG (mg/dL) | 123 ± 56* | 143 ± 160 | 162 ± 84 | 165 ± 82 |
| BMI (kg/m$^2$) | 29.4 ± 5.5 | 29.5 ± 6.1 | 29.2 ± 5.2** | 27.3 ± 5.9 |
| Recipient age (years) | 54.4 ± 11.6** | 47.6 ± 13.6 | 55.8 ± 12.2** | 48.9 ± 15.6 |
| Years of diabetes | 19.7 ± 9.2 | 17.8 ± 7.2 | 21.7 ± 11.4 | 19.5 ± 11.8 |
| Current PRA | 17.8 ± 29.6 | 16.9 ± 28.8 | 15.9 ± 30.3 | 17.3 ± 30.3 |
| PRA ≥ 20% | 28.5 | 27.7 | 21.5 | 25.9 |
| PRA > 80% | 9.3 | 8.5 | 9.3 | 9.8 |
| Insurance | | | | |
|   Medicare | 81.1* | 74.1 | 68.8* | 60.7 |
|   Medicaid | 22.1** | 31.5 | 8.9** | 17.0 |
| Below HS education | 60.6 | 55.1 | 40.0 | 42.5 |
| Primary ESRD etiology | | | | |
|   Diabetes | 37.4** | 26.8 | 28.3** | 14.1 |
|   Hypertension | 33.1 | 40.2 | 20.6 | 19.3 |
|   PKD | 4.6 | 3.8 | 14.2 | 12.1 |
|   FSGS | 10.3 | 8.2 | 2.8 | 5.6 |
| Past medical history | | | | |
|   Smoker | 12.1* | 17.8 | 19.8 | 21.6 |
|   Heart disease | 21.7** | 10.2 | 29.1** | 16.4 |
|   Hyperlipidemia | 68.7** | 24.8 | 67.6** | 32.1 |
|   Stroke | 10.0 | 8.2 | 7.3 | 4.3 |
|   CABG | 5.0** | 1.2 | 14.2** | 2.6 |
|   Acute MI | 4.3 | 2.9 | 8.5* | 3.9 |
|   CHF | 7.1 | 4.7 | 6.1 | 3.6 |
|   PVD | 3.2 | 3.2 | 6.9 | 4.3 |
| Type of dialysis | | | | |
|   Preemptive | 14.2* | 8.5 | 34.0 | 34.8 |
|   PD | 13.9 | 11.4 | 17.4 | 18.7 |
|   HD | 71.9 | 80.2 | 48.6 | 46.6 |
|   Retransplant | 6.8 | 7.3 | 9.3* | 15.7 |
|   Donor ECD | 14.1 | 10.2 | 18.9 | 12.0** |
| Calcineurin inhibitors | | | | |
|   Tacrolimus | 94 | 96 | 95 | 96 |
|   Cyclosporine | 1 | 2 | 1 | 4 |
|   Mycophenolic acid | 96* | 96 | 97** | 98 |
| Cardiovascular drugs | | | | |
|   ACEI/ARBs | 63** | 74 | 56** | 69 |
|   Beta blockers | 74** | 91 | 70** | 87 |
|   Antiplatelet | 59** | 80 | 55** | 71 |

ACEI = angiotensin-converting-enzyme inhibitor, ARBs = angiotensin II receptor blockers, BMI = body mass index, CABG = coronary artery bypass grafting, CHF = congestive heart failure, ECD = expanded criteria donor, ESRD = end stage renal disease, FSGS = focal segmental glomerulosclerosis, HD = hemodialysis, HS = high school, LDL = low-density lipoprotein, MI = myocardial infarction, PD = peritoneal dialysis, PKD = polycystic kidney disease, PRA = panel reactive antibody, PVD = peripheral vascular disease, TG = triglycerides.
  * Level of significance $P < 0.05$; all values are percentages unless otherwise specified.
  ** Level of significance $P < 0.001$.

therapy at least 50% of the post-transplant follow-up time. High statin use did not influence risk of death or acute rejection in the overall population. However, after stratification by race, African Americans (AA) had a significant mortality benefit from high statin use, which was not demonstrated in non-AA.

Recipients race had no effect modification for statin efficacy on either graft survival or acute rejection.

