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The Impact of Cardiovascular Disease Risk Factors on Late Graft Outcome Disparities in Adult African American Kidney Transplant Recipients

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ABSTRACT

Introduction: Although outcome disparities for non-Hispanic Black (NHB) kidney transplant recipients are well known and documented, there is paucity in the data assessing the impact of cardiovascular disease (CVD) risk factors and risk control on racial disparities in kidney transplantation.

Methods: Longitudinal study of a national cohort of veteran kidney recipients transplanted between Jan 2001 and Dec 2007 (follow up through Dec 2010) with the aim of determining the prevalence and impact of CVD risk factor and control, compared between NHB and non-Hispanic White (NHW) recipients, on death-censored graft loss (DCGL), overall graft loss and mortality. Data included comprehensive baseline characteristics acquired through the USRDS with detailed follow up clinical, laboratory and medication regimen information acquired through linkage to the VA electronic health records. Analyses were conducted using sequential multivariable modeling (Cox regression), incorporating blocks of variables into iterative nested models.

Results: 3,139 patients with complete data were included (2,095 NHW [66.7%] and 1,044 NHBs [33.3%]). At five years post-transplant, NHBs had a higher prevalence of hypertension (100% vs. 99.2%, p<0.01) and post-transplant diabetes (58.9% vs. 53.3%, p<0.01) with reduced control of hypertension (BP <140/90, 60% vs. 69% p<0.01), diabetes (A1c <7%, 35% vs. 47%, p<0.01) and LDL (<100 mg/dL, 55% vs. 61%, p<0.01), when compared to NHWs. Adherence to several medication classes used to manage CVD risk factors was significantly lower in NHBs, as compared to NHWs. The unadjusted risk of DCGL was two-fold higher in NHBs, when compared to NHWs (HR 2.00, 95% CI 1.61-2.49). After adjustment for recipient sociodemographics, donor criteria, transplant characteristics, CVD risk factors and control and post-transplant events, the adjusted independent risk of DCGL was substantially reduced (HR 1.49, 1.11-1.99). CVD risk factors and risk control reduced the influence of NHB race on DCGL by 8.7-17.5%. Similar trends were noted for the outcomes of overall graft loss and mortality and were consistent in multiple sensitivity analyses.

Conclusion: These results demonstrate that NHB kidney transplant recipients have substantially higher rates of CVD risk factors and reduced CVD risk control, as compared to NHWs. These issues may be partly related to medication non-adherence and meaningfully contribute to disparities for graft outcomes within NHBs.

SPECIFIC AIMS

African-American (AA) renal transplant recipients experience a 42% increased risk of graft loss at 5 years post-transplant.[1] This disparity in transplant outcomes was first recognized in 1977, when Opelz et al published a landmark study demonstrating AAs had a 10% absolute lower graft survival rate at 3 years post-transplant, as compared to Caucasian recipients (25% vs. 35%, $p<0.001$).[2] Almost forty years later, the scope and magnitude of this disparity is remarkably similar. The most recent Scientific Registry of Transplant Recipients (SRTR) annual report demonstrates that AA kidney transplant recipients have a 12% lower graft survival rate at 5 years post-transplant.[1] Significant efforts have been made to identify and address immunologic and pharmacologic factors that are likely contributing to this disparity, including HLA mismatches,[3] donor APO L1 gene variants,[4] immune hyper-responsiveness[5-7] and genetic variants leading to altered immunosuppressant pharmacokinetics.[8-11] In addition, socioeconomic barriers, including late referral to transplant,[12,13] reduced access to care,[14,15] longer time on dialysis,[16,17] lower rates of living donation,[13] poorer socioeconomic status[18,19] and medication non-adherence[20-22] have been identified as significant contributors to the disparate outcomes established in AA kidney transplant recipients. Despite this previous research, interventional studies demonstrating significant and sustained improvements in this racial inequality are lacking, suggesting these previously identified factors are predominantly immutable or there are additional contributing factors.[23-25]

Studies demonstrate that death with a functioning graft is the predominant etiology for late graft loss, with cardiovascular disease (CVD) leading to 30–40% of these deaths.[26-28] It is well recognized that AA transplant recipients have a significantly greater burden of CVD risk factors, particularly hypertension and diabetes.[29-32] However, few studies have examined the contribution of CVD risk factor control, including hypertension, diabetes and dyslipidemia, on racial disparities in graft survival.[23] Three large-scale trials (DeKAF,[33] PORT[34] and FAVORIT[35]) demonstrated that CVD risk factors are frequent and poorly managed post-transplant, but AA patients are under-represented in these studies. AA represented 9 to 18% of these study patients, while the U.S. transplant population is comprised of 25% AAs.[1] Data from our transplant center, which has approximately 60% AA recipients, demonstrates that CVD risk factors are common, poorly controlled and associated with reduced graft survival.[36,37] Consequently, it is imperative to gain a better understanding of the

contribution of CVD risk factor control on racial disparities in graft survival, which may lead to the identification of interventions that can improve CVD risk factor control as a mechanism to improve graft survival and ameliorate disparities in AA recipients.

The central hypothesis for the proposed thesis is that the increased burden and lack of CVD risk factor control in AA renal transplant recipients are significant contributors to disparities in graft survival. This hypothesis will be tested by using a previously assembled dataset to conduct a 10-year retrospective longitudinal cohort study from a national sample of U.S. transplant recipients. A unique dataset was developed by linking the United States Renal Data System (USRDS) with Veterans Affairs (VA) data. The USRDS data will provide baseline demographics, transplant characteristics and graft outcomes, while the VA data will provide additional sociodemographics, medication use and clinical data, including laboratory values and vital signs. Thus, this compiled dataset will allow for the comprehensive assessment of CVD risk factor burden, management and control. Conducting this study will result in a better understanding of issues that contribute to racial disparities in kidney transplants recipients, particularly those related to CVD risk factors.

Specific Aim. Using a 10-year retrospective cohort of national VA and USRDS data, examine the prevalence of CVD risk factors, rates of CVD risk factor control and the impact of CVD risk factor control on graft survival after the first year post-transplant and AA disparities in kidney transplant recipients.

Hypothesis 1: AA kidney transplant recipients have a greater burden of CVD risk factors and poorer risk factor control, when compared to Caucasian recipients.

Hypothesis 2: In multivariable modeling, adjusting for CVD risk factor control significantly diminishes the impact of AA race as a risk factor for late (≥1 year) graft loss.

SIGNIFICANCE

AAs have a high prevalence of chronic kidney disease (CKD) and end stage renal disease (ESRD). AAs are at substantially higher risk of developing advanced CKD and ESRD, as compared to Caucasians; a disparity that has not significantly changed for more than 50 years.[32] The predicted lifetime prevalence of stage 4 CKD is 15.8% for AA men and 18.5% for AA women; this compares to 9.3% and 11.4% for non-Hispanic White (NHW) men and NHW women, respectively. AAs have more than a 60% higher risk of developing at least stage 4 CKD during their lifetimes. The risk disparities for developing ESRD in AAs are even more profound. The lifetime prevalence of ESRD in AAs is 8.5% for men and 7.8% for women. These rates are nearly three times higher, as compared to those seen in NHWs (3.3% in NHW men and 2.2% in NHW women).[32,38] As this represents one of the largest known racial disparities within a defined chronic disease state, there have been considerable research efforts focusing on its etiologies, yet the magnitude of this difference has not significantly changed.[39]

Kidney transplantation is a life-prolonging procedure that substantially improves quality of life in those with ESRD.[40-43] A recent analysis of the United Network for Organ Sharing (UNOS) database demonstrated that over the past 25 years, kidney transplantation has led to an estimated 1.37 million life-years saved, when compared to patients remaining on the waiting list. The median survival time was 12.4 years in those that received a kidney transplant, as compared to 5.4 years in those remaining on dialysis.[42] However, because kidney graft survival is significantly shorter in AA recipients and graft function is correlated with mortality, this survival advantage is substantially lower in AA recipients.[44] AA kidney transplant recipients have significantly higher rates of acute rejection and graft loss. Based on recent Scientific Registry of Transplant Recipients (SRTR) data, AA recipients have a 42% higher risk of graft loss at five years post-transplant. Thus, the average kidney transplant functions just over half as long in an AA patient.[1] Despite over 30 years of focused research endeavors into this disparity, little has changed in this racial inequality. In a 1977 landmark analysis exposing this disparity, Opelz et al demonstrated a 10% absolute difference in three-year graft survival rates between AA and Caucasian recipients (25% vs. 35%, $p<0.001$).[45] Thirty-five years later, these racial

differences are stubbornly similar; in the 2012 SRTR annual report, the graft survival inequity between AA and non-AA recipients was 12% at five years post-transplant.[1]

Supplemental Figure 1 displays the Kaplan Meier curves for death censored graft survival in adult U.S. kidney recipients transplanted between October 1, 1987 and September 30, 2014, stratified by donor type (living or deceased) and compared between Caucasians and AAs. This analysis includes 337,236 kidney transplants, of which 220,676 (65%) were from deceased donors and 80,854 (24%) were AA recipients. In living donors, the 1, 5, 10 and 25 year death censored graft survival rates in Caucasians were 97%, 89%, 77% and 42%; in AAs these were 96%, 79%, 60% and 24%. Thus, at 25 years post-transplant, AA had 75% higher risk of graft loss ($p<0.0001$). This difference is even larger for deceased donor recipients, with the 1, 5, 10 and 25 year death censored graft survival rates in Caucasians being 92%, 82%, 67% and 33%; this compares to rates of 91%, 71%, 50% and 17% in AAs. Thus, AAs have 94% higher risk of graft loss, as compared to Caucasians at 25 years post-transplant ($p<0.0001$). This racial disparity in kidney transplantation has primarily been attributed to biologic and immunologic differences leading to higher rejection rates,[46-49] lower socioeconomic status (SES),[18,19] reduced access to healthcare, medication non-adherence,[50,51] and comorbidities.[29,52,53]

Research focused on reducing the higher acute rejection rates in AA transplant recipients has been successful, yet the graft loss disparity persists. AA renal transplant recipients have disadvantageous immunologic characteristics placing them at higher risk for graft loss. These include more MHC polymorphisms,[3] pre-sensitization to MHC antigens,[54] greater HLA mismatches,[55] immune hyper-responsiveness,[6] and cytokine polymorphisms.[5,7] Therefore, most of the past research trying to eliminate outcome disparities in AA patients was focused on reducing acute rejection rates through immunosuppressant pharmacotherapy.[23,25] Despite decreases in acute rejection rates, the disparity in graft loss among AA recipients remain largely unchanged.

Studies evaluating the influence of SES and medication adherence on racial disparities in kidney transplant recipients have produced conflicting results. Studies conducted in French[56] and Canadian[57] recipients demonstrate equal graft survival rates between AA and non-AA patients and suggested SES or lack of universal health care was the predominant factor for the racial disparities seen within the US. However, a pivotal trial comparing US AA kidney transplant patients in and outside the VA system demonstrated poorer graft survival in all AA patients and suggested universal healthcare access did not reduce this disparity.[58] It is interesting to note that both the French and Canadian studies had low rates of diabetes (7-19%) and hypertension (20-22%) within the AA patients, while the VA study had significantly higher rates of both (28% and 84%, respectively). Similar contradictions in results are noted for medication non-adherence (MNA); several studies have demonstrated that MNA is an important factor for racial disparities,[19,59] while other analyses have found the opposite.[22,60]

A potentially important factor impacting racial disparities in kidney transplant outcomes is CVD and CVD risk factors. In the general population, it is well-established that AAs have a significantly higher prevalence of diabetes and hypertension, which occurs at an earlier age and is more progressive, leading to end-organ damage, including ESRD and stroke.[61-66] Yet studies assessing the impact of CVD and CVD risk factors control on racial disparities in transplantation is quite limited.[36,37] Because of this discrepancy in evidence, addressing this area of research is likely to provide a good opportunity to assess modifiable factors that may influence racial disparities in transplant.

PREVIOUS LITERATURE

As racial disparities in kidney transplant have persisted for nearly 50 years, numerous researchers have investigated potential causes of this issue, focusing efforts on a wide array of domains.[1,45] The following sections will review the previous literature within each of these domains attempting to explain the predominant factors contributing to racial disparities; these include biologic factors, socioeconomics, access issues, behavioral factors and finally comorbidities, focusing on the prevailing CVD risk factors.

Biologic Factors

There are a number of well-known biologic differences identified in AAs that may be disadvantageous to optimal long-term graft survival. These are primarily genetic variants that are either inherently associated with a higher proclivity to develop ESRD, alter pharmacokinetic properties of the immunosuppressant medications or induce immunologic risk. One fairly recent gene variant discovery that encodes for the apolipoprotein L1 (APOL1) protein only exists in AAs and may have a profound impact on the risk of developing non-diabetic ESRD and post-transplant graft failure. APOL1 is the minor apoprotein component of high-density lipoprotein (HDL), and is found in vascular endothelium, liver, heart, lung, placenta, podocytes, proximal tubules, arterial cells and has a secreted form that circulates in the blood. Two gene variants of APOL1 (G1 and G2) have been identified in AAs. Individuals with at least one of these gene variants are protected against infection from *Trypanosoma brucei*, a common infection encountered in West Africa; while those with at least two copies of either variant are at a significantly higher risk of developing ESRD.[67-69] Recent studies suggest that donor organs from AAs with at least two of these gene variants have substantially diminished graft survival.[4,70] As AA recipients are more likely to receive kidneys from AA donors, it is likely that this gene variant contributes to racial disparities in transplantation.[1]

The cornerstone of maintenance immunosuppression in transplantation is the use of the calcineurin inhibitors (CNIs). These agents have led to revolutionary reductions in acute rejection and improved graft survival, yet are not without significant limitations.[71,72] One of these is the fact that the CNIs have very complex

pharmacokinetic properties, including high intra and inter-patient variability. The CNIs are cleared from the body via metabolism through the cytochrome P450 (CYP) 3A iso-enzyme system, which is highly expressed in enterocytes and hepatocytes. One gene variant within this system, CYP 3A5*1, leads to phenotypical expression of a rapid metabolic state, thus requiring substantially higher doses of the CNIs to produce therapeutic blood concentrations.[73,74] It is well-established that AAs are substantially more likely to carry this CYP 3A5*1 gene variant, with a prevalence of 60-70%, as compared to a rate of 5-18% in Caucasians. Thus, under-exposure to the CNIs, as a function of rapid metabolism, is likely a contributor to the higher acute rejection rates in AAs, which is a major risk factor for graft loss.[75-77]

AAs are more likely to have major histocompatibility (MHC) polymorphisms that increase the risk of allorecognition leading to acute rejection and graft loss. MHC, also called the human leukocyte antigens (HLA) in humans, is the primary method to match organ transplants, beyond blood-typing. It is well recognized that genetic differences in MHC expression within AAs leads to higher numbers of mismatches with donor organs, a well-known risk factor for acute rejection and graft loss.[3] AAs also demonstrate a greater proclivity to be sensitized to MHC antigens, measured in transplantation through the panel reactive antibody (PRA) levels. This is likely due to the more vigorous immunologic response AAs have towards blood transfusions and other HLA exposure. PRA is a well-known risk factor for acute allograft rejection and this issue likely contributes to racial disparities in graft outcomes for AA recipients.[5-7]

A number of polymorphisms related to immune responsiveness have also been linked to AA disparities in transplantation. Hutchings et al demonstrated that AAs were significantly more likely to express high levels of costimulatory molecules which are crucial for T-lymphocyte activation.[5] McDaniels et al found that cytokine gene variants led to higher expression of cytokines in AA renal transplant recipients. Finally, AAs are known to demonstrate a more aggressive mixed lymphocyte response leading to more lymphocyte proliferation. As it is well established that acute rejection is more common in AAs, these genetic differences that lead to hyperimmune responses are clinically relevant and likely contribute to this graft survival disparity. It is clear

that intense immunosuppression, in a dose-dependent fashion, reduces the risk of acute rejection particularly within AA recipients; however, these short-term improvements in outcomes have not translated into long-term graft survival equity. Thus, other variables are likely significant factors involved in this disparity.[6,7]

Socioeconomic factors

The long and turbulent history of the social, cultural and economic oppression of AAs in the U.S. has led to a significant gap with regards to SES status.[78] Yet, the influence of SES differences on racial disparities in kidney transplantation has not been consistently demonstrated in research studies and it is not fully clear how or if these socioeconomic factors directly lead to detrimental outcomes. There are a number of studies that have demonstrated that SES significantly impacts AA more so than Caucasians. Golfarb-Rumyantzev et al utilized the USRDS registry to determine the influence of baseline education, citizenship, and insurance on post-transplant outcomes across race. The authors demonstrated that education and insurance were significant predictors of graft loss and patient death, with the magnitude of the association being stronger in AA recipients.[79] Butkus et al demonstrated that graft loss due to immunologic etiologies was most prominent in young AA recipients, which was also more common in those with lower education levels and non-adherence to transplant medications. Non-immunologic graft loss was not significantly associated with SES factors. In multivariable analysis, non-adherence was the strongest risk factor for immunologic graft loss, which was associated with pre-transplant substance abuse.[80] In a longitudinal analysis our research group recently published, we demonstrated that high SES indicators, measured through the social adaptability index (SAI), are strongly predictive of acute rejection and graft loss only in AA kidney transplant recipients. The SAI includes five SES factors, including education, income (insurance), substance abuse, employment and marital status. The SAI, neither at baseline nor follow-up was significantly predictive of outcomes in non-AA patients.[81]

However, there is also research to suggest that SES may not be as influential on racial disparities as these previous studies suggest. Chakkera et al conducted an analysis of the influence of race on kidney transplant outcomes, comparing these within and outside the Department of Veteran Affairs. Using multivariable analyses, the authors demonstrated that AAs were at increased risk of graft failure, compared to non-AAs (RR

1.31, 1.26-1.36), which was similar for veterans (1.31 1.11-1.54) and non-veterans (RR 1.31, 1/26-1.36). The authors concluded that racial disparities persist even after universal access to care is provided, suggesting the SES factors may not be as important as previous literature suggests.[58] Contrary to this finding, analyses from French[56] and Canadian[57] researchers demonstrate equivalent outcomes in Black versus non-Black kidney transplant recipients. These authors suggest that universal access to care and similar SES among patients likely account for these outcomes, as compared to the disparities demonstrated within the U.S. population. Thus, the impact of SES on racial disparities in transplant has been demonstrated in numerous studies, but there is also conflicting data that clouds this picture.

