CARDIOVASCULAR DISEASE AND KIDNEY DISEASE PROGRESSION IN KIDNEY TRANSPLANT RECIPIENTS

A thesis submitted by

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Abstract

Background: Kidney transplant recipients have a high prevalence of cardiovascular disease (CVD) and CVD risk factors. The relationship of CVD and CVD risk factors with kidney disease progression in transplant recipients remains uncertain. **Methods:** We performed a post hoc analysis of the Folic Acid for Vascular Outcomes Reduction in Transplantation (FAVORIT) Trial cohort to assess the association of CVD and CVD risk factors with kidney failure and all-cause mortality in stable kidney transplant recipients. CVD was defined as prior myocardial infarction, coronary, carotid or peripheral artery revascularization, stroke, or aortic aneurysm repair. Unadjusted and multivariable adjusted Cox proportional hazards models were used to explore the association of CVD history and risk factors with development of ESRD and all-cause mortality. **Results:** In 3,721 participants with complete data, mean age was 52 years, 18% were black, and 37% women; median graft vintage was 4.0 (1.7-7.4) years, 58% received deceased donor kidneys and 20% had prior CVD. Mean baseline eGFR was 48 +/-17 ml/min/1.73m^2. There were 296 kidney failure events and 440 deaths, with 666 individuals having the composite of kidney failure or death. Following adjustment, prior CVD was associated with a borderline significant increased risk of kidney failure [HR=1.33 (95% CI 0.98-1.73)] and significantly increased risk of all-cause mortality [HR=1.51 (1.23-1.85)] and the composite of kidney failure and death [HR=1.32 (1.11 – 1.58)]. Other risk factors for kidney failure included black race, higher SBP, lower HDL cholesterol, current smoking status as well as lower eGFR and deceased donor transplant. **Conclusion:** In stable kidney transplant recipients, CVD and CVD risk factors are associated with development of kidney failure; future trials should explore CVD risk factor modification to slow kidney disease progression.

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List of abbreviations

CVD: cardiovascular disease

ESRD: end stage renal disease

CKD: chronic kidney disease

GFR: glomerular filtration rate

KTRs: kidney transplant recipients

SBP: systolic blood pressure

DBP: diastolic blood pressure

BMI: body mass index

HDL: high density lipoprotein

LDL: low density lipoprotein

TG: triglycerides

DM: diabetes mellitus

Introduction

Despite substantial decreases in the rates of acute rejection of kidney transplants over the last 30 years, there have not been corresponding improvements in overall graft survival[1-3]. Therefore, improving patients' long term outcomes by preventing late allograft loss remains a clinical priority. In the general population, cardiovascular disease (CVD) and CVD risk factors are associated with increased risk for the development and progression of chronic kidney disease (CKD) [4,5].

In diseases of the native kidneys, decreased GFR is the major risk factor for subsequent kidney failure [6]. As decreased GFR is associated with an increased burden of CVD and CVD risk factors, including diabetes, hypertension, obesity, hypercholesterolemia, and smoking [4,5], one likely explanation for this association is a shared pathogenesis of CKD and CVD. CVD and CVD risk factors are common in kidney transplant recipients (KTRs), with CVD accounting for 30% of the deaths with a functioning graft[7]. Despite this, examination of the association of CVD and CVD risk factors with the risk of kidney failure in KTRs has not been extensively studied. Decreased GFR in KTRs is associated with late graft loss, but decreased GFR may reflect different pathogenetic mechanisms than in patients with native kidney disease. First, the transplant kidney has not been exposed to a life-time of CVD risk factors. Second, decreased GFR in KTRs may reflect donor factors, immunologic factors and kidney toxicity from the use of immunosuppressive medications. CVD risk factors and CVD are modifiable, and a better understanding of their association with the progression of kidney disease in KTRs could suggest treatment targets for future clinical trials to prevent late allograft loss.

The FAVORIT trial was a large randomized controlled trial to reduce CVD events in kidney transplant recipients, which had a systematic and detailed ascertainment of CVD risk factors, CVD and kidney disease events. This study examines the relative importance of pre-existing CVD and CVD risk factors in the progression of kidney disease in KTRs in the FAVORIT trial.

Materials and Methods

2.1 FAVORIT trial

This is a *post hoc* analysis of data from the FAVORIT trial [8]. FAVORIT was a multi-center double-blind randomized controlled clinical trial that evaluated whether lowering homocysteine levels with vitamin therapy reduced the rate of CVD outcomes in first time KTRs. The rationale and design of this multinational randomized controlled clinical trial have been previously published.[9] The protocol was approved by the human subjects' research entity with oversight at each center, and patients provided written informed consent prior to trial participation. The trial was registered with ClinicalTrials.gov (NCT00064753) in July 2003. This study was reviewed by the Tufts Medical Center IRB was determined to be non-human subject research exempt.