The lower likelihood of graft loss in the overall study population with high statin use may be due to reduction in graft atherosclerosis.[19] Although the mortality benefit of high statin

**TABLE 2.** Clinical Outcomes Incidence by Race and Statin Use

| | African Americans | | Non-African Americans | |
| --- | --- | --- | --- | --- |
| | **Low Statin** | **High Statin** | **Low Statin** | **High Statin** |
| Acute rejection | 16.6% | 11.0% | 7.9% | 6.1% |
| Graft loss | 19.2% | 9.6% | 15.4% | 9.7% |
| Death | 11.1% | 5.0% | 7.2% | 8.5% |
| Follow-up period | | | | |
| Mean (years) | 3.7 ± 2.4 | 3.7 ± 2.1 | 3.5 ± 2.3 | 3.9 ± 2.2 |
| Total person years | 1253 | 1053 | 1078 | 953 |

use among AA is unclear, we speculate that this could be related to high prevalence of cardiovascular risk factors and cardiovascular disease in AA compared to non-AA[20] and due to the cardioprotective effects of statins.[21,22] This mortality benefit of high statin use was apparent early and the survival curves continued to diverge for upwards of 7 years post-transplant. These findings are of great significance given the well-established health disparities that currently exist in renal transplant outcomes; aggressive statin therapy especially in AA renal transplant recipients (RTR) may contribute to narrowing this existing disparity.

The findings of our study are consistent with most previous studies, which demonstrate that statin therapy has no effect on acute rejection. Although statin therapy has been postulated to have pleiotropic immunomodulatory effects, which theoretically may reduce the risk of acute rejection, there is a lack of consistent clinical evidence to support this hypothesis.[10–12] The ALERT extension study,[7] a 2-year preplanned extension of the largest prospective randomized statin therapy trial conducted in RTR, demonstrated that statins did not reduce all-cause mortality or graft loss. However, this study utilized a low-potency statin (fluvastatin), was conducted in patients receiving cyclosporine-based therapy, and contained a predominantly homogenous non-Black population. Thus, it is difficult to compare data from previous trials as the population studied lacks significant numbers of AA and received vastly different immunosuppression, leading to different cardiovascular risk factors and factor control rates. A retrospective analysis by Lisik et al [23] demonstrated that statin therapy was beneficial in the outcomes of acute rejection, graft loss and death, which differed from our findings in regard to acute rejection.[13] It is not fully clear why this difference exists, but it may be related to the use of very different immunosuppressant regimens (sirolimus and cyclosporine), which are known to have a significantly larger influence on serum lipoprotein concentrations. Consistent with this, the baseline LDL and TG levels of patients in the Lisik study were substantially higher than our study patients.

The results of this study are novel in that previous studies assessing statin efficacy in RTR have failed to include a significant number of AA recipients and thus did not analyze the impact of race on statin therapy efficacy. Previous studies conducted in dialysis patients demonstrate that AA are less likely to receive statin therapy over time,[14] our findings indicate that AA have a substantial benefit from statins and thus a compelling reason to optimize statin therapy AA renal transplant recipients. Ultimately, these results suggest clinicians should thoroughly assess the need for statin therapy in all RTR, regardless of race.
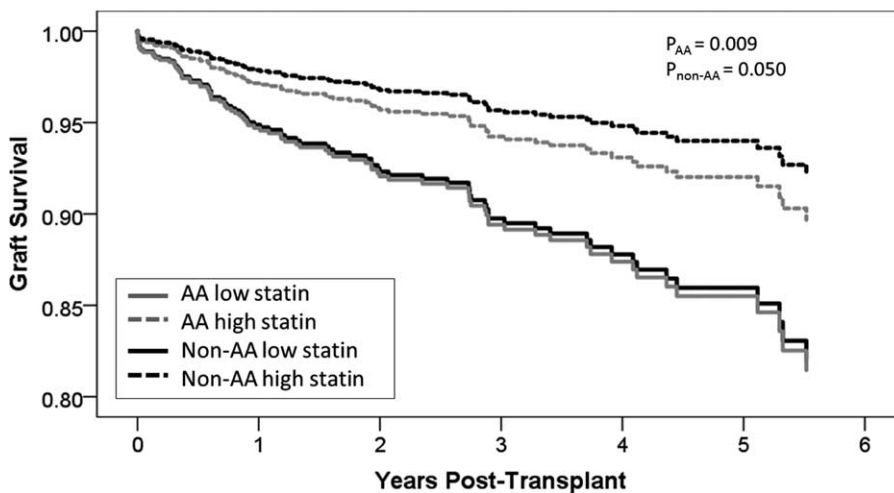


**FIGURE 1.** Cox regression survival estimates stratified by statin therapy on graft survival outcome, adjusted for by age, gender, insurance, cardiovascular risk factors, transplant characteristics, immunologic risk factors, beta blocker, ACEI/ARB, and antiplatelet therapy. AA = African Americans, ACEI = angiotensin-converting-enzyme inhibitor, ARBs = angiotensin II receptor blockers.