Access issues

Access, both to evaluation for transplant and to deceased and living donors, is a major issue affecting racial disparities in kidney transplant. As such, it has been extensively studied and discussed in the biomedical literature. As of 2012, AA represents approximately 38% of the US dialysis population, 32% of the waiting list and 25% of those who underwent kidney transplant.[32] Thus, AAs with ESRD are significantly less likely to be referred for evaluation, be listed or receive a kidney transplant. Johansen et al conducted an analysis of the USRDS, which included 426,489 patients beginning dialysis between Jan 2005 and Sept 2009. At all ages, AA were 5% more likely not to be assessed for transplant (RR 1.05, 1.02-1.07), which was most pronounced in those under 35 years of age (RR 1.27, 1.13-1.43). In multivariable modelling AA race was associated with a 29% lower likelihood of not be listed for transplant (RR 0.71, 0.69-0.73) and a 39% lower likelihood of not receiving a kidney transplant within 4 years of initiating dialysis (RR 0.61, 0.53-0.70).[82] Patzer et al, in a more recent analysis, conducted a study by linking individual patient's medical records with the USRDS and American Community Survey Census data to assess the role of race and poverty on steps towards kidney transplant. Among the 2,291 patients referred for transplant, 48.5% of AAs did not start the evaluation process (Caucasian 39.4%, $p<0.0001$) and were 2.5 times more likely to have incomplete evaluation requirements (45.7% AA vs. 17.9% Caucasian, $p<0.0001$). Interestingly, in multivariable models, demographic and clinical factors explained 20.8% of the reduced transplant rates among AAs versus Caucasians, while neighborhood SES factors explained an additional 30.6%. Yet, within all multivariable models which were adjusted for clinical, demographic and SES factors, AA race continued to be a significant independent risk factor for time

from ESRD start to referral (HR 0.70, 0.61-0.80), time from referral to evaluation start (HR 0.72, 0.63-0.83), time from wait listing to transplant (HR 0.62, 0.42-0.91) and time from ESRD start to receipt of a transplant (HR 0.41, 0.28-0.58).[83] These data provide clear and consistent results that demonstrate AAs are at a significant disadvantage for receiving access to kidney transplantation, which is only partially explained by demographics, clinical variables and SES factors. This has important implications post-transplant, as time on dialysis is a major risk factor for deleterious outcomes post-transplant.[17]

AAs are also significantly less likely to identify and receive living donor transplants. As the advantages for living donor kidney transplant recipients are profound, this issue has enormous implications on racial disparities in transplantation. As Figure 1 demonstrates, median graft survival rates are 1.5 times higher in living, as compared to deceased donors (16-18 years vs 10-12 years). Yet, it should also be pointed out that the magnitude of racial disparities is similar in both donor types. AA have a living donor kidney transplant rate of 0.4 per 100 dialysis patients, which compares to rates of 1.8 in Caucasians, 2.1 in Asians and 2.0 in other races.[32] There have been numerous studies focused on the etiology of this issue, with results suggesting that it is due to a complicated myriad of factors, including SES factors (education, income, health insurance), medical factors (comorbid conditions in potential donors), provider factors (physician biases pertaining to race and religion) and cultural issues (reluctance to burden family members and friends).[84] Currently, there are ongoing efforts to increase the rate of living donor kidney transplantation in AAs, with the predominant interventions focused on culturally-sensitive education strategies, aimed at the recipients, their families and support networks, as well as the AA community at large.[85-87] Although increasing living donation in AA patients is an important step towards improving outcomes, it is clear that this alone with not significantly abrogate racial disparities in transplantation.

Behavioral factors

Nonadherence, either to prescribed medications, lifestyle recommendations or follow up care appointments is a major issue implicated with poor outcomes following kidney transplant. Nonadherence to medications in transplant recipients is estimated to occur at a rate of 18-65%, depending on how it was measured and organ

type. Medication nonadherence has received more attention recently, as a number of publications demonstrate that this behavior is attributed to late graft loss in a substantial proportion of cases. There are also other types of nonadherence that may impact transplant outcomes, although the data supporting this is quite nebulous.[51,88-90]

A meta-analysis conducted by Dew et al provides the best estimates of nonadherence rates across a wide array of behaviors. This analysis reported that nonadherence was common in transplant recipients, particularly for medications, following diet or exercise recommendations and keeping clinic or blood work appointments. Substance abuse to tobacco, alcohol and illicit substances was estimated to be low, ranging from 0.9 to 3.6 cases per 100 patients per year. Nonadherence to following exercise and diet recommendations was estimated to be 19.1 and 25.0 cases per 100 patients per year, while nonadherence to follow up blood work and clinic appointments was reported at 12.0 and 5.8 cases per 100 patients per year. Finally, nonadherence to medications was estimated to be 22.6 cases per 100 patients per year. The impact of race on nonadherence was also assessed in this meta-analysis. AA race was a significant risk factor for medication nonadherence (Effect size 0.06, 95% CI 0.01 to 0.12). However, race did not impact other nonadherence behaviors, including missing appointments, diet, exercise or substance abuse.[91] Contrary to these findings, Baum et al conducted an assessment of 506 kidney transplant recipient transplanted between 1983 and 1998 and demonstrated that AA race was a significant risk factor for weight gain at 12 months post-transplant (β 11.5, $p<0.001$) and AAs were more likely to die of CV disease. Since weight gain is likely directly related to nonadherence to diet and exercise recommendations, these results suggest AAs may be at higher risk for this behavior.[92] Thus, conflicting evidence supporting the influence of nonadherent behaviors on racial disparities suggests that other factors are likely more important contributors to this issue.

CVD and CVD risk factor control

At the time of transplant, AA kidney recipients have a substantially higher prevalence of diabetes[30,31] and hypertension[29,32] compared to non-AA recipients. Data from the general population demonstrate that both hypertension and diabetes occur at an earlier age, are of a more aggressive phenotype and more likely to lead

to end-organ damage in AA patients.[61-63,65] Death due to CVD is the leading cause of graft loss,[26-28] but data examining the impact of CVD death on racial disparities is limited. There are conflicting studies, with some demonstrating higher rates of CVD events and death within AA kidney transplant recipients,[92,93] while other studies have contradicting results.[94,95] Analysis of data from the USRDS demonstrates that AA patients are less likely to die as compared to Caucasian patients while receiving dialysis; however, following transplant, this survival advantage is mostly eliminated.[32,96] An analysis identifying the specific etiologies of graft loss through biopsy results demonstrate that glomerular pathologies (including diabetic glomerulonephropathy) are the leading cause of graft loss; the second most common histology was fibrosis/atrophy, which, coupled with glomerular nephropathy, are classic lesions associated with hypertension in non-transplant AA patients. However less than 10% of this study population was AA patients; therefore, racial comparisons could not be conducted.[97] This data, taken in its entirety, suggests that CVD and predominant CVD risk factors, especially diabetes and hypertension, are likely important factors leading to higher rates of graft loss in AA transplant recipients.

Globally, there is a lack of data analyzing the influence of CVD risk factor control on graft survival disparities in AA transplant recipients. Studies in the general population indicate that there is suboptimal CVD risk factor control in AA patients, leading to higher rates of renal failure and CV events.[62,98] However, with the exception of hypertension[29,99] and data from our own transplant center,[36,37] there is paucity in data demonstrating similar results within transplant recipients. Cosio et al conducted a single-center retrospective analysis, which included 547 recipients of deceased donor kidney transplants. The results demonstrated that the mean arterial pressure (MAP) at 6-months post-transplant was higher in AAs compared to Caucasians (105±8 vs. 102±7 mmHg, p=0.002). Furthermore, increasing MAPs were significantly correlated with shorter graft survival in AAs (p=0.0002), which was not demonstrated in Caucasians (p=0.84). Allograft survival was eight times shorter in AAs with elevated MAPs, as compared to Caucasians with elevated MAPs (3.1±0.7 vs 24.6±7 years).[29] Scantlebury et al conducted a retrospective study of 361 kidney transplant recipients from 1987 to 1992, demonstrating that the mean number of anti-hypertensive medications used was significantly higher in AAs versus non-AAs (2.2±0.9 vs. 1.9±1.0).[99] Our research group conducted a single-center retrospective study,

which included 1,003 adult kidney transplant recipients from 2000 to 2008. Congruent to the findings from previous studies conducted in the general population, AAs had a significantly higher prevalence of diabetes and hypertension and reduced diabetes control post-transplant (AA 74% vs. non-AA 82%, p=0.053). After adjusting for CV events and CVD risk factor control, race was no longer an independent risk factor for graft loss (HR 1.48 (1.06-2.08) vs. 1.12 (0.79-1.58).[36]

Our research group has also demonstrated that diabetes, in and of itself, impacts racial disparities as well. In a study including 987 adult kidney transplant recipients, including diabetes as a factor in multivariable modeling reduced the impact of race on the outcome of graft survival by 19%; including diabetes control, using hemoglobin A1C, further reduced the impact of race on this outcome by 28%, demonstrating both the prevalence and control of diabetes attenuates the independent influence of race on graft survival. This suggests that diabetes is likely to be an important factor in this relationship.[100] Finally, using the same dataset, our research group examined the use of CVD medications based on race. For the treatment of hypertension, AA patients were significantly more likely to be prescribed vasodilators, clonidine, and calcium channel blockers, but equally likely to receive ACE inhibitors/ARBs and beta-blockers. AAs were also less likely to receive non-statin based anti-lipemics. These differences in prescribing patterns of relevant CVD medications may have an influence on racial disparities, but further research is needed to explore these associations.[37]

Thus, this research plan is novel and significant, as it will be the first large-scale study using a national cohort to determine the prevalence and rate of control of CVD risk factors in adult renal transplant recipients and compare these across race. It will also be the first to assess the impact of CVD medication prescribing differences between AA and Caucasian transplant recipients and whether this has an impact on graft outcomes.

ORIGINAL MANUSCRIPT

INTRODUCTION

Kidney transplantation is a life-prolonging procedure that substantially improves quality of life in those with end stage renal disease (ESRD).[41-43] A recent analysis of the United Network for Organ Sharing (UNOS) registry demonstrated that over the past 25 years, kidney transplantation has led to an estimated 1.37 million life-years saved, when compared to patients remaining on the waiting list. The median survival time was 12.4 years in those that received a kidney transplant, as compared to 5.4 years in those remaining on the list.[42] However, because kidney graft survival is significantly shorter in African-American (AA) recipients and graft function is highly correlated with mortality, this survival advantage is likely substantially lower in AA recipients.[44] AA kidney transplant recipients have significantly higher rates of acute rejection and graft loss. Based on recent Scientific Registry of Transplant Recipients (SRTR) data, AA recipients have a 42% higher risk of graft loss at five years post-transplant. Thus, the average kidney transplant functions just over half as long in an AA patient.[1] Despite over 30 years of focused research endeavors into this disparity, little has changed in this racial inequality. In a 1977 landmark analysis exposing this disparity, Opelz et al demonstrated a 10% absolute difference in three-year graft survival rates between AA and Caucasian recipients (25% vs. 35%, $p<0.001$).[45] Thirty-five years later, these racial differences are quite similar; in the 2012 SRTR annual report, the graft survival inequity between AA and non-AA recipients was 12% at five years post-transplant.[1]

This racial disparity in kidney transplantation has primarily been attributed to biologic and immunologic differences leading to higher rejection rates,[46-49] socioeconomic status (SES) disadvantages,[18,19] reduced access to healthcare, medication non-adherence,[50,51] and comorbidities.[29,52,53] Research focused on reducing the higher acute rejection rates in AA transplant recipients has been successful, yet graft loss disparities persist. AA renal transplant recipients have disadvantageous immunologic characteristics placing them at higher risk for graft loss. These include more MHC polymorphisms,[3] pre-sensitization to MHC antigens,[54] greater HLA mismatches,[55] immune hyper-responsiveness,[6] and cytokine polymorphisms.[5,7] Therefore, most of the past research trying to eliminate outcome disparities in AA patients was focused on reducing acute rejection rates through immunosuppressant pharmacotherapy.[23,25]

Studies evaluating the influence of SES and medication adherence on racial disparities in kidney transplant recipients have produced conflicting results. Studies conducted in French[56] and Canadian[57] recipients demonstrate equal graft survival rates between patients of African and non-African ancestry and suggested SES or lack of universal health care was the predominant factor for the racial disparities seen within the US. However, a pivotal trial comparing US AA kidney transplant patients in and outside the VA system demonstrated poorer graft survival in all AA patients and suggested universal healthcare access did not reduce this disparity.[58] It is interesting to note that both the French and Canadian studies had low rates of diabetes (7-19%) and hypertension (20-22%) within the AA patients, while the VA study had significantly higher rates of both (28% and 84%, respectively). Similar contradictions in results are noted for medication non-adherence (MNA); several studies have demonstrated that MNA is an important factor for racial disparities,[19,59] while other analyses have found the opposite.[22,60]

A potentially important but under-studied factor impacting racial disparities in kidney transplant outcomes is cardiovascular disease (CVD) and CVD risk factors. In the general population, it is well-established that AAs have a significantly higher prevalence of diabetes and hypertension, which occurs at an earlier age and is more progressive, leading to end-organ damage, including ESRD and stroke.[61-66] Yet studies assessing the impact of CVD and CVD risk factors control on racial disparities in transplantation is quite limited.[36,37] Because of this discrepancy in evidence, addressing this area of potential risk is likely to provide a strong opportunities to assess modifiable factors that may influence racial disparities in transplant. Thus, the objective of this study was to assess the burden of CVD risk factors and risk control in AA renal transplants and determine the influence of CVD risk factors on racial disparities for post-transplant outcomes.

METHODS

Study Design and Patients

This was a longitudinal cohort study of national data obtained through developing a unique dataset by linking the United States Renal Data System (USRDS) and Veterans Affairs (VA) electronic health records. The study population included veteran recipients of solitary kidney transplant recipients, transplanted between January 1, 2001 and December 31, 2007 (7 years) with longitudinal follow up through December 31, 2010. Pediatrics, non-renal transplant recipients, those that were not NHW or NHB, transplant events that occurred outside the study time frame and those with graft loss or follow up <1 year were excluded. After local IRB, VA HSR&D and USRDS approval, the VA system was queried for eligible kidney transplant recipients using ICD-9 codes (V42.0 or 996.81) without a history of a liver, heart, lung, pancreas or intestine transplant. This list of patients was merged with USRDS data through scrambled social security numbers to create the study cohort which contained detailed baseline and clinical follow up data. Further details regarding the study design and data sources to create this cohort have previously been published.[101]

Outcome Measures

The primary outcome for this analysis was death-censored graft loss (DCGL). This was defined as either a return to chronic dialysis or retransplantation. For this outcome, death was not included as an event and patients were censored at this time point. The outcome was assessed as a time to event analyses, with the reference time being the date of transplant and the end time being the date of either graft loss (event), death (censored) or the end of the study period (censored). Secondary outcome measures included death and overall graft loss, which was a composite event of either DCGL or death.

Exposure Measurements

There were two primary exposures for this study, race and CVD risk factors and risk control. The study cohort was restricted to two racial groups, NHWs and NHBs. Race information was gathered from the USRDS dataset and cross-validated with the VA vital records data. CVD risk factors and control was focused on the three predominant risks: hypertension, diabetes and dyslipidemia. Hypertension was defined as a blood

pressure of greater than 140/90 mmHg or the use of anti-hypertensive medications. Diabetes was defined as a hemoglobin A1c of >7% or use of anti-glycemic therapy. Dyslipidemia was defined as a LDL of >130 mg/dL, triglyceride level of >150 mg/dL or use of anti-lipemic therapy.