2.2 Study Population

FAVORIT investigators at transplant centers in the United States, Canada, and Brazil enrolled kidney transplant recipients who were at least 6 months post-transplant, had elevated total serum homocysteine levels (≥ 11 μmol/L for women; and ≥ 12 μmol/L for men), and had stable kidney function, initially defined by an estimated creatinine clearance ≥ 30mL/min in both men and women and redefined after July 7, 2005 in women only as ≥ 25 mL/min, and met other eligibility criteria.[9] Participants were randomized to receive either a standard multivitamin with high doses of folic acid (5 mg), vitamin B6 (pyridoxine; 50 mg) and vitamin B12 (cyanocobalamin; 1 mg) or a multivitamin containing low doses of vitamin B6 (1.4 mg) and vitamin B12 (2 μg) without folic acid. Since the high dose vitamin intervention had no impact on risk of kidney failure, CVD, or all-cause death in

comparison to the low dose vitamin (6), data from the two treatment groups were combined with a term retained for randomization allocation in all analyses. Complete details of the study population have been described previously. [23]

2.3 Study Variables

The primary independent variable for this study was a history of CVD. This was defined as the presence of prior myocardial infarction, coronary artery revascularization, stroke, carotid arterial revascularization, abdominal or thoracic aortic aneurysm repair, and/or lower extremity arterial revascularization. We also considered several CVD risk factors, including a history of diabetes, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI) category, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) cholesterol, and triglycerides (TG). Other variables of interest include demographics, transplant characteristics, and estimated GFR (eGFR) from serum creatinine. Race was defined as white, black, or other, with 'other' being defined as white for GFR estimation. Diabetes mellitus was defined as use of insulin or oral hypoglycemic medications or patient history. Smoking status was classified as current, former, or never by patient report. Seated blood pressure was measured twice at 5-10 minute intervals during each clinic visit, with the average value used for analyses. Body mass index was calculated using the formula: weight [kg]/ height $[m]^2$. BMI category was defined as "underweight" with a BMI <18.5, "normal" defined as 18.5-24.9, "overweight" defined as 25-29.9, and "obese" as >30 kg/m^2, respectively. Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald equation at triglyceride levels below 400 mg/dL and measured in the 234 participants with triglyceride levels above 400 mg/dL. Transplant characteristics include donor type defined as living versus non-

living donor and time since transplant. Serum creatinine was measured using frozen sera from the baseline visit at the FAVORIT central lab using an IDMS calibrated assay; GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[24, 25]

2.4 Study Outcomes

The primary outcome for this analysis was time since randomization to kidney failure, defined as the initiation of dialysis and described as end stage renal disease (ESRD) in FAVORIT. The secondary outcome was time to all-cause mortality and, to account for semi-competing risks, we examined the composite outcome of ESRD and all-cause mortality. Participants were censored at the time of development of a CVD outcome, the primary outcome for the parent study. For sensitivity analyses, we considered subsequent CVD as an outcome in combination with ESRD, all-cause mortality and the composite of ESRD and all-cause mortality. For these analyses, subsequent CVD was defined as pooled incident or recurrent CVD, comprised of CVD death, MI, resuscitated sudden death, stroke, coronary artery revascularization, lower extremity revascularization or amputation above the ankle for severe arterial disease, carotid endarterectomy or angioplasty, abdominal aortic aneurysm repair, or renal artery revascularization. The first four components were centrally reviewed and adjudicated with the remaining identified through medical record abstraction.

2.5 Statistical Analyses

Baseline characteristics were compared across eGFR strata using one-way ANOVA for normally

distributed variables and Chi-square tests for categorical variables. The non-parametric Kruskall-Wallis test and Fisher exact test were used for non-normally distributed continuous variables and categorical variables respectively.

Cox proportional-hazards regression was used to examine the association between baseline covariates and time to primary and secondary study outcomes in univariate analysis. Kaplan-Meier survival analysis was used to compare survival curves among groups based on CVD status.

All variables described above were examined using sequential multivariable models. Parsimonious models (Model 1) were *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG. The proportional hazards assumption was examined using log-log plot of survival by eGFR strata, and also Schoenfeld residuals for all variables included in the multivariable model. For potential interaction terms we have assessed CVD history with age, sex, and diabetes, and eGFR. All analyses were performed using Rexcel version 2.15.1. Dr. John had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Results

3.1 Baseline characteristics

Figure 1 describes the derivation of the FAVORIT cohort for these analyses. Between August 2002 and January 2007, 4110 participants were enrolled at 30 transplant centers in the United States (N=27), Canada (N=2), and Brazil (N=1). Among the 4110 enrolled participants, 94 were excluded for missing baseline creatinine and 295 participants were excluded for missing demographic characteristics, lab values, and clinical characteristics. The final population with complete data is 3,721 participants. Characteristics of the subjects included did not differ significantly from those excluded (Table 9).