**TABLE 3.** Multivariate Analyses Using Cox Regression Assessing the Influence of Statin Therapy on Clinical Outcomes Stratified by Race

| Outcome | African Americans | | | Non-African Americans | | |
|---|---|---|---|---|---|---|
| | Hazard Ratio | 95% CI Interval | *P* Value | Hazard Ratio | 95% CI Interval | P-value |
| Acute Rejection | 0.71 | 0.36–1.41 | 0.325 | 2.64 | 0.62–11.2 | 0.188 |
| Graft loss | 0.32 | 0.14–0.76 | 0.009 | 0.39 | 0.16–0.99 | 0.050 |
| Death | 0.43 | 0.20–0.94 | 0.034 | 1.09 | 0.49–2.43 | 0.828 |

Model adjusted for age, gender, insurance, hypertension, diabetes, pretransplant dialysis, retransplant, current panel reactive antibody (PRA), human leukocyte antigen (HLA) mismatches, donor extended criteria donor (ECD), delayed graft function (DGF), smoking, history of heart disease, stroke, coronary artery bypass grafting (CABG), cardiac catheterization and acute myocardial infarction (MI); medications-beta blocker, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blockers (ACEI/ARB), antiplatelet therapy, tacrolimus, cytolytic induction therapy.
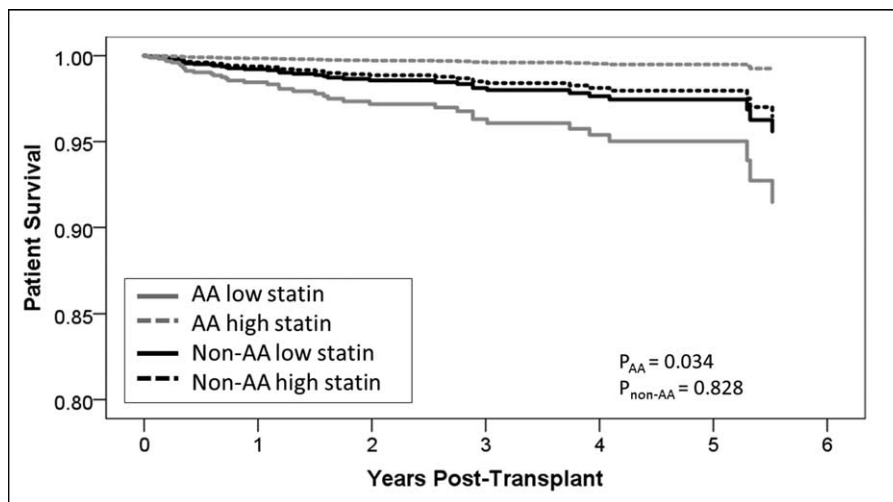


**FIGURE 2.** Cox regression survival estimates of influence of statin therapy on patient survival stratified by race and adjusted for by age, gender, insurance, cardiovascular risk factors, transplant characteristics, immunologic risk factors, beta blocker, ACEI/ARB, and antiplatelet therapy. AA = African Americans, ACEI = angiotensin-converting-enzyme inhibitor, ARBs = angiotensin II receptor blockers.

This study is not without limitations. It is a single-center retrospective study, which may affect generalizability. Also, there could have been selection bias and misclassification. Bias was addressed by including most patients transplanted during this time period, with limited exclusions. Misclassification was limited by developing clear definitions for the exposure (statin use) and outcomes. Although any post-transplant statin use could have been used as the exposure definition, the investigators felt that defining statin exposure by having consistent documentation of therapy during the follow-up time would allow for optimal analysis of the effects of this therapy. Finally, data on BK virus infection, cardiovascular events and medication adherence during the post-transplant follow-up period were not available. However, confounding was minimized by using multivariate modeling, with detailed and comprehensive collection of all covariates known to influence outcomes in renal transplant recipients (RTR).

In conclusion, this single-center cohort study showed that graft loss was significantly less likely in RTR that were high statin users and in the overall cohort, high statin use did not influence the risk of death or acute rejection. However, African Americans (AA) had a significant mortality benefit from high statin therapy, which was not demonstrated in non-AA. Optimal utilization of statins in RTR, especially in AA, may help to improve long-term outcomes in this high-risk patient population; further prospective studies are warranted to confirm these findings.

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