CVD risk factor control assessment was defined as follows: diabetes control was classified as a mean follow up A1c of ≥8% (referent group) vs. <8% (we also assessed A1c of ≥7% vs. <7% as well). Hypertension control was classified as a mean follow up BP ≥140/90 (referent group) vs BP <140/90 mmHg. For lipid control, patients were classified as a mean follow up LDL ≥100 or TG ≥150 (referent group), vs. LDL<100 and TG <150 mg/dL. Medications to treat CVD comorbidities were grouped according to class and patients were categorized based on the prescribing of this agent (yes vs no) and their adherence to the therapy (medication possession ratio [MPR] ≥80% vs <80%). Medications were groups as follows: oral anti-hyperglycemic agents, insulin, HMG CoA reductase inhibitors (statins), other anti-lipid therapy, beta blockers, angiotensin converting enzyme inhibitors [ACE inh] or angiotensin receptor blockers [ARBs], calcium channel blockers (CCBs), diuretics and anti-platelet therapies.

Additional covariates that were included in multivariable models included recipient sociodemographics (age, gender and marital status), recipient comorbidities (history of CAD/angina, previous transplant and years on dialysis), donor characteristics (living donor, expanded criteria donor [ECD] and donor after cardiac death [DCD]), immunologic characteristics (HLA mismatches, current panel reactive antibody level [PRA]), baseline immunosuppression (induction therapy, calcineurin inhibitors, adjunctive agents and corticosteroids) and post-transplant events (delayed graft function [DGF] and acute rejection).

Statistical Analysis

The initial univariate analyses compared baseline variables and clinical outcomes by race (NHBs vs NHWs), assessed the baseline and follow up prevalence and control of hypertension, diabetes and dyslidemia and determined CVD medication use and adherence using the chi square test, the Student's t-test or Mann

Whitney U test, depending on data type and normality assumptions. Multivariable modeling was performed using Cox proportional hazard regression, using the Fine and Gray competing risk model for DCGL to estimate the cumulative incidence function (CIF) and standard Cox models to estimate the survival function for death and overall graft loss.[102] Model assumptions of proportionality of hazard over time and linearity in the logit were first tested and confirmed, followed by residual assessments to ensure we used the most appropriate data fit and to identify any potential outliers or influential observations. Moderators were assessed through interaction terms with race.

Sequential forward entry of blocks of variables were added to the model and at each step the overall impact of NHB race on the outcome was assessed by comparing the change in β to the previous model. The Akaike information criterion (AIC) was used to assess and compare models as the goodness of fit measure. Large decreases in the AIC after the addition of a block of variables suggested strong influence of that block on explaining the variability associated with the outcome. Covariance between repeated transplants in the same individual was accounted for during modelling to prevent under-estimating variance. Sensitivity analyses were conducted to ensure the robustness of the estimates, which included standard Cox regression vs. competing risk modeling, varying the entry of variable blocks during sequential modelling, using multiple imputation for missing data and using longitudinal analyses through joint modelling to first estimate individual-level random intercepts and slopes for A1c, BP and lipid levels, followed by entry of these estimates in Cox models. All data analyses were conducted using SAS (version 9.4, SAS Institute Inc, Cary, NC). Statistical significance was defined using two-sided tests with α set at 0.05.

RESULTS

There were 5,757 kidney transplants performed between Jan 1, 2001 and Dec 31, 2007 that met inclusion criteria and were capable of being linked between the VA and USRDS databases. Of these, 382 were excluded for being Hispanic, 112 were excluded for being Asian or other races, 345 were excluded for receiving a transplant outside the time period and 275 for excluded for having graft loss or follow up <1 year post-transplant, leaving 4,643 eligible for inclusion. Of these, 1,504 were missing data for at least one variable, leaving 3,139 cases with complete data, which included NHWs (66.5%) and NHBs (33.5%, see Figure 1 for the study flowchart). Baseline sociodemographics, donor criteria and transplant characteristics are summarized and compared between NHWs vs. NHBs in Table 1. At the time of transplant, NHBs were significantly younger (59.5±10.0 vs. 57.5±10.4 years), less likely to be married (57.3% vs. 68.4%), had differences in the level of education (finished high school and attended college), differences in the primary cause of ESRD (hypertension, diabetes, and FSGS) and pre-transplant comorbidities (coronary artery disease, hypertension and previous transplant). There were also significant differences between NHBs and NHWs for donor criteria (age, gender, race, less living donors and more donors after cardiac death), immunologic risks (more HLA mismatches, longer cold ischemic times), baseline immunosuppression and post-transplant outcomes; particularly death censored graft loss (NHBs 14.7% vs. NHWs 8.0%), acute rejection (NHBs 14.8% vs. NHWs 11.4%) and delayed graft function (NHBs 24.0% vs. NHWs 11.7%).

The prevalence and control of CVD risk factors at baseline and at 1, 3 and 5 years post-transplant significantly differed by race (see Table 2). At baseline, NHBs had a higher prevalence of hypertension (96.4% vs. 92.3%) and lower prevalence of dyslipidemia (40.7% vs. 46.4%). During post-transplant follow-up, the prevalence of hypertension remained significantly higher in NHBs at 1, 3 and 5 years, while the prevalence of diabetes significantly increased in NHBs, as compared to NHWs. Dyslipidemia prevalence substantially increased in both groups, but always remained higher in NHWs until 5 years post-transplant. The baseline and post-transplant control of hypertension, diabetes and LDL was significantly better in NHWs vs. NHBs at most time points. The use of medication classes to treat CVD risk factors and adherence to these medications also

differed by race. NHBs were more likely to be prescribed anti-hypertensive therapy but, in general, had lower rates of adherence to these therapies. This was also demonstrated for post-transplant insulin therapy. Post-transplant statin prescribing was similar, but adherence to this therapy was lower in NHBs. Supplemental Figures 2 and 3 display the data from Table 2 in chart form.

The fully adjusted model for the primary outcome of DCGL is displayed in Table 3, demonstrating that after adjusting for all baseline and follow up variables, including CVD risk and control, NHB race continued to be a significant risk factor for DCGL (aHR 1.490, 1.11-1.99, p=0.0072). The fully adjusted model reduced the risk associated with NHB race by 26%. Beyond race, there were seven variables that were significant independent predictors of DCGL. This included receiving an expanded criteria donor kidney (aHR 1.387, 1.01-1.91, p=0.0455), receiving and being adherent to ACE inh/ARB therapy (aHR 0.446, 0.29-0.68, p=0.0002), being non-adherent to diuretic therapy (aHR 1.956, 1.49-2.57, p<0.0001), being non-adherent to insulin therapy (aHR 1.585, 1.02-2.47, p=0.0414), receiving and being adherent to statin therapy (aHR 0.534, 0.36-0.80, p=0.0022), uncontrolled hypertension (aHR 1.636, 1.29-2.07, p<0.0001) and developing acute allograft rejection (AHR 1.914, 1.46-2.51, p<0.0001).

Table 4 summarizes the results for the sequential modelling for the primary outcome of DCGL with varied entry of the blocks of variables through iterative processes. The results demonstrate that donor characteristics (-13.4 to -4.2%), immunologic risks (-9.6 to -4.7%), CVD risks and control (-17.5 to -8.7%), and post-transplant events (-5.5 to -0.7%) had the largest impact on reducing the independent risks associated of NHB race on DCGL. CVD risk factors and risk control produced the largest reduction in the model AIC, suggesting that including these variables in the model substantially improved the model performance in capturing the variability associated with DCGL and enhancing model goodness of fit. Figure 2 displays the cumulative incidence estimates for DCGL, comparing these curves between NHBs vs. NHWs for the unadjusted model (Figure 2A) and the fully adjusted model (Figure 2B). After full adjustment, the estimated incidence curves significantly converge, demonstrated a reduction in the independent risk associated with NHB race on DCGL.

The results for the secondary outcomes of overall graft loss and mortality are displayed in supplemental Tables 1 and 2 (full models), supplemental Tables 3 and 4 (sequential modeling) and supplemental Figures 4 and 5 (unadjusted and fully adjusted survival estimates). After full adjustment, NHB race was not a significant risk factor for overall graft loss (aHR 1.041, 0.86-1.26, p=0.6775). Mycophenolate therapy, adherence to medications used to treat CVD risk factors, uncontrolled hypertension and acute rejection were all independent predictors of overall graft loss (Supplemental Table 1). Sequential modeling demonstrated that sociodemographics (mainly age) was a significant suppressor, while donor characteristics, immunologic risks, CVD risk factors and control and post-transplant events were significant explanatory variables for racial disparities. CVD risk factors and control again reduced the model AIC to the greatest extent (Supplemental Table 3).

The full model for mortality demonstrated that NHB race was a significant protective factor for risk of post-transplant death (aHR 0.753, 0.60-0.94, p=0.0132). Additional independent predictors for death included marital status, living donor, mycophenolate therapy, mTOR therapy, adherence to CVD medications, the presence of diabetes and uncontrolled hypertension (Supplemental Table 2). Sequential modeling for death demonstrated that sociodemographics (mainly age) were a significant suppressor, while donor characteristics, immunologic risks and CVD risk factors and control were all significant explanatory variables. Similar to modeling for other outcomes, CVD risk factors and control produced the largest reduction in AIC, suggesting it explains a substantial portion of the variability associated with the risk of death after transplant.

Four sensitivity analyses were performed to ensure robustness of the estimates from the modelling. This included varied entry of blocks of variables into the sequential modelling, using standard Cox regression for the outcome of DCGL, modeling random and fixed effects for CVD risk factor control variables through joint modeling and using multiple imputation for missing data. The results of these analyses demonstrated

consistent estimates, trends and results. The full model for the outcome of DCGL with the imputed missing data (n=4,643) is displayed in Supplemental Table 5. Race continued to be an independent risk factor for DCGL and after adjustment, the reduction in risk for NHBs was similar to the analysis using cases with complete data (25.5% vs. 27.8%); in the imputed model, similar to the model using cases with complete data, CVD risk factors and CVD risk control had the largest impact on model performance and significantly reduced the independent influence of NHB race on graft loss.

DISCUSSION

The results of this study demonstrate that NHB transplant recipients have a considerably larger burden of CVD risk factors, which meaningfully contribute to racial disparities in post-transplant graft outcomes. Specifically, NHBs have a higher prevalence of hypertension and post-transplant diabetes with reduced control of hypertension, diabetes and LDL, when compared to NHWs. In addition, adherence to medications used to manage CVD risk factors appears to be significantly lower in NHBs, as compared to NHWs. These data provide novel information to demonstrate that focusing on improving the management of CVD risk factors within kidney transplant recipients offers a promising mechanism to both enhance graft outcomes for the entire population while also potentially impacting racial disparities. To our knowledge, this is the first study to comprehensively assess CVD risk factors and risk control in a large national cohort of contemporary U.S. kidney transplant recipients and specifically assess the impact of these on racial disparities.

Racial disparities for outcomes in kidney transplant recipients have been long-standing and well-documented, with the literature exposing this issue dating back to the late 1970s, when kidney transplantation was still considered an experimental procedure. Recent evidence suggests that over the past 20 years, the absolute disparity in graft survival has improved. Yet, in relative terms, NHBs are still at substantially higher risk of late graft loss (5 year relative risk of graft loss is 2.2 in living donors and 1.8 in deceased donors, comparing NHBs to NHWs).[103] Some aspects that contribute to this disparity have been well-studied. It is clear that NHBs have unique immunologic characteristics that increase their risk of acute rejection and have socioeconomic disadvantages which create barriers to access to transplant, access to living donors and access to optimal post-transplant care.[19,104] Thus, to date, most of the interventions designed to reduce this disparity have focused on using potent immunosuppression to mitigate immunologic risk and improve access to deceased and living donor transplants.[25] There have been some documented successes in this capacity. Recent evidence suggests that acute rejection rate disparities in NHBs have been mostly resolved and access to deceased donor organ transplant is improving in NHBs. However, improving living donation rates within the NHB community has been an area of marginal regional success, with national data demonstrating reduced

rates of living donation within NHBs, when compared to NHWs.[103,105] Our results corroborate these previous findings, in that immunologic risks and donor characteristics continue to be significant explanatory variables for racial disparities.

There is paucity in the research assessing CVD risk factors and risk factor control as a potential cluster of explanatory factors for racial disparities in kidney transplant outcomes. This is despite the fact that these risks are decidedly mutable and that there is strong evidence to suggest these issues drive disparate outcomes in the general non-transplant population with diabetes and hypertension.[106,107] Previous work from our research group has demonstrated similar results within a single transplant center, and the data from this analysis further support these findings.[37,108] Hypertension, diabetes and LDL have significantly lower rates of control post-transplant in NHBs, as compared to NHWs. This is despite the increased use of anti-hypertensives and insulin in NHBs. The higher rates of medication non-adherence in these patients may likely contribute to this issue, and represents an opportunity for future interventions designed to improve CVD risk factor control in NHBs. It is interesting to note that our study only included veterans obtaining medications through the VA system. Thus, the issues surrounding access and cost of medications should not be a significant factor leading to medication non-adherence in this population. Other factors, included regimen complexity, health literacy and self-efficacy may be producing the higher rates of non-adherence that were seen within NHBs in this study.[107]

The prescribing of two medication classes, ACE inh/ARBs and statins, demonstrated a substantial protective benefit for graft loss and death. In our study, only about 50-60% of the population was prescribed ACE inh/ARBs at five years post-transplant; and of these, only 40-50% were adherent (MPR ≥80%). For statins, about three-quarters were prescribed this therapy by five years and 40-60% were adherent. One could argue that due to the prevailing CVD and CVD risks that are highly correlated with CKD, these therapies should be prescribed to nearly all kidney transplant recipients that do not have absolute contraindications.[109] Yet, data from this study and other non-VA national and single-center studies of kidney transplant recipients demonstrate the utilization of these therapies is on the rise, but remains substantially below optimal levels.[34,35]

Given the body of evidence in the general non-transplant population and the inherent CVD risk within the kidney transplant population, these results provide evidence to support future interventional studies designed to optimize utilization and adherence to these therapies in kidney transplant recipients as a mechanism to improve long-term graft and patient outcomes.[34,35,109]

It is also noteworthy that non-adherence to a number of medication classes was a significant and independent risk-factor for both graft loss and death. This included diuretics, insulin, beta blockers, calcium channel blockers and anti-platelet therapy. This risk was independent of CVD disease and CVD risk factor control. These results may be a true cause and effect relationship, in that medication non-adherence to these therapies may actually lead to increased rates of graft loss and death, or could also be a proxy for other risks that are highly correlated to medication non-adherence and which were not measured as a part of this study.[110] In particular, these include social determinants of health (finances, living conditions, social support), health literacy and self-efficacy.[111] Thus, further research is needed to ascertain whether non-adherence to these medication classes truly causes increased rates of graft loss and death in kidney transplant recipients.

There are a number of limitations to this analysis that are worthy of discussion. First, this analysis was confined to a veteran transplant population and the number of female recipients is quite low. Thus, generalizability of these results to the female transplant recipients is limited. Using a veteran population also restricts the ability of this analysis to assess the impact of insurance coverage and access to care on outcomes. However, previous studies have demonstrated that racial disparities are similar in magnitude between VA and non-VA populations, and using VA data will allow us to include numerous clinical variables that are missing or not available from previous studies that solely utilized the USRDS or CMS datasets.[58] Therefore, for the purposes of this analysis, which focuses on racial disparities as it relates to CVD risk factor control, the benefits provided by the use of VA data greatly outweigh the limitations of solely focusing on veteran patients.

Another limitation of this analysis is its retrospective design, which may increase the risk for confounding and misclassification, potentially biasing the results. However, because we were able to link two databases with unique and overlapping data in a longitudinal format, we dramatically minimized these risks. We validated data elements by comparing them between the two databases for accuracy and were able to include the largest number of covariates ever reported in a transplant racial disparities analysis.[101] In addition, retrospectively accurately assessing control of CVD risk factors is a difficult endeavor, and using means during the entire follow up may not truly capture the time dependency of this exposure. However, using the means does allow for a more straightforward analysis and presentation of the data. To assess if longitudinal analyses improve the primary exposure classification, we also conducted a separate analysis, using a longitudinal data technique to assess for the fixed and random effects (intercept and trajectory) of the BP, A1c, LDL and TG on the outcomes.[112] The results of this assessment were similar with respect to direction and magnitude; thus, for ease of display and interpretation, we utilized the mean values, which appear to be an accurate reflection of CVD risk. Another limitation with this analysis is that we fail to measure and account for biologic and socioeconomic differences between NHB and NHW transplant recipients that may explain some of the disparity. This includes genetic variants that are more prevalent in NHB recipients, including cytochrome P450 3A5 and APOL1 and the aforementioned social determinants of health.[4,77,81,113] Although we recognize there are a number of limitations with using a veteran dataset, the overall objectives of this analysis require the use of detailed longitudinal clinical data that is currently unavailable within any other national dataset that we are aware of.