Table 1 describes the baseline characteristics of the 3,721 participants stratified by eGFR. For the overall population, the mean (SD) age was 52 (9) years, 18% were black, 37% were women, median graft vintage was 4.03 (1.7-7.4) years , 42% had a living donor kidney, and 20% had a prior history of CVD. Mean eGFR was 48 (17) ml/min/1.73m^2. Patients with lower eGFR were slightly older in age, more often women, had a longer graft vintage, were more likely to have had a deceased donor transplant, had a higher prevalence of a history of CVD, and were more likely to have higher BMI, higher total cholesterol and lower HDL level. Table 2 describes the same participants stratified by history of CVD. Patients with a baseline history of CVD were more likely to be of older age, women, have a decreased donor transplant, have a higher SBP and lower DBP, lower total, lower HDL, and lower LDL cholesterol, have a higher serum creatinine and lower eGFR, and have a history of diabetes.

3.2 Endpoints

Follow-up ranged from 0 to 82 months, with a median of 42 months (IQR 33, 61). Table 3 shows outcomes of the participants with complete data stratified by baseline eGFR. Altogether, there were 296, 440 and 666 ESRD, all-cause mortality and composite events, respectively, with corresponding event rates of 22.1, 29.2, and 45.3 per 1,000 patient years, respectively. Patients with lower GFR were more likely to develop ESRD, die and reach the composite outcome. For the lowest eGFR group (eGFR of <30 ml/min/1.73m^2), the event rates per 1,000 patient years were 65.1 for ESRD, 51 for all-cause mortality, and 99.6 for the composite outcome. Table 4 shows outcomes of the same participants stratified by baseline CVD history. For those with a baseline CVD history the event rates per 1,000 patient years were 27.2 for ESRD, 51.8 for all-cause mortality, and 67.5 for the composite outcome.

3.3 Risk Factor Analysis

Table 5 describes univariate associations with each outcome. In addition to eGFR and transplant characteristics, a history of CVD and all CVD risk factors were significant for all outcomes. Older age was associated with a lower risk for ESRD but a higher risk for mortality. As seen in Figure 3, kidney transplant recipients with a history of CVD were significantly more likely to develop each of the 3 outcomes.

After adjustment for demographic factors, eGFR, and transplant factors, a history of CVD was associated with a HR (95%CI) for ESRD of 1.45 (1.10-1.92), although this was modestly attenuated after further adjustment for CVD risk factors [HR of 1.33 (0.98-1.73)]

(Table 6). For all-cause mortality and the composite outcome, a history of CVD was associated with a HR of 1.51 (1.23-1.85) and 1.32 (1.11-1.58), respectively, in fully adjusted models (Table 7 and 8). As in univariate analysis, older age was associated with a lower risk ESRD, but a higher risk for mortality and the composite outcome. Other significant risk factors for all 3 outcomes included lower eGFR, deceased donor transplant, history of diabetes, current smoking status, higher SBP, and lower HDL cholesterol. Plots of linearity failed to reject the (null) hypothesis of a linear association of eGFR with each outcome (Figure 4). There were no violations of the proportional hazards assumption (Figure 5). There were no significant interaction terms when assessing CVD history with age, sex, and diabetes, and eGFR for the outcome of ESRD (Table 10).

3.4 Sensitivity Analysis

Table 11 describes the univariate associations with each outcome (CVD/ESRD, CVD/all-cause mortality, and CVD/ESRD/all-cause mortality). As can be noted in Table 11 and Figure 6, kidney transplant recipients with a history of CVD were significantly more likely to develop each of the outcomes described. Altogether there were 527 CVD events and 732, 732, and 914 events for the CVD/ESRD, CVD/all-cause mortality and CVD/ESRD/all-cause mortality outcomes, respectively. For the outcomes of CVD, CVD/ ESRD, CVD/ mortality, and CVD/ESRD/all-cause mortality, a baseline history of CVD was associated with HRs of 2.09 (1.74, 2.52), 1.75 (1.49, 2.06), 1.84(1.57, 2.16) and 1.65 (1.43, 1.91), respectively, after extended multivariable adjustment of CVD risk factors (Model 5, Tables 12-15).