In conclusion, these results demonstrate that NHB kidney transplant recipients have significantly higher rates of CVD risk factors and reduced CVD risk control, as compared to NHWs. These issues may be partly related to medication non-adherence, meaningfully contribute to disparities for graft outcomes within NHBs and represent a promising area for future interventional studies designed to improve CVD risk factor control as a mechanism to optimize graft outcomes and reduce racial disparities in kidney transplantation.

Table 1 – Baseline and outcomes variables for the entire cohort and stratified by recipient race

Characteristics	Total Cases with Complete Data (n=3,139)	Non-Hispanic Whites (n=2,095)	Non-Hispanic Blacks (n=1,044)
Age (mean±SD)	57.5±10.4	59.5±10.0	53.6±10.1*
Male Gender	98.0%	98.2%	97.7%
Married	64.6%	68.4%	57.3%*
Education, n=2,660			
Less than high school	1.6%	2.1%	0.6%*
High school	47.0%	46.7%	47.6%
Attended college/technical school	29.8%	28.3%	32.9%*
Received associate/bachelor degree	16.5%	17.5%	14.5%
Attended graduate school	5.1%	5.4%	4.5%
Primary Cause of ESRD			
Hypertension	26.8%	18.5%	43.4%*
Diabetes	29.0%	30.2%	26.4%*
Focal Segmental Glomerulosclerosis	6.7%	5.3%	9.6%*
Any type of Glomerulonephritis	13.2%	12.6%	14.6%
Comorbidities			
Angina or Coronary Artery Disease	13.0%	15.3%	8.5%*
Hypertension	93.7%	92.3%	96.4%*
Diabetes	38.5%	38.4%	38.8%
Previous Kidney Transplant	3.4%	4.3%	1.6%*
Donor Information			
Age (mean±SD)	40.1±14.9	40.5±14.9	39.1±14.8*
Living	34.5%	39.7%	23.9%*
Female	47.4%	49.3%	43.6%*
Non-Hispanic Black	15.1%	4.3%	36.9%*
Expanded Criteria Donor	13.4%	13.3%	13.6%
Donor after Cardiac Death	4.6%	3.9%	5.9%*
Immunologic Risks			
Cold Ischemic Time (mean hrs±SD), n=2,575	14.2±10.4	13.3±10.5	15.8±10.0*
Warm Ischemic Time (mean min±SD), n=1,972	40.1±24.6	39.5±24.7	41.3±24.2
HLA mismatches (mean±SD)	3.4±1.8	3.2±1.8	4.0±1.5*
Panel Reactive Antibody (mean±SD)	2.7±11.1	2.6±10.9	3.0±11.5
Years on Dialysis (mean±SD)	2.3±2.5	1.9±2.1	3.3±2.9*
Pre-emptive Transplant	21.0%	24.5%	14.1%*
Baseline Immunosuppression			
IL-2 Receptor Antagonist Antibody Induction	31.5%	34.5%	25.6%*
Cytolytic Induction	34.1%	31.6%	39.2%*
Tacrolimus	71.9%	70.2%	75.5%*
Cyclosporine	22.1%	23.7%	18.8%*
Mycophenolate	86.6%	86.7%	86.2%
Azathioprine	1.5%	1.8%	0.9%*
mTOR	10.3%	10.2%	10.4%
Prednisone	94.5%	94.5%	94.5%
Clinical Outcomes			
Death	19.6%	21.7%	15.4%*
Overall Graft Loss	25.1%	24.9%	25.6%
Death-Censored Graft Loss	10.2%	8.0%	14.7%*
Acute Rejection	12.5%	11.4%	14.8%*
Delayed Graft Function	15.8%	11.7%	24.0*

*p<0.05 comparing NHB vs. NHW

Table 2 - CVD risk factor prevalence and control, compared between NHB and NHW adult kidney transplant recipients

CVD Variable	Baseline		One Year		Three Years		Five Years	
	NHW	NHB	NHW	NHB	NHW	NHB	NHW	NHB
Prevalence of Hypertension[1]	92.3%	96.4%**	97.2%	99.0%**	98.7%	99.9%**	99.2%	100.0%**
Prevalence of Diabetes[2]	38.4%	38.8%	46.9%	50.3%	49.4%	52.9%	53.3%	58.9%**
Prevalence of Dyslipidemia[3]	46.4%	40.7%**	69.2%	63.3%**	81.4%	77.2%**	86.3%	83.9%
Mean Systolic BP (±SD)	140±18	141±19	137±14	139±15**	136±12	138±12*	135±11	137±12**
Mean Diastolic BP (±SD)	75±10	79±11**	73±9	76±9**	73±8	76±8**	73±8	77±8**
Blood Pressure <140/90 mmHg	51%	46%*	60%	52%**	65%	58%**	69%	60%**
Mean Hemoglobin A1c (±SD)	6.6±1.3	6.5±1.5	7.1±1.	7.8±1.7**	7.2±1.3	7.8±1.6**	7.2±1.2	7.7±1.6**
Hemoglobin A1c <7%[4]	57%	61%	53%	35%**	46%	31%**	47%	35%**
Hemoglobin A1c <8%[4]	92%	93%	87%	78%**	83%	74%**	86%	83%
Mean LDL (±SD)	86±32	86±31	100±34	103±34	97±30	102±32**	95±28	99±30**
LDL <100 mg/dL	72%	70%	52%	51%	56%	52%*	61%	55%**
Mean TG (±SD)	200±149	164±105**	198±150	161±104**	194±126	160±98**	187±120	154±86**
TG < 150 mg/dL	46%	57%**	44%	59%**	43%	57%**	45%	60%**
Prescribed ACE inhibitor or ARB[5]	48%	50%	35%	38%*	50%	54%*	56%	61%**
MPR ≥80%	23%	18%*	56%	49%*	53%	51%	52%	40%**
Prescribed Beta Blocker[5]	49%	51%	59%	64%*	70%	73%*	73%	78%*
MPR ≥80%	34%	23%**	61%	56%*	56%	47%**	51%	46%
Prescribed Oral Anti-hyperglycemic[4]	34%	35%	30%	33%	36%	38%	39%	42%
MPR ≥80%	17%	19%	60%	49%*	44%	47%	49%	43%
Prescribed Insulin[4]	48%	44%	62%	66%	70%	73%	70%	74%
MPR ≥80%	69%	45%**	86%	78%**	83%	82%	84%	76%*
Prescribed Statin[6]	84%	80%*	74%	70%	77%	76%	78%	78%
MPR ≥80%	37%	22%**	62%	52%**	57%	50%*	58%	43%**
Prescribed Other Anti-Lipemic[6]	19%	17%	13%	7%**	19%	12%**	20%	12%**
MPR ≥80%	18%	7%**	58%	60%	46%	43%	51%	40%
Prescribed Anti-platelet	10%	7%**	7%	5%	10%	7%**	13%	9%**
MPR ≥80%	27%	21%	51%	42%	51%	35%*	44%	24%

*p<0.05 **p<0.01

[1]Defined as documentation, blood pressure >140/90 mmHg or treatment with anti-hypertensive therapy

[2]Defined as documentation, hemoglobin A1c >7% or treatment with anti-glycemic therapy

[3]Defined as a LDL >130 mg/dL, TG >150 mg/dL or treatment with anti-lipemic therapy

[4] Only in those with a diagnosis of diabetes

[5] Only in those with a diagnosis of hypertension

[6] Only in those with a diagnosis of dyslipidemia

Table 3 – Fully adjusted competing risk model for the primary outcome of death censored graft loss

Variable	Reference	Hazard Ratio	95% CI	p-Value
NHB Race	**NHW Race**	**1.490**	**1.11-1.99**	**0.0072**
Age (per year)	18 years old	0.997	0.99-1.01	0.6683
Female Gender	Male Gender	1.132	0.52-2.48	0.7570
Not Married	Married	0.968	0.76-1.23	0.7933
Angina or CAD History	No Cardiac History	0.947	0.68-1.33	0.7550
Previous Transplant	No Previous Transplant	1.255	0.68-2.33	0.4705
Living Donor	Deceased Donor	0.897	0.67-1.20	0.4581
Expanded Criteria Donor	**Standard Deceased Donor**	**1.387**	**1.01-1.91**	**0.0455**
Cardiac Death Donor	Brain Dead Donor	1.150	0.62-2.12	0.6536
NHB Donor	Any Other Donor Race	1.087	0.79-1.50	0.6088
HLA Mismatches – 0	1-5 HLA Mismatches	0.964	0.64-1.46	0.8626
MLA Mismatches – 6		1.204	0.86-1.68	0.2784
PRA 0%	PRA 1-20%	1.056	0.73-1.53	0.7715
PRA >20%		0.977	0.50-1.91	0.9463
Years on Dialysis	0 Years	1.044	1.00-1.09	0.0739
Preemptive Transplant	On Dialysis	0.896	0.63-1.28	0.5474
IL-2 Receptor Antagonist Induction	No Induction Therapy	0.986	0.74-1.31	0.9223
Cytolytic Induction		0.916	0.69-1.22	0.5525
Tacrolimus Maintenance Therapy	No Calcineurin Inhibitor Therapy	0.720	0.44-1.17	0.1877
Cyclosporine Maintenance Therapy		0.845	0.51-1.41	0.5186
Mycophenolate Maintenance Therapy	No Adjunct Agent	0.935	0.65-1.35	0.7213
Azathioprine Maintenance Therapy		0.762	0.29-2.02	0.5849
mTOR Maintenance Therapy	No mTOR	0.755	0.49-1.17	0.2046
Corticosteroids Maintenance Therapy	No Corticosteroids	1.422	0.75-2.68	0.2764
ACE inh/ARB Therapy MPR 0-79%	**No ACE inhibitor or ARB**	0.959	0.74-1.24	0.7455
ACE inh/ARB Therapy MPR ≥80%	**Therapy**	**0.446**	**0.29-0.68**	**0.0002**
Beta Blocker Therapy MPR 0-79%	No Beta Blocker Therapy	1.363	0.99-1.88	0.0599
Beta Blocker Therapy MPR ≥80%		0.934	0.64-1.37	0.7276
Calcium Channel Blocker MPR 0-79%	No Calcium Channel Blocker	1.238	0.93-1.65	0.1488
Calcium Channel Blocker MPR ≥80%	Therapy	0.946	0.64-1.39	0.1488
Diuretic Therapy MPR 0-79%	**No Diuretic Therapy**	**1.956**	**1.49-2.57**	**<0.0001**
Diuretic Therapy MPR ≥80%		1.025	0.63-1.67	0.9207
Anti-Platelet Therapy MPR 0-79%	No Anti-Platelet	1.198	0.83-1.73	0.3376
Anti-Platelet Therapy MPR ≥80%		1.218	0.64-2.32	0.5486
Insulin Therapy MPR 0-79%	**No Insulin Therapy**	**1.585**	**1.02-2.47**	**0.0414**
Insulin Therapy MPR ≥80%		1.220	0.80-1.86	0.3522
Oral Anti-Hyperglycemic Therapy MPR 0-79%	No Oral Anti-Hyperglycemic	1.191	0.85-1.66	0.3021
Oral Anti-Hyperglycemic Therapy MPR ≥80%	Therapy	0.766	0.40-1.48	0.4258
Statin Therapy MPR 0-79%	**No Statin Therapy**	0.836	0.62-1.14	0.2529
Statin Therapy MPR ≥80%		**0.534**	**0.36-0.80**	**0.0022**
Other Dyslipidemia Therapy MPR 0-79%	No Other Dyslipidemia Therapy	1.240	0.89-1.73	0.2088
Other Dyslipidemia Therapy MPR ≥80%		1.464	0.80-2.67	0.2149
Diabetes	No Diabetes	0.657	0.43-1.01	0.0541
Dyslipidemia	No Dyslipidemia	0.851	0.56-1.29	0.4454
Dyslipidemia Not Controlled	Dyslipidemia Controlled	1.083	0.83-1.42	0.5607
Diabetes Not Controlled	Diabetes Controlled	0.831	0.58-1.19	0.3167
Hypertension Not Controlled	**Hypertension Controlled**	**1.636**	**1.29-2.07**	**<0.001**
Delayed Graft Function	No Delayed Graft Function	0.925	0.68-1.27	0.6248
Acute Rejection	**No Acute Rejection**	**1.914**	**1.46-2.51**	**<0.001**

Table 4 – Comparison of hazard ratios for NHBs vs. NHWs and assessment of model fit across all sequential competing risk modeling analyses for the primary outcome of death censored graft loss

Model	Domain	Fixed Entry				Varied Entry*	
		HR for NHB vs. NHW	95% CI	p-Value	Model AIC	Relative change in NHB HRs vs. NHW as compared to previous model	Change in AICs from previous model
Model 1	Race Only	1.999	1.61-2.49	<0.0001	4868	NA	NA
Model 2	+Sociodemographics	2.054	1.64-2.57	<0.0001	4875	-2.8 to 2.1%	5 to 7
Model 3	+Comorbidities	2.057	1.65-2.57	<0.0001	4877	0.1 to 1.3%	2 to 4
Model 4	+Donor Characteristics	1.781	1.36-2.32	<0.0001	4870	-13.4 to -4.2%	-7 to 3
Model 5	+Immunologic Risks	1.697	1.30-2.22	0.0001	4878	-9.6 to -4.7%	6 to 8
Model 6	+Immunosuppression	1.691	1.29-2.22	0.0001	4885	-0.4 to 0.7%	7 to 9
Model 7	+CVD Risk Factors & Control	1.501	1.12-2.01	0.0059	4773	-17.5 to -8.7%	-118 to -106
Model 8	+Post-Transplant Events	1.490	1.11-1.99	0.0072	4757	-5.5 to -0.7%	-28 to -16

* Varied entry was conducted using iterative modeling and changing the introduction of the blocks of variables into the model in order to determine their impact on racial disparities. For all scenarios, race was initially entered into the model (unadjusted risk), followed by entry of blocks of variables which varied across different iterations.

Figure 1 – Flowchart summarizing the creation of the study cohort of NHW and NHB adult solitary kidney transplants from Jan 1, 2001 to Dec 31, 2007 with data available within the VA Health System

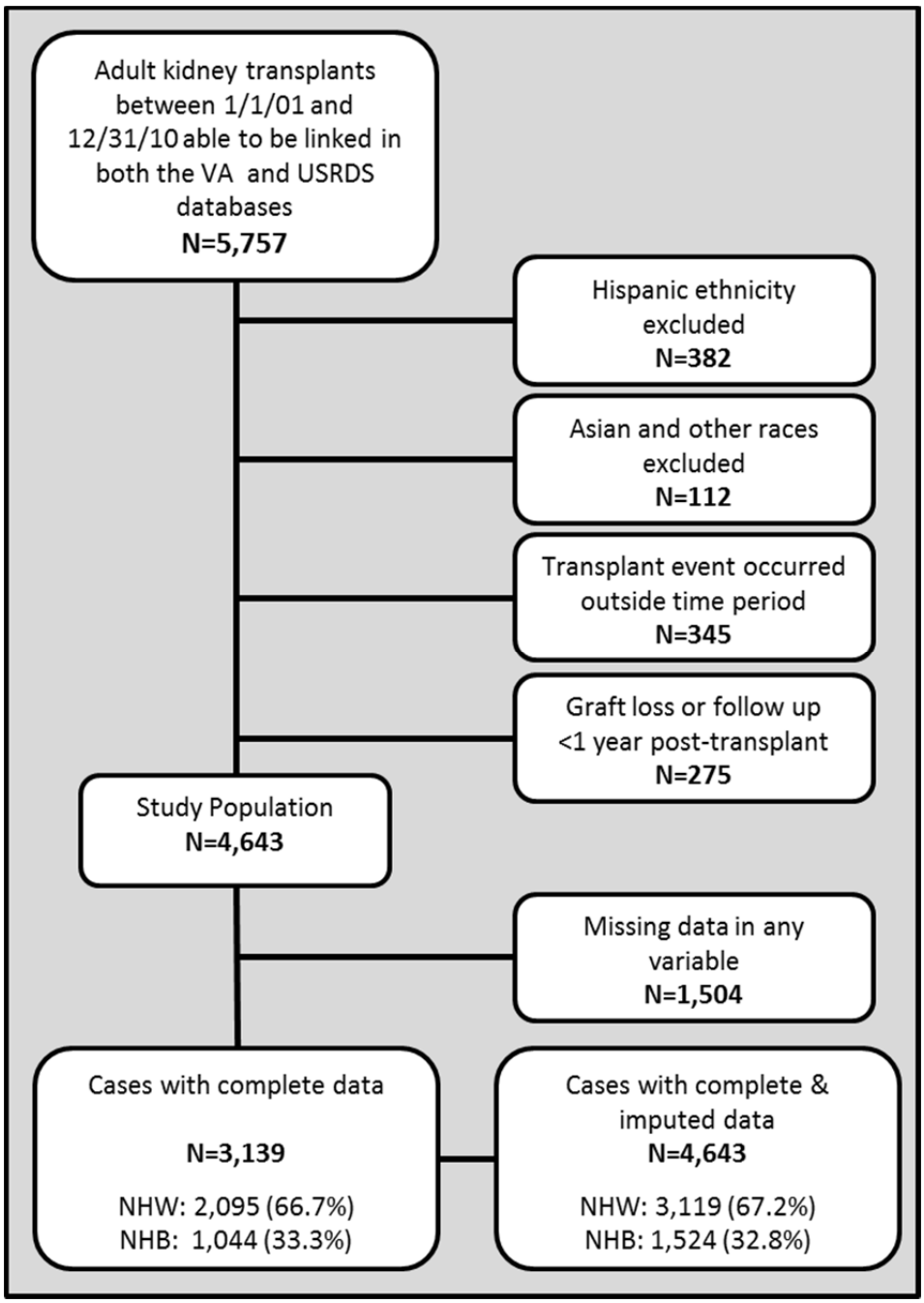
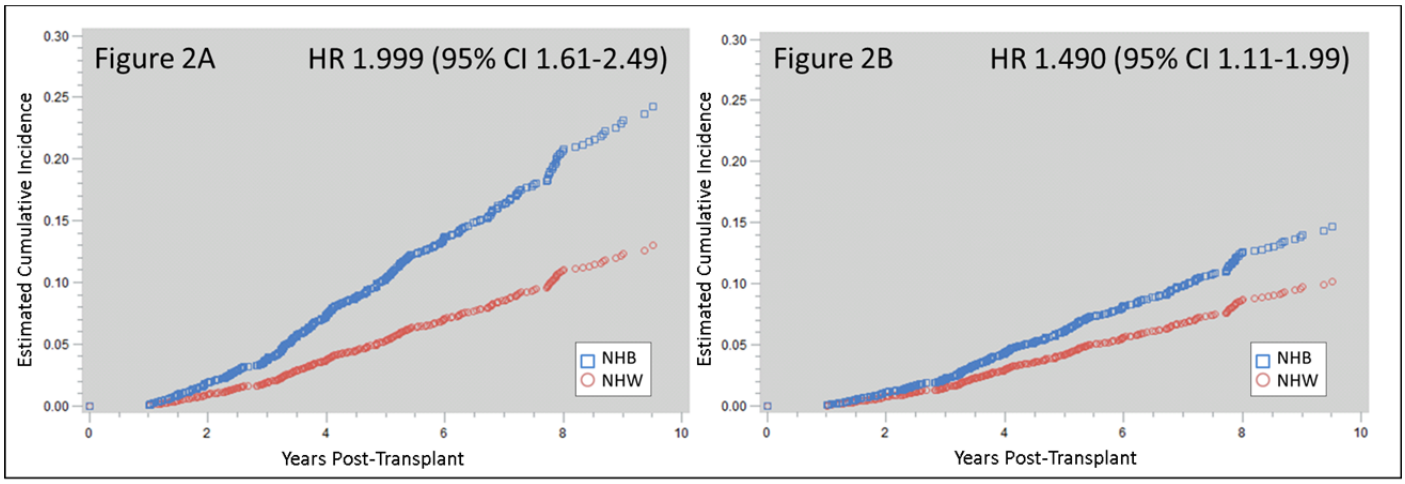


Figure 2 – Cumulative incidence function curve estimates for the primary outcome of death-censored graft loss in NHB vs. NHW kidney transplants for the unadjusted model (Figure 2A) and the fully adjusted model (Figure 2B) demonstrating a 24% relative reduction in risk for NHBs when controlling for all measured variables



IMPLICATIONS AND FUTURE INITIATIVES

The results of this research demonstrate that CVD risk factors and risk control account for a significant component of the variability associated with DCGL in adult kidney transplant recipients, while also meaningfully contribute to racial disparities. Further, adherence to medication classes used to manage CVD risk factors, as measured by the MPR, appears to differ by race and likely influences the risk of developing DCGL and mortality rates.

These factors are mutable, and previous interventional research has demonstrated that with the appropriate multimodal approach, CVD risk factor control can be improved in the general population. However, to date, there are very few studies assessing this within the transplant population. Thus, these results provide substantial data to support interventional endeavors with the goal of improving CVD risk factor control. Long-term improvements have the promise of optimizing patient and graft longevity while also reducing racial disparities.

The next steps of this research endeavor are to apply this information and conduct a pilot study that assesses the feasibility and potential effectiveness of a pharmacist-led multi-level intervention to improve CVD risk factor control in adult kidney transplant recipients. The intervention will provide monthly educational sessions to long-term kidney transplant recipients in hopes of improving medication adherence, accurate monitoring and self-efficacy. We hope to establish that patients are willing to enroll in the study and capable of following the six month intervention schedule, while also demonstrating a signal of potential effectiveness of the intervention. If successful, we plan to use this data to support the development of a larger randomized controlled clinical trial.

APPENDIX A – DETAILED METHODS

RESEARCH PLAN

Study Population

The target population for this proposal is all adult U.S. solitary kidney transplant recipients receiving contemporary care, which includes modern immunosuppression regimens and monitoring techniques. We expect that the study population will be an accurate representation of the target population, based on the preliminary analyses and comparisons to the most recent SRTR annual report.

The study population includes veteran recipients of solitary kidney transplant recipients, transplanted between January 1, 2001 and December 31, 2007 (7 years) with follow up through December 31, 2010. A review of the national VA data in the corporate data warehouse (CDW, stored in VINCI) demonstrated there were 14,927 veterans with a diagnosis of kidney transplant (V42.0 or 996.81) without a history of a liver, heart, lung, pancreas or intestine transplant. This includes all patients available in the VINCI data starting in 1976 through 2014. The USRDS identified 9,133 veteran kidney recipients transplanted between January 1, 2001 and December 31, 2007. The USRDS cohort includes those veterans that receive care outside the VA system and those that receive non-renal transplants. When these two datasets were merged, a total of 5,757 unique transplant events were identified that met inclusion and exclusion criteria. Of these, 382 were excluded for being Hispanic, 112 were excluded for being Asian or other races, 345 were excluded for receiving a transplant outside the time period and 275 for excluded for having graft loss or follow up <1 year post-transplant, leaving 4,643 eligible for inclusion. Of these, 1,504 were missing data for at least one variable, leaving 3,139 cases with complete data, which included NHWs (66.5%) and NHBs (33.5%). On initial analysis, it was determined that by including those with early graft loss, the proportionality of the hazard over time assumption did not hold. Because of this and the fact that CVD risk factors predominantly impact late graft loss, we chose to exclude those with graft loss or follow up <1 year post-transplant. This additional exclusion criterion allowed for the proportionality of the hazard over time to hold.

As this is a rolling cohort, it is expected that the number of patients within each calendar year will vary. To standardize this for time to event analyses, we will use the date of transplant as the reference date for entry into the cohort and the date of the event or censoring date as the final date. Within the 3,139 patients that have complete data and are included in the analysis, 320 (10.2%) had the outcome event of interest, death-censored graft loss. This significantly differed when stratified by race (NHW 8.0% vs. NHB 14.7%).

Data sources

For the VA data, we will utilize the national patient care database (NPCD). The NPCD is located at the Austin Information Technology Center and is a part of the National Medical Information Systems. The NCPD collects integrated patient care data from all Veterans Health Information Systems and Technology Architecture (VistA) systems. Data collected and stored in NPCD system includes all information on patient treatment, including outpatient encounters, inpatient encounters, medications, laboratory values, radiology, pathology, progress notes, as well as other information. This data has been compiled and organized into datasets for ease of download and use, termed the VHA Medical SAS Datasets. The laboratory data used for this analysis will be extracted from the Decision Support System Clinical National Data Extracts Lab Results (DSS NDEs LAR) database, which contains laboratory data for VA patients that is organized and has been standardized using national codes for ease of analysis. The Pharmacy Benefits Management (PBM) database contains every VA patient that has activity at a VA pharmacy. The database includes medication utilization information for every prescription filled in the VA. The Outpatient Pharmacy Package comprises prescriptions dispensed at the site's pharmacy, either as a new fill or a refill, within that month. In addition, all prescriptions filled by a Consolidated Mail Outpatient Pharmacy (CMOP) are included. The PBM data will be used to assess prescribing patterns and medication adherence.

The patient-specific transplant data will be obtained using the USRDS. The USRDS is a national data system that collects and distributes information about CKD, ESRD and kidney transplantation in the U.S. The transplant data contained within the USRDS is obtained through an agreement with UNOS. Thus, the USRDS dataset contains a complete list of all kidney transplants performed within the US dating back to 1987. The

data contained within the USRDS dataset includes baseline patient and donor sociodemographics, immunologic risks, transplant characteristics, immunosuppression regimens and clinical follow up events, including delayed graft function, acute rejection, graft loss and death. Although these events are reported through mandatory form completion by each transplant center, graft loss and death are further validated by using the Medicare ESRD Prospective payment System (PPS) and the Social Security Master Death Index (SSDI). Thus, even unreported events by transplant centers can be identified through this validation process. Supplemental Table 6 displays the variables that will be created and utilized for this analysis and the source of the data; this includes the primary outcome variable of death-censored graft loss and all of the independent variables, including the primary exposure variables of race and CVD risk factors and control.

The VA NPCD data will be linked to the USRDS using scrambled social security numbers that are sent with the datasets. The date of transplant will provide further delineation of follow up data as it pertains to laboratory results and medication utilization (i.e. the date of the result or medication prescription will be matched to the correct transplant event based on the transplant date). To ensure data security and that IRB and HSR&D requirements are met, all patient level data will be stored and analyzed on the VA Informatics and Computing Infrastructure (VINCI) network in the VINCI Workspace.

Outcome Measurement

The primary outcome for this analysis is death-censored graft loss. This is defined as either a return to chronic dialysis or retransplantation, which is consistent with previous studies and the source of the data (USRDS). Death will not be included as an event and patients will be censored at this time point, and accounted for using a competing risk model to estimate the cumulative survival function (CIF). The outcome will be assessed as a time to event analyses, with the reference time being the date of transplant and the end time being the date of either graft loss (event), death (censored) or the end of the study period (censored). Graft loss is a required reportable event by transplant centers to UNOS, the source of the data.

Exposure Measurement

There are two primary exposures for this study, race and CVD risk factor control. For ease of analysis and presentation of the data, the study cohort will be restricted to two racial groups, NHWs and NHBs. Race information was gathered from the USRDS dataset and cross-validated with the VA vital records data. For this study, race is self-reported and is not corroborated with genotyping or ancestral documentation. CVD risk factor control will be focused on the three predominant risks most strongly associated with the development of CVD events: hypertension, diabetes and dyslipidemia. Hypertension will be defined as documentation in the medical record, a blood pressure of greater than 140/90 mmHg or the use of anti-hypertensive medications. Diabetes will be defined as documentation in medical record, a hemoglobin A1c of >7% or use of anti-glycemic therapy. Dyslipidemia will be defined as a LDL of >130 mg/dL, triglyceride level of >150 mg/dL or use of anti-lipemic therapy.

CVD risk factor control assessment will be defined using the definitions outlined in the third column of Supplemental Table 6. Diabetes and diabetes control will be classified as either no diabetes, a mean follow up A1c of <8% vs ≥8% (we will also assess A1C cutoffs of 7%). Hypertension and hypertension control will be classified based on both the systolic (SBP) and diastolic blood pressure (DBP). Patients will be classified as no hypertension or mean follow up SBP <140 and DBP <90 vs. SBP ≥140 or DBP ≥90 mmHg. For dyslipidemia and lipid control, patients will be classified based on both low density lipoprotein (LDL) and triglyceride (TG) levels. Patients will be classified as either no dyslipidemia or mean follow up LDL <100 and TG <150 vs LDL ≥100 or TG ≥150 mg/dL. These definitions for diabetes, hypertension and dyslipidemia were developed by balancing clinical guidelines recommendations with assessing the distribution of data in the cohort to ensure groups were adequately sized for stable and reliable analysis.[114-117]

As part of the analysis assessing control of prevailing CVD risk factors, it is important to measure and control for medication use, as this is known to influence both the ability to control these comorbidities and also impact

outcomes independent of control. We will measure and adjust for prescribing and adherence to these therapies, as outlined in Supplemental Table 6. Medications to treat CVD comorbidities will be grouped according to class and patients will be categorized based on the prescribing of this agent (yes vs no) and their adherence to the therapy (medication possession ratio [MPR] ≥80% vs <80%). Thus, for each medication category, patients will be coded into three possible groups, prescribed the class of agent and an MPR ≥80% (referent group), prescribed the class of agent and an MPR <80% or not prescribed the therapy.[118] These medication classes will be assessed as follows: 2 for diabetes (oral agent and insulin), 2 for dyslipidemia (HMG CoA reductase inhibitors [statins] and other anti-lipid therapy), 4 for hypertension (beta blockers, calcium channel blockers, diuretics and angiotensin converting enzyme inhibitors [ACE inh] or angiotensin receptor blockers [ARBs]) and anti-platelet therapy (aspirin or clopidogrel). These are the predominant CVD risk factor medication classes utilized in transplant recipients and thus will be the focus of this analysis.

Conceptual Model

Supplemental Figure 6 displays the conceptual model that was developed after extensive review of the previous literature describing the prevailing etiologies and factors leading to racial disparities in kidney transplantation. This model is based upon King's conceptual model that globally describes racial disparities for health outcomes. In King's model, there are five domains that explain racial disparities, including biologic factors, cultural factors, socioeconomic factors, racism and political factors.[119] Our model has modified racism and political factors to access issues and added in behavioral facts as well. These domains are further delineated into specific variables that likely impact racial disparities in transplantation. These factors are fully described under the previous literature section of this proposal. This conceptual model displays five predominant areas that eventually lead to disproportionately high rates of graft failure in NHB recipients; these include acute rejection episodes, ischemia reperfusion (I/R) injury, subclinical immunologic events, and reduced CVD risk factor control. This analysis will determine the magnitude of each of these factors on racial disparities, with the exception of subclinical events, as this is an unmeasured factor. The central hypothesis surrounding this study is that even after controlling for acute rejection, and I/R injury, CVD risk factor control

significantly influences the impact of race on graft loss. The bolded text within the factors and events columns are issues we have the ability to adjust for in this analysis, as these are measured and reported within the data captured for this study. This conceptual model provides the basis for helping to explain why NHB recipients are at an increased risk of graft loss, while also providing the foundation for why we expect CVD risk factor control to impact this disparity in a significant manner.

Confounders

As the causes of racial disparities are multifactorial and complex, in order to isolate the potential of CVD risk factor control as a significant contributor to this issue, it is important to adjust for as many potential confounders as possible. By assembling a dataset that contains both USRDS and VA data, we will be able to control for a large number of potential confounders. Covariates that will be added to the multivariable models include recipient sociodemographics (age, gender and marital status), recipient comorbidities (history of CAD/angina, previous transplant and years on dialysis), donor characteristics (living donor, ECD and DCD), immunologic characteristics (HLA mismatches and current panel reactive antibody level [PRA]), baseline immunosuppression (induction therapy, CNI type, adjunct agent type and corticosteroids) and post-transplant events (delayed graft function [DGF] and acute rejection). Previous studies have demonstrated that these variables significantly differ by recipient race and usually impact the outcome of graft loss; thus, there likelihood of being contributors to racial disparities is high.[23-25]

The covariates will be added into the model in eight sequential blocks (recipient race, recipient sociodemographics, recipient comorbidities, donor characteristics, immunologic characteristics, baseline immunosuppression, post-transplant events and CVD risk factor control), as detailed in the analysis plan, in order to assess their impact on the independent effect of race on death-censored graft loss. Order of variable entry into the models will vary for sensitivity analysis.

Effect Modifiers

It may be that a number of these covariates influence the outcome of graft loss differently based on recipient race. Although the primary objective of this study is to assess CVD risk factor control as a significant factor contributing to racial disparities in kidney transplantation, we will also assess if the influence of CVD risk factor control (A1c, BP and lipids) on death-censored graft loss varies by race. Other effect modifiers that will be tested in this analysis include medications prescribed to treat CVD risk factors and post-transplant events, including acute rejection and DGF. The analysis plan details how we will assess for effect modification for these variables.

Data Analysis

Initially, the distribution of each variable will be analyzed to assess for adequate group size for categorical variables and normality assumptions for continuous variables. If a categorical variable has a group that contains <5% of the study population, we will recategorize the variable, particularly if the referent group is <5%. If a continuous variable is not normally distributed, it will be modified, either through a log transformation or into clinically relevant categories. Additionally, during this data understanding process, we will assess if ordinal variables are linear in the logit for modeling purposes. If this assumption cannot be met, we will also transform these variables into clinically relevant categories.