Discussion

Both CVD history and CVD risk factors are strongly associated with the development of ESRD and all-cause mortality in KTRs, independent of kidney function. These associations persist after adjusting for demographic and clinical characteristics and remain significant with adjustment for transplant characteristics including donor type and graft vintage. To our knowledge, this is the first large study in KTRs with detailed ascertainment of CVD history and use of extensively adjusted models to evaluate these associations. Our findings extend the findings from previous studies and have important implications for clinical research.

In the general population, CVD risk factors are associated with development and progression of CKD.[4,5]

Similar to the general population, several prior studies have also studied the progression to ESRD in the kidney transplant population. CVD risk factors that have been noted to have an association with decreased graft survival include older recipient age, diabetes, hypertension, dyslipidemia, and smoking status.[1,3, 10-14] Additional factors that may lead to decreased graft survival in KTRs may be divided as immunologic causes (donor specific antibodies, acute cellular rejection, retransplantation [15,16] and non-immunologic causes (male sex, increasing donor age, ischemic reperfusion injury, calcineurin inhibitor nephrotoxicity, viral infections, and anemia)[17,18] (Figure 2). Based on our study, we can add a history of prior CVD to the non-immunologic risk factors for decreased graft survival.

One likely explanation for the association of CVD and CVD risk factors with development and progression of native kidney disease is a shared pathogenesis of CKD and CVD, operating through several mechanisms. First, high blood pressure, diabetes, hyperlipidemia and smoking are shared risk factors for both CVD and CKD in native kidneys. Second, complications of interventions for CVD may cause acute and chronic kidney disease, such as toxicity associated with radiographic contrast or atheroemboli during cardiac catheterizations. Third, some cardiovascular conditions have a direct effect on kidney function, such as heart failure and renal artery stenosis. However, it is not known whether these mechanisms would be observed in KTRs because of the short duration of exposure of the allograft to recipient CVD risk factors and CVD.

Finding similar associations between CVD and CVD risk factors with kidney disease progression in kidney transplant recipients as in the general population raises the possibility that even the short duration of exposure to these factors may cause damage to the allograft. This novel idea would be consistent with the description by Nankivell et al of distinctive phases of injury. In the first year following transplant, early tubulointerstitial damage correlates with immunologic factors, including severe acute rejection, persistent subclinical rejection, and ischemia-reperfusion injury. Pathologic findings include new-onset tubulointerstitial damage and rapidly increasing Banff scores for interstitial fibrosis and tubular atrophy. In later years, the patterns of allograft injury change and reflect microvascular injury. Pathologic findings include persistent arteriolar hyalinosis, progressive ischemic glomerulosclerosis, and additional interstitial fibrosis. Possibly, the

late microvascular pathology may be the result, in part, to an ongoing exposure to CVD risk factors, complications of CVD interventions and CVD conditions.[19,20]

There have been few trials evaluating CVD risk factor modification in kidney transplant recipients. The ALERT trial was a randomized controlled trial of the LDL lowering agent, fluvastatin versus placebo on kidney allograft survival in 2102 KTRs. Fluvastatin treatment reduced mean serum LDL cholesterol levels by 32% but had no effect on the risk of the composite endpoint of kidney graft loss or doubling of serum creatinine (RR of 1.02, CI 0.86, 1.21).[21] The FAVORIT trial evaluated the impact of a vitamin intervention to lower total homocysteine levels in KTRs. Prior observational trials had suggested that increased homocysteine is a risk factor for CVD. Treatment with the high-dose multivitamin reduced plasma homocysteine levels by 26% but did not reduce the rates of dialysis-dependent kidney failure (HR 1.15 and CI 0.93 to 1.43).[8]

Our findings suggest that KTRs with a history of CVD or CVD risk factors may be an important population in which to study strategies for CVD risk factor modification. Guidelines recommend monitoring of blood pressure, lipid profile, screening for tobacoo use, assessing BMI, and aspirin use in those with atherosclerotic CVD, but the strength of evidence is weak because it is based on extrapolation of studies from the general population. However, KTRs may be at higher risk of adverse effects of risk factor modification; for example, a higher incidence of statin-related myopathy may occur due to an interaction between statins and calcineurin inhibitors and a higher incidence of

metformin-related lactic acidosis may occur in patients with decreased GFR. Accordingly, trials in KTRs are necessary to determine the risks and benefits of these interventions.

Our study has several limitations that must be kept in mind in interpreting the findings. First, the transplant recipients participating in FAVORIT may differ from the general population of KTRs; however, the study population is similar to SRTR in age, sex and race distribution.[22] Second, we have combined treatment groups for our analysis; however the clinical trial was negative, finding no effect of the vitamin intervention on outcomes.[8] Additionally, we adjusted for the intervention assignment in all analyses. Third, there may be informative censoring due to loss to follow up after CVD events. Sensitivity