Hypothesis 1

The initial univariate analysis will compare baseline variables and clinical outcomes by race (AA vs. Caucasians). To meet the objective of answering hypothesis 1, we will assess and baseline prevalence of the three measured CVD risk factors (hypertension, diabetes and dyslidemia) by comparing these in AAs vs. Caucasians. It is expected that AAs will have a significantly higher prevalence of pre-transplant hypertension,

diabetes and dyslipidemia, as compared to Caucasians. We will then assess the prevalence of obtaining optimal post-transplant CVD risk factor control, comparing these rates between AA and Caucasians. We expect AAs will have significantly lower rates of CVD risk factor control as compared to Caucasians, as defined in the exposure section; thus fulfilling the first criterion for CVD risk factor control to be a significant factor influence of this disparity (a significant association between the primary exposure variable and the variable of interest). This will be done using the chi square test or Fisher's exact test, depending on cell counts and the number of categories being analyzed, with the equations for each test as follows:

Chi square test equation

$$\chi^2 = \sum_{i=1}^{r} \sum_{j=1}^{c} \frac{(O_{ij} - E_{ij})^2}{E_{ij}}$$

Fisher's exact test equation

$$p = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{n!\,a!\,b!\,c!\,d!}$$

We will also compare the baseline and follow up means or medians of SBP, DBP, A1c, LDL and TG by race, using either the Student's t-test or Mann Whitney U test, depending on normality assumption violations. The equations for each test are as follows:

Student's T test equation

$$t = \frac{\overline{x_1} - \overline{x_2}}{\sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}}}$$

Mann Whitney U test equation

$$U = (N_1 \times N_2) + \frac{N_1 \times (N_1 + 1)}{2} - R_1$$

As the second step, we will assess if the prevalence of pre-transplant CVD risk factors (hypertension, diabetes and dyslipidemia) and post-transplant CVD risk factor control is associated with the primary outcome, death-censored graft loss. We expect that the prevalence and control of these three CVD risk factors will be significantly associated with graft loss, thus fulfilling the second criterion establishing CVD risk factor control as a significant contributor to racial disparities in kidney transplantation (a significant association between the variable of interest and the primary outcome). We will also use the chi square test or Fisher's exact test for this analysis. The follow up means or medians of the CVD risk factor control variables (SBP, DBP, A1c, LDL and TG) will also be compared between those that developed death censored graft loss vs. those that did not,

using either the Student's t-test or Mann Whitney U test, depending on normality assumption violations. It is expected that these will differ in a statistically significantly manner.

Hypothesis 2

The objective of hypothesis 2 is to qualitatively determine if CVD risk factors and CVD risk factor control is a significant factor that influences racial disparities in kidney transplantation, after adjusting for other known and measured covariates. To accomplish this, we will utilize multivariable modeling, using Cox proportionate hazard regression. The outcome in each of these models will be time to death censored graft loss. Initially, we will ensure that the hazard ratio is proportional over time for each of the variables included in the models by including a time*variable interaction, conducting log-log plots and categorizing the time variable to compare HR across this. If the time*variable interaction term has an insignificant p-value (>0.05), the lines on the log-log plot are parallel and the HRs do not significant change as a function of time, then the assumption of proportionality in the hazard ratios over time is not violated. We will also ensure that for ordinal and continuous variables, there is linearity in the logit. If these assumptions do not hold, we will include appropriate terms in the model to compensate for lack of proportionality and transform variables as needed. Following this, we will conduct a series of seven models as described in the next paragraph. The equation for Cox regression is as follows:

Cox proportional hazard regression equation

$$\ln\left(\frac{\mathrm{H}(t)}{\mathrm{H}_0(t)}\right) = b_1X_1 + b_2X_2 + b_3X_3 + \cdots + b_kX_k$$

Supplemental Table 7 displays the complete list of variables that will be included in these models and details how each model will be set up for analysis. Sequential forward entry of blocks of variables will be added to the model and at each step the overall impact of race on death censored graft loss will be assessed by comparing the β for AA race (Caucasian referent group), to the previous model. For all models, race will be entered into

the model first, to determine the unadjusted impact of AA race on time to death censored graft loss. Following this, blocks of variables will be entered into each model as detailed in Supplemental Table 7. For instance, in the first modeling sequence, after adding race into the model, the following entry order will commence: sociodemographics (age, gender and marital status), comorbidities (CAD/angina, previous transplant), donor characteristics (living, ECD, DCD), immunologic risks (HLA mismatches, PRA, years on dialysis), immunosuppression (IL2 receptor antagonist induction, cytolytic induction, tacrolimus, cyclosporine, mycophenolate, azathioprine, corticosteroids), CVD risk factors and control (diabetes, hypertension and dyslipidemia and CVD medications) and finally, post-transplant outcomes (DGF and acute rejection). At each of step, the β for race will be compared to the previous β. It is expected that significant blocks associated with racial disparities will reduce the β by at least 10%.

In subsequent modeling procedures, the varying entry of blocks of variables into the model will provide a sensitivity analysis and allow for an assessment of the relative variability of each block's influence on racial disparities. Blocks with a robust impact on racial disparities should maintain influence on the race β, regardless of entry position. During each step of the modeling procedure, the Akaike information criterion (AIC) will be assessed and compared between models as a goodness of fit measure. As covariate blocks are added to the models, it is expected that the AIC will decrease in a significant manner, indicating the models with more covariates will have improved ability to explain the variability associated with the outcome of death censored graft loss. Large changes in the AIC after the addition of a block of variables suggest a strong influence of that block on the variability associated with the outcome of death censored graft loss. Because all patients included in the analysis have complete data, all models will be fully nested (all patients in every sequential model), and thus comparisons between models for goodness-of-fit are valid.

There will also be a number of additional sensitivity analyses. Firstly, we will conduct multiple imputation to replace missing data for CVD risk factor control measurements and other important variables that influence outcomes. The sequential modeling will then be repeated using the imputed data and the results will be compared to the results of the modeling using just the complete dataset without any missing data. Second, we

will conduct modeling using competing risk, as censoring for death removes the randomness of the censoring time point. Finally, as previously discussed, we will model the data using longitudinal methodology as an additional sensitivity analysis.

Moderator Analysis

Although not a primary aim of the study, if CVD risk factors and CVD risk factor control significantly influences racial disparities, then as a secondary step, we will determine if this varies by race. To do so, we will add interaction terms into the fully adjusted model. The interaction terms will be added for hypertension, diabetes and dyslipidemia, as well as control of these CVD risk factors. We will also add interaction terms for the medication used to treat these conditions. To prevent over fitting the model, we will add the interaction terms through separate models, conducting a series of models to assess for interaction. This will also be assessed for other potential post-transplant variables known to influence outcomes, including DGF and acute rejection. The moderation inquiry is an exploratory component of the analysis plan, and the results of this are primarily for hypothesis generation of future analyses or studies.

Data was obtained through linking of scrambled SSN between the USRDS national registry database with the VA data as previous described. All data analyses will be conducted using SAS (version 9.2, SAS Institute Inc, Cary, NC). In general, statistical significance will be defined using two-sided tests with α set at 0.05.

Statistical Power

For the first hypothesis, the prevalence of the three predominant CVD risk factors (diabetes, hypertension and dyslipidemia) will be compared between NHB and NHW kidney transplant recipients using either the chi square test or Fisher's exact test. The prevalence of hypertension in the total population is 82.1% and we will have >99% power to detect a difference between NHB and NHW of at least 5%. We will have 80% power to detect a 3.5% difference in the prevalence of hypertension. For diabetes, the overall prevalence in the entire population is 55% and we will have >90% power to detect a difference between NHB and NHW of at least 5%. We will have 80% power to detect a 4.5% difference in the prevalence of diabetes. The estimated prevalence

of dyslipidemia is 30%, we will have >90% power to detect a difference between NHB and NHW of at least 5%. We will have 80% power to detect a 4% difference in the prevalence of dyslipidemia. These calculations were based upon a two-tailed $\alpha=0.05$.

For the assessment of CVD risk factor control, we expect to have ample power to detect a difference, if one truly exists. We estimate that hypertension control will be approximately 35% for a mean BP of less than 130/80 and 60% for a mean BP of less than 140/90. Given these estimates, we will have >90% power to detect at least a 5% difference in hypertension control and 80% power to detect a 4.5% difference in control. Similar power calculations were achieved for control of diabetes and dyslipidemia. As a 5% difference in prevalence and control would be the minimum needed for clinical significance, this study is well-powered to detect differences that are clinically meaningful, as it pertains to the first hypothesis.

The second hypothesis will use multivariable modeling to determine the influence CVD risk factors and CVD risk factor control has on racial disparities. We have 3,057 transplant observations that have complete data for every variable included in these models, with 367 (12%) events. Given a rule of thumb of needing 5-10 events per variable included in the model to prevent overfitting, we expect to have ample power to include the 45 variables that are proposed in the fully adjusted model. Thus, for both hypotheses, we feel the sample size, incident rate of CVD risk factors and event rate for graft loss provide ample power to conduct the proposed analysis and if clinically meaningful differences between NHW and NHB recipients exist, we expect to be capable of finding statistically significant results.

APPENDIX B – ADDITIONAL TABLES AND FIGURES

Supplemental Table 1 - Fully adjusted Cox regression model for the outcome of overall graft loss

Variable	Reference	Hazard Ratio	95% CI	p-Value
NHB Race	NHW Race	1.041	0.86-1.26	0.6775
Age (per year)	**18 years old**	**1.035**	**1.04-1.04**	**<0.0001**
Female Gender	Male Gender	0.710	0.38-1.37	0.3088
Not Married	Married	1.095	0.94-1.28	0.2596
Angina or CAD History	No Cardiac History	1.151	0.95-1.40	0.1542
Previous Transplant	No Previous Transplant	0.980	0.66-1.45	0.9179
Living Donor	Deceased Donor	0.860	0.72-1.03	0.1006
Expanded Criteria Donor	Standard Deceased Donor	1.118	0.91-1.38	0.2918
Cardiac Death Donor	Brain Dead Donor	0.846	0.56-1.28	0.4311
NHB Donor	Any Other Donor Race	1.028	0.82-1.29	0.6199
HLA Mismatches – 0	1-5 HLA Mismatches	0.997	0.78-1.28	0.9793
MLA Mismatches – 6		1.112	0.891.39	0.3514
PRA – 0%	PRA 1-20%	0.985	0.78-1.24	0.9019
PRA >20%		1.039	0.69-1.57	0.2487
Years on Dialysis	0 Years	1.021	0.99-1.06	0.2487
Preemptive Transplant	On Dialysis	0.862	0.70-1.07	0.1734
IL-2 Receptor Antagonist Induction	No Induction Therapy	0.967	0.81-1.16	0.7137
Cytolytic Induction		1.039	0.87-1.25	0.6781
Tacrolimus Maintenance Therapy	No Calcineurin Inhibitor Therapy	0.805	0.59-1.09	0.1649
Cyclosporine Maintenance Therapy		0.819	0.59-1.13	0.2274
Mycophenolate Maintenance Therapy	No Adjunct Agent	**1.319**	**1.01-1.72**	**0.0416**
Azathioprine Maintenance Therapy		0.915	0.48-1.76	0.7917
mTOR Maintenance Therapy	No mTOR	1.247	0.95-1.64	0.1119
Corticosteroids Maintenance Therapy	No Corticosteroids	1.364	0.92-2.02	0.1200
ACE inh/ARB Therapy MPR 0-79%	**No ACE inhibitor or ARB Therapy**	0.905	0.77-1.07	02329
ACE inh/ARB Therapy MPR ≥80%		**0.415**	**0.32-0.54**	**<0.001**
Beta Blocker Therapy MPR 0-79%	**No Beta Blocker Therapy**	**1.454**	**1.19-1.78**	**0.0003**
Beta Blocker Therapy MPR ≥80%		0.872	0.68-1.11	0.2727
Calcium Channel Blocker MPR 0-79%	**No Calcium Channel Blocker**	**1.203**	**1.01-1.44**	**0.0430**
Calcium Channel Blocker MPR ≥80%	**Therapy**	**0.727**	**0.57-0.93**	**0.0112**
Diuretic Therapy MPR 0-79%	**No Diuretic Therapy**	**1.571**	**1.33-1.86**	**<0.0001**
Diuretic Therapy MPR ≥80%		1.130	0.85-1.51	0.4015
Anti-Platelet Therapy MPR 0-79%	No Anti-Platelet	1.222	0.981.52	0.0698
Anti-Platelet Therapy MPR ≥80%		0.811	0.51-1.29	0.3753
Insulin Therapy MPR 0-79%	**No Insulin Therapy**	**1.487**	**1.14-1.95**	**0.0039**
Insulin Therapy MPR ≥80%		0.856	0.67-1.10	0.2206
Oral Anti-Hyperglycemic Therapy MPR 0-79%	No Oral Anti-Hyperglycemic Therapy	0.898	0.73-1.11	0.3186
Oral Anti-Hyperglycemic Therapy MPR ≥80%		0.814	0.56-1.18	0.2726
Statin Therapy MPR 0-79%	**No Statin Therapy**	**0.745**	**0.62-0.90**	**0.0027**
Statin Therapy MPR ≥80%		**0.428**	**0.34-0.55**	**<0.0001**
Other Dyslipidemia Therapy MPR 0-79%	No Other Dyslipidemia Therapy	1.017	0.82-1.27	0.8780
Other Dyslipidemia Therapy MPR ≥80%		0.838	0.54-1.30	0.4320
Diabetes	No Diabetes	1.023	0.79-1.32	0.8613
Dyslipidemia	No Dyslipidemia	1.021	0.78-1.34	0.8845
Hypertension	No Hypertension	1.071	0.11-10.2	0.9524
Dyslipidemia Not Controlled	Dyslipidemia Controlled	1.089	0.92-1.29	0.3239
Diabetes Not Controlled	Diabetes Controlled	0.951	0.76-1.20	0.6687
Hypertension Not Controlled	**Hypertension Controlled**	**1.265**	**1.09-1.48**	**0.0027**

Delayed Graft Function	No Delayed Graft Function	1.070	0.88-1.30	0.5003
Acute Rejection	**No Acute Rejection**	**1.418**	**1.17-1.72**	**0.0004**

Supplemental Table 2 - Fully adjusted Cox regression model for the outcome of death

Variable	Reference	Hazard Ratio	95% CI	p-Value
NHB Race	**NHW Race**	**0.753**	**0.60-0.94**	**0.0132**
Age (per year)	**18 years old**	**1.058**	**1.05-1.06**	**<0.0001**
Female Gender	Male Gender	0.651	0.29-1.46	0.2969
Not Married	**Married**	**1.197**	**1.00-1.43**	**0.0467**
Angina or CAD History	No Cardiac History	1.226	1.00-1.51	0.0556
Previous Transplant	No Previous Transplant	0.993	0.64-1.53	0.9763
Living Donor	**Deceased Donor**	**0.806**	**0.66-0.99**	**0.0384**
Expanded Criteria Donor	Standard Deceased Donor	1.031	0.83-1.29	0.7875
Cardiac Death Donor	Brain Dead Donor	0.770	0.49-1.20	0.2476
NHB Donor	Any Other Donor Race	0.964	0.73-1.27	0.7909
HLA Mismatches – 0	1-5 HLA Mismatches	0.962	0.73-1.27	0.7780
MLA Mismatches – 6		1.100	0.85-1.42	0.4631
PRA – 0%	PRA 1-20%	0.964	0.75-1.25	0.7831
PRA >20%		0.855	0.52-1.42	0.4631
Years on Dialysis	0 Years	1.009	0.97-1.05	0.6657
Preemptive Transplant	On Dialysis	0.788	0.62-1.01	0.0565
IL-2 Receptor Antagonist Induction	No Induction Therapy	1.010	0.83-1.23	0.9237
Cytolytic Induction		1.074	0.88-1.32	0.4953
Tacrolimus Maintenance Therapy	No Calcineurin Inhibitor Therapy	0.803	0.57-1.13	0.2031
Cyclosporine Maintenance Therapy		0.805	0.56-1.15	0.2369
Mycophenolate Maintenance Therapy	**No Adjunct Agent**	**1.368**	**1.01-1.86**	**0.0440**
Azathioprine Maintenance Therapy		0.849	0.38-1.90	0.6905
mTOR Maintenance Therapy	**No mTOR**	**1.424**	**1.05-1.93**	**0.0218**
Corticosteroids Maintenance Therapy	No Corticosteroids	1.365	0.90-2.07	0.1440
ACE inh/ARB Therapy MPR 0-79%	**No ACE inhibitor or ARB Therapy**	0.833	0.69-1.00	0.0543
ACE inh/ARB Therapy MPR ≥80%		**0.426**	**0.31-0.58**	**<0.0001**
Beta Blocker Therapy MPR 0-79%	**No Beta Blocker Therapy**	**1.547**	**1.23-1.95**	**0.0002**
Beta Blocker Therapy MPR ≥80%		0.826	0.62-1.10	0.1917
Calcium Channel Blocker MPR 0-79%	**No Calcium Channel Blocker**	1.159	0.95-1.41	0.1405
Calcium Channel Blocker MPR ≥80%	**Therapy**	**0.638**	**0.48-0.85**	**0.0023**
Diuretic Therapy MPR 0-79%	**No Diuretic Therapy**	**1.391**	**1.15-1.69**	**0.0008**
Diuretic Therapy MPR ≥80%		1.107	0.79-1.54	0.3597
Anti-Platelet Therapy MPR 0-79%	No Anti-Platelet	1.141	0.90-1.45	0.2879
Anti-Platelet Therapy MPR ≥80%		0.685	0.40-1.17	0.1685
Insulin Therapy MPR 0-79%	No Insulin Therapy	1.337	1.00-1.79	0.0500
Insulin Therapy MPR ≥80%		0.812	0.62-1.06	0.1280
Oral Anti-Hyperglycemic Therapy MPR 0-79%	No Oral Anti-Hyperglycemic	0.846	0.67-1.07	0.1579
Oral Anti-Hyperglycemic Therapy MPR ≥80%	Therapy	0.744	0.50-1.12	0.1515
Statin Therapy MPR 0-79%	**No Statin Therapy**	**0.741**	**0.60-0.92**	**0.0066**
Statin Therapy MPR ≥80%		**0.418**	**0.32-0.55**	**<0.0001**
Other Dyslipidemia Therapy MPR 0-79%	No Other Dyslipidemia Therapy	0.861	0.66-1.12	0.2633
Other Dyslipidemia Therapy MPR ≥80%		0.636	0.36-1.11	0.1113
Diabetes	**No Diabetes**	**1.377**	**1.04-1.82**	**0.0246**
Dyslipidemia	No Dyslipidemia	1.139	0.84-1.54	0.3966
Hypertension	No Hypertension	1.944	0.09-9.62	0.9610
Dyslipidemia Not Controlled	Dyslipidemia Controlled	1.016	0.84-1.23	0.8704
Diabetes Not Controlled	Diabetes Controlled	1.016	0.79-1.31	0.9012
Hypertension Not Controlled	Hypertension Controlled	1.179	0.99-1.40	0.0643
Delayed Graft Function	No Delayed Graft Function	1.073	0.86-1.34	0.5342
Acute Rejection	No Acute Rejection	1.202	0.96-1.51	0.1104

Supplemental Table 3 – Comparison of hazard ratios for NHBs vs. NHWs and assessment of model fit across all sequential modeling analyses for the outcome of overall graft loss

Model	Domain	Fixed Entry				Varied Entry	
		HR for NHB vs. NHW	95% CI	p-Value	Model AIC	Relative Change in NHB HRs vs. NHW	Change in AICs
Model 1	Race Only	1.102	0.95-1.28	0.1979	11661	NA	NA
Model 2	+Sociodemographics	1.366	1.17-1.59	<0.0001	11567	22.3 to 24.9%	-103 to -70
Model 3	+Comorbidities	1.379	1.18-1.61	<0.0001	11558	0.2 to 2.5%	-9 to 2
Model 4	+Donor Characteristics	1.223	1.03-1.45	0.0205	11543	-11.3 to -1.8%	-35 to 2
Model 5	+Immunologic Risks	1.179	0.99-1.40	0.0628	11543	-9.8 to -3.2%	-15 to 40
Model 6	+Immunosuppression	1.181	0.99-1.41	0.0613	11548	-0.6 to 1.3%	-31 to 7
Model 7	+CVD Risk Factors & Control	1.044	0.87-1.26	0.6543	11218	-19.4 to -9.5%	-349 to -324
Model 8	+Post-Transplant Events	1.041	0.86-1.26	0.6775	11208	-5.2 to -0.3%	-23 to -7

Supplemental Table 4 – Comparison of hazard ratios for NHBs vs. NHWs and assessment of model fit across all sequential modeling analyses for the outcome of death

Model	Domain	Fixed Entry				Varied Entry	
		HR for NHB vs. NHW	95% CI	p-Value	Model AIC	Relative Change in NHB HRs vs. NHW	Change in AICs
Model 1	Race Only	0.727	0.61-0.87	0.0005	9120	NA	NA
Model 2	+Sociodemographics	1.018	0.84-1.23	0.8514	8935	33.3 to 40.0%	-189 to -138
Model 3	+Comorbidities	1.032	0.85-1.25	0.7464	8931	0.4 to 3.0%	-9 to 1
Model 4	+Donor Characteristics	0.941	0.77-1.15	0.5567	8919	-10.3 to 0.1%	-36 to 1
Model 5	+Immunologic Risks	0.912	0.74-1.12	0.3819	8920	-9.3 to -2.6%	-15 to 5
Model 6	+Immunosuppression	0.913	0.74-1.12	0.3905	8924	-0.8 to 1.3%	-1 to 8
Model 7	+CVD Risk Factors & Control	0.756	0.61-0.94	0.0137	8668	-23.2 to -15.4%	-309 to -253
Model 8	+Post-Transplant Events	0.753	0.60-0.94	0.0132	8668	-4.7 to 0.2%	-7 to 3

Supplemental Table 5 - Fully adjusted competing risk model for death censored graft loss using both complete cases and imputed values for missing data (n=4,643)

Variable	Reference	Hazard Ratio	95% CI	p-Value
NHB Race	**NHW Race**	**1.355**	**1.13-1.71**	**0.0046**
Age (per year)	**18 years old**	**0.991**	**0.98-1.00**	**0.0430**
Female Gender	Male Gender	1.166	0.75-1.85	0.5053
Not Married	Married	0.991	0.83-1.18	0.9235
Angina or CAD History	No Cardiac History	1.047	0.8-2.07	0.8462
Previous Transplant	No Previous Transplant	0.865	0.68-1.15	0.2831
Living Donor	Deceased Donor	0.815	0.67-1.01	0.0595
Expanded Criteria Donor	**Standard Deceased Donor**	**1.494**	**1.25-1.98**	**0.0008**
Cardiac Death Donor	Brain Dead Donor	1.197	0.76-1.79	0.4102
NHB Donor	Any Other Donor Race	1.161	0.92-1.47	0.2189
HLA Mismatches – 0	1-5 HLA Mismatches	0.772	0.57-1.04	0.1027
MLA Mismatches – 6		1.149	0.90-1.47	0.2658
PRA – 0%	PRA 1-20%	1.028	0.79-1.26	0.8179
PRA >20%		0.810	0.55-1.24	0.3145
Years on Dialysis	0 Years	1.001	0.96-1.04	0.9567
Preemptive Transplant	On Dialysis	0.906	0.68-1.11	0.4336
IL-2 Receptor Antagonist Induction	No Induction Therapy	1.077	0.85-1.32	0.5121
Cytolytic Induction		1.050	0.86-1.29	0.6424
Tacrolimus Maintenance Therapy	No Calcineurin Inhibitor	0.961	0.62-1.36	0.8518
Cyclosporine Maintenance Therapy	Therapy	1.014	0.64-1.46	0.9480
Mycophenolate Maintenance Therapy	No Adjunct Agent	1.037	0.76-1.37	0.8088
Azathioprine Maintenance Therapy		0.946	0.58-1.84	0.8542
mTOR Maintenance Therapy	No mTOR	1.151	0.86-1.61	0.3798
Corticosteroids Maintenance Therapy	No Corticosteroids	1.336	0.89-2.32	0.2368
ACE inh/ARB Therapy MPR 0-79%	**No ACE inhibitor or ARB**	0.971	0.76-1.16	0.7827
ACE inh/ARB Therapy MPR ≥80%	**Therapy**	**0.521**	**0.36-0.71**	**0.0001**
Beta Blocker Therapy MPR 0-79%	**No Beta Blocker Therapy**	**1.451**	**1.16-1.87**	**0.0024**
Beta Blocker Therapy MPR ≥80%		0.805	0.60-1.16	0.1905
Calcium Channel Blocker MPR 0-79%	No Calcium Channel	1.204	1.00-1.53	0.0820
Calcium Channel Blocker MPR ≥80%	Blocker Therapy	0.826	0.59-1.16	0.2618
Diuretic Therapy MPR 0-79%	**No Diuretic Therapy**	**1.737**	**1.46-2.19**	**<0.0001**
Diuretic Therapy MPR ≥80%		0.922	0.57-1.44	0.7292
Anti-Platelet Therapy MPR 0-79%	**No Anti-Platelet**	**1.543**	**1.10-2.25**	**0.0178**
Anti-Platelet Therapy MPR ≥80%		1.170	0.81-1.66	0.3943
Insulin Therapy MPR 0-79%	No Insulin Therapy	0.989	0.75-1.32	0.9353
Insulin Therapy MPR ≥80%		0.755	0.42-1.34	0.3425
Oral Anti-Hyperglycemic Therapy MPR 0-79%	No Oral Anti-	1.063	0.82-1.40	0.6511
Oral Anti-Hyperglycemic Therapy MPR ≥80%	Hyperglycemic Therapy	1.165	0.68-1.96	0.5670
Statin Therapy MPR 0-79%	**No Statin Therapy**	0.924	0.74-1.24	0.5626
Statin Therapy MPR ≥80%		**0.684**	**0.50-0.99**	**0.0290**
Other Dyslipidemia Therapy MPR 0-79%	No Other Dyslipidemia	1.321	0.97-1.68	0.0514
Other Dyslipidemia Therapy MPR ≥80%	Therapy	1.196	0.69-1.77	0.4575
Diabetes	No Diabetes	0.673	0.40-1.04	0.1180
Dyslipidemia	No Dyslipidemia	0.675	0.45-1.06	0.0814
Hypertension	No Hypertension	0.678	0.24-1.75	0.4164
Dyslipidemia Not Controlled	Dyslipidemia Controlled	1.127	0.90-1.47	0.3495
Diabetes Not Controlled	Diabetes Controlled	0.942	0.70-1.32	0.7164
Hypertension Not Controlled	**Hypertension Controlled**	**1.321**	**1.09-1.64**	**0.0081**
Delayed Graft Function	No Delayed Graft Function	1.083	1.09-1.64	0.4727
Acute Rejection	**No Acute Rejection**	**1.961**	**1.09-1.64**	**<0.0001**

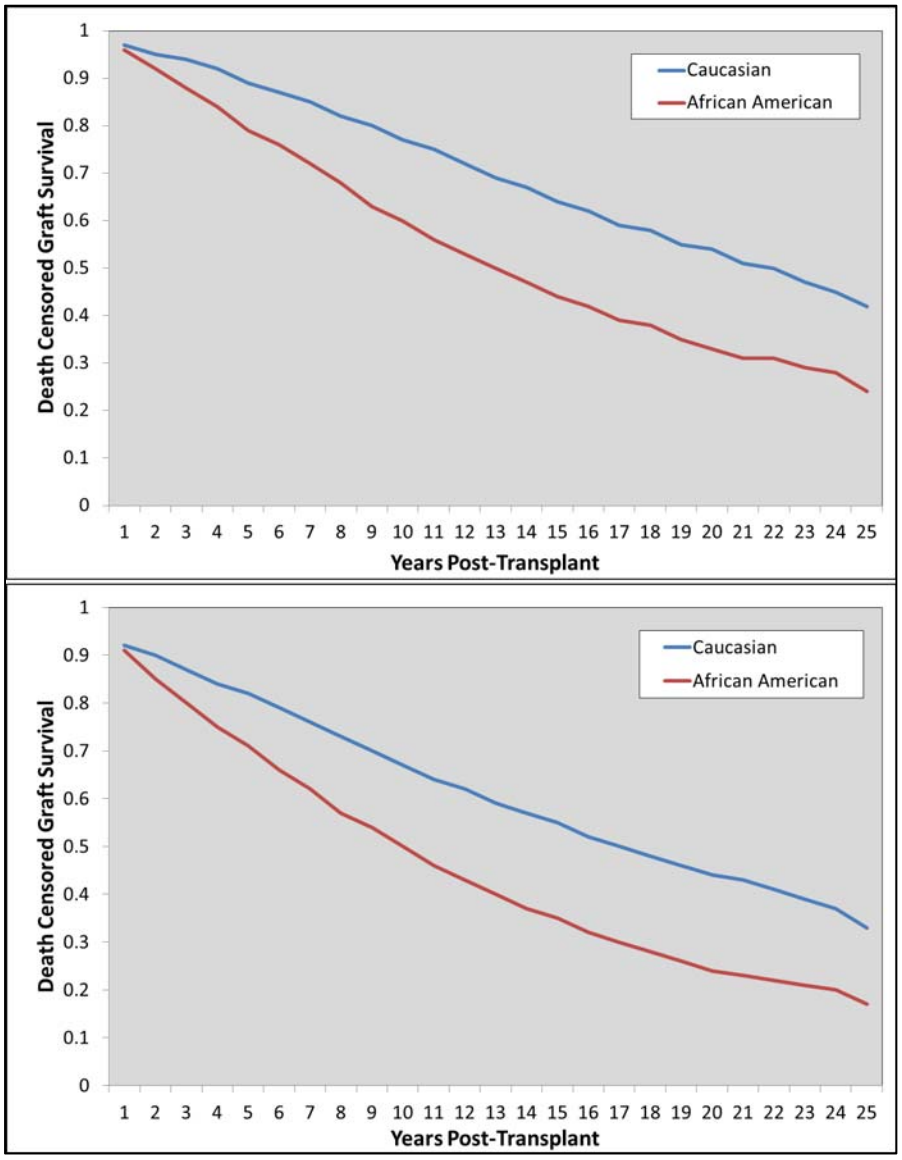
Supplemental Table 6 – Variables, Definitions, and Analysis Plan for Aim 1

Variable	Data Source	Definition(s)	Analysis Plan
Outcome Variables			
Death Censored Graft Loss	USRDS/CMS PPS	Return to chronic dialysis or retransplantation	Time to event survival analysis
Mortality	USRDS/SSDI	Documented patient death	Time to event survival analysis
Overall Graft Loss	USRDS/SSDI	Composite of the two above outcomes	Time to event survival analysis
Sociodemographics, Transplant and CVD Variables			
Sociodemographics	USRDS	Age, race, gender, marital status, comorbidities	Cross sectional assessment
Transplant Characteristics	USRDS	Donor characteristics, HLA mismatch, PRA, retransplant, delayed and rejection	Cross sectional assessment, with rej as longitudinal assessment
Diabetes Control[88]	VA DSS NDEs LAR and Patient Laboratory Data prior to 2004	Categorized as no diabetes or a mean A1C of <8% or ≥8%	Longitudinal assessment
Hypertension Control[89, 90]	VA DSS NDEs LAR and Patient Laboratory Data prior to 2004	Categorized as no hypertension or SBP <140 and DBP <90 or SBP ≥140 or DBP ≥90	Longitudinal assessment
Dyslipidemia Control[90, 91]	VA DSS NDEs LAR and Patient Laboratory Data prior to 2004	Categorized as no dyslipidemia or LDL<100 and TG<150 or LDL ≥100 or TG ≥150	Longitudinal assessment
Medication Variables			
Medications to treat diabetes	VA PBM	Grouped by class, insulin and other, categorized as not on therapy, on with MPR <80% or on with MPR ≥80%	Longitudinal assessment
Medications to treat hypertension	VA PBM	Grouped by class, beta blockers, ACE/ARBs, CCB, diuretic, categorized as not on therapy, on with MPR <80% or on with MPR ≥80%	Longitudinal assessment
Medications to treat dyslipidemia	VA PBM	Grouped by class, HMG CoA reductase inhibitors, and other anti-lipemics, categorized as not on therapy, on with MPR <80% or on with MPR ≥80%	Longitudinal assessment
Medications to treat CVD	VA PBM	All anti-platelet therapy, categorized as not on therapy, on with MPR <80% or on with MPR ≥80%	Longitudinal assessment

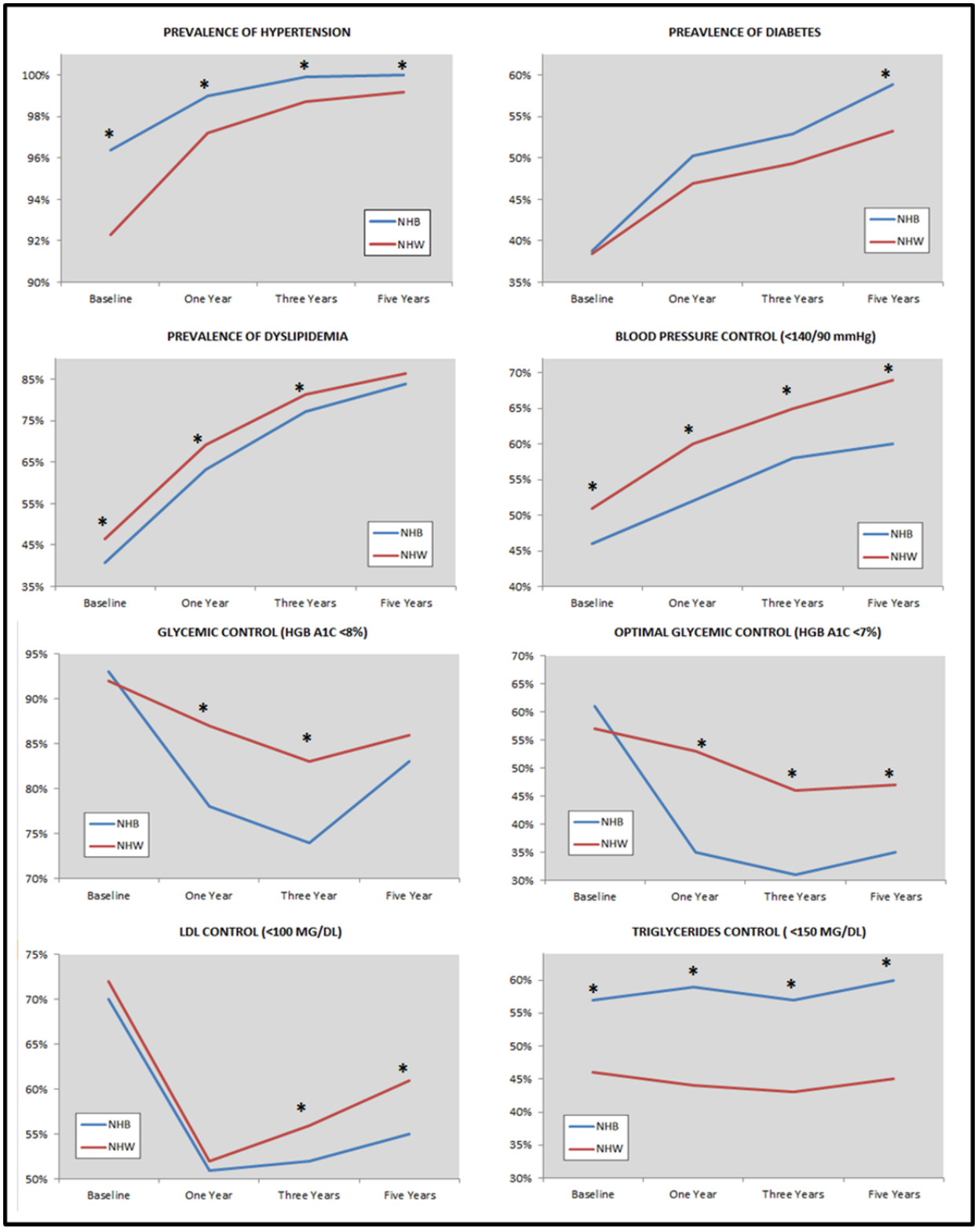
Supplemental Table 7 – Modeling procedure for Cox proportional hazard regression analysis, including the blocks of variables and entry variations for each model

Variables	Variable Number	Model 1 Entry Order	Model 2 Entry Order	Model 3 Entry Order	Model 4 Entry Order	Model 5 Entry Order	Model 6 Entry Order	Model 7 Entry Order
Recipient Race	1	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Recipient Age	2	**2**	**8**	**7**	**6**	**5**	**4**	**3**
Recipient Gender	3							
Recipient Marital Status (yes/no)	4							
CAD/Angina (yes/no)	5	**3**	**2**	**8**	**7**	**6**	**5**	**4**
Previous transplant (yes/no)	6							
Living Donor (yes/no)	7	**4**	**3**	**2**	**8**	**7**	**6**	**5**
Donor DCD	8							
Donor ECD	9							
0 HLA mismatches	10	**5**	**4**	**3**	**2**	**8**	**7**	**6**
1-5 HLA mismatches	11							
6 HLA mismatches	12							
Current PRA 0%	13							
Current PRA >20%	14							
Years on dialysis	15							
Preemptive Transplant	16							
IL2 Induction (yes/no)	17	**6**	**5**	**4**	**3**	**2**	**8**	**7**
Cytolytic Induction	18							
Tacrolimus	19							
Cyclosporine	20							
Mycophenolate	21							
Azathioprine	22							
mTOR inhibitors	23							
Corticoteroids	24							
No diabetes	25	**7**	**6**	**5**	**4**	**3**	**2**	**8**
A1C<8%	26							
A1C≥8%								
SBP <140 AND DBP <90	27							
SBP ≥140 or DBP ≥90								
No dyslipidemia	28							
LDL <100 AND TG <150	29							
LDL ≥100 or TG ≥150								
CVD Meds (statin, other lipid, beta blocker, ACE/ARB, CCB, diuretic, antiplatelet, Insulin, oral agent), categorized as not on therapy, on with MPR <80% or on with MPR ≥80%	47							
Acute Rejection	48	**8**	**7**	**6**	**5**	**4**	**3**	**2**
DGF	49							

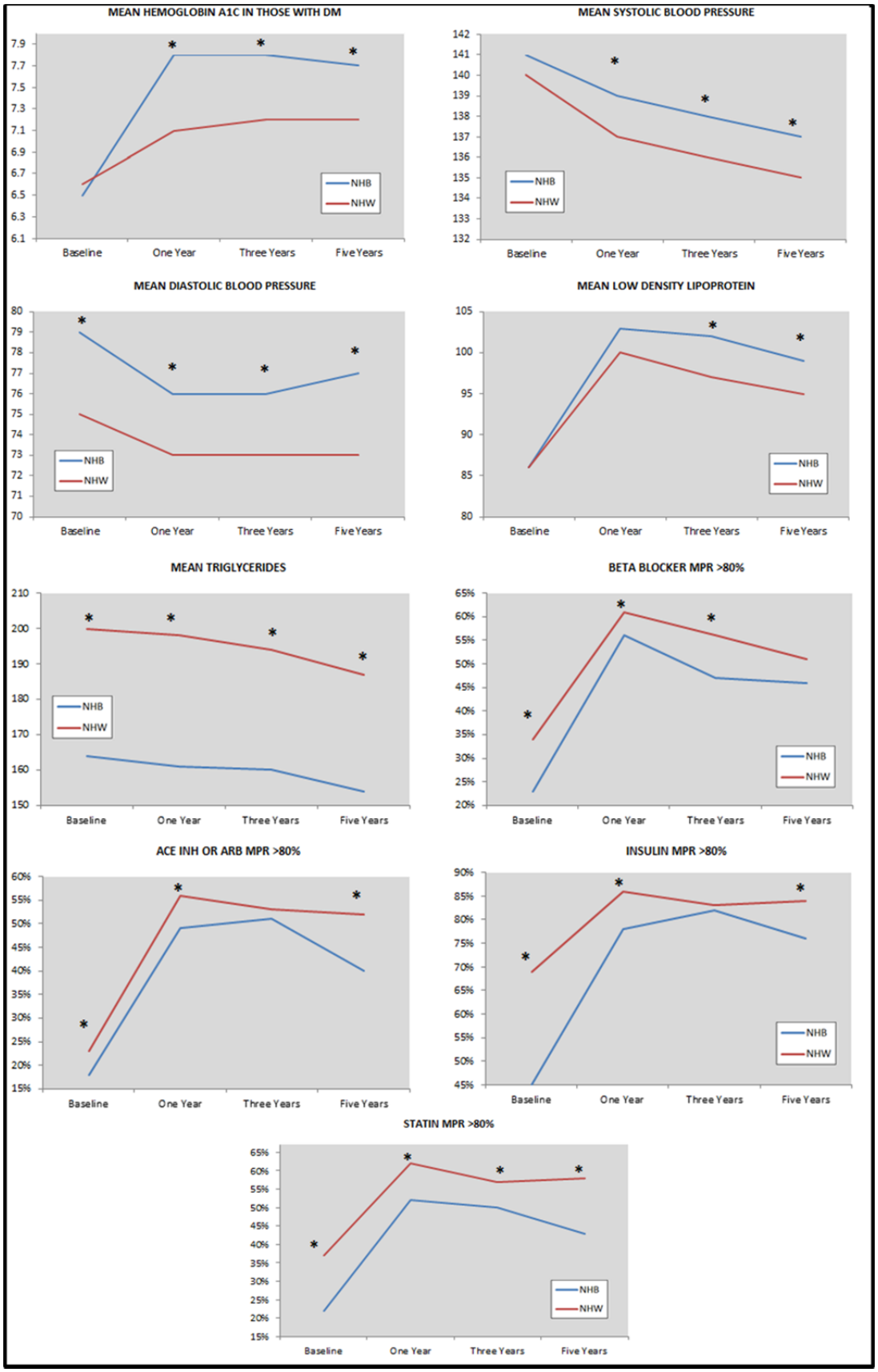
Supplemental Figure 1 Legend – Kaplan Meier curves depicting estimated death censored graft survival rates for living (top) and deceased (bottom) donors kidney recipients transplanted between Oct 1987 and Sept 2014 in the U.S.; the data is grouped by race, comparing NHB and NHW recipients, demonstrating a significant disparity in outcomes which starts early post-transplant and continues to diverge. The disparity is similar in magnitude based on donor type (living vs. deceased).



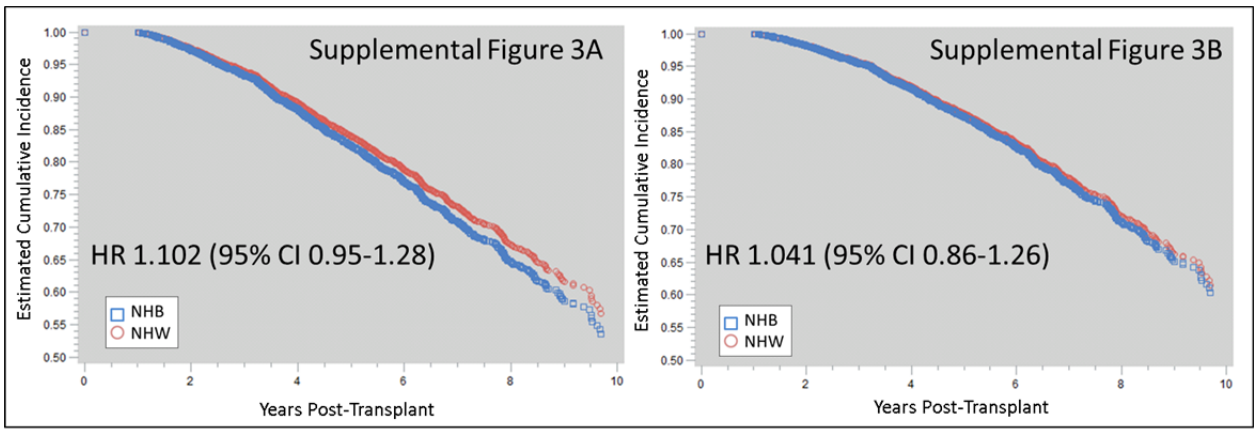
Supplemental Figure 2 Legend – Prevalence and control of hypertension, diabetes and dyslipidemia over time in adult kidney transplant recipients



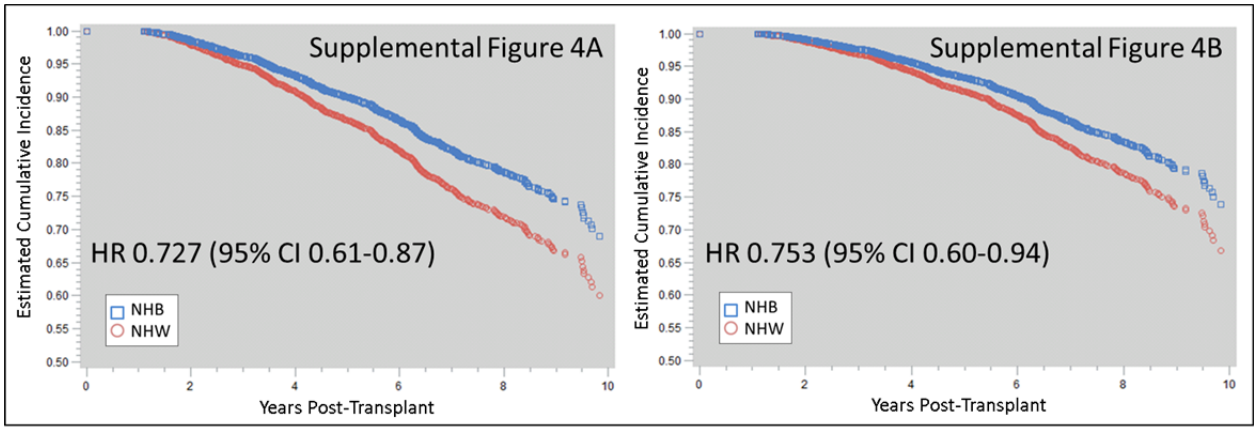
Supplemental Figure 3 Legend – Mean cardiovascular risk factor indices and adherence of predominant medications used to treat risks over time in adult kidney transplant recipients



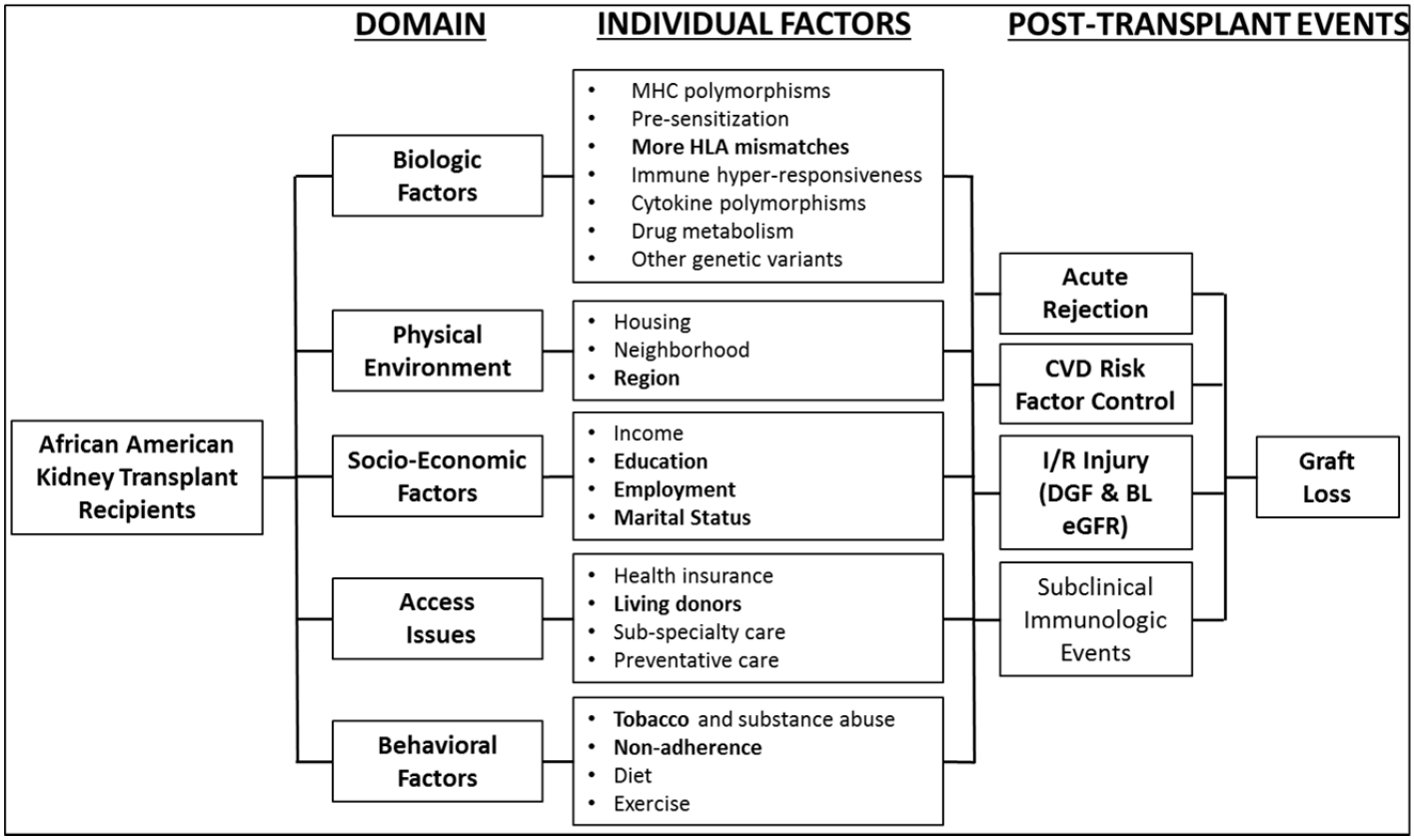
Supplemental Figure 4 Legend – Survival function curve estimates for the outcome of overall graft loss in NHB vs. NHW kidney transplants for the unadjusted model (3A) and the fully adjusted model (3B)



Supplemental Figure 5 Legend – Survival function curve estimates for the outcome of death in NHB vs. NHW kidney transplants for the unadjusted model (4A) and the fully adjusted model (4B)



Supplemental Figure 6 Legend – Conceptual model developed to explain the prevailing etiologies surrounding racial disparities in graft outcomes for kidney transplant recipients. There are five domains with individual factors listed within each domain. These factors lead to post-transplant events that eventually lead to disproportionately higher rates of graft loss in NHB recipients. This analysis will focus on the magnitude of CVD risk factor control as variables that influence racial disparities, after controlling for all other measured covariates.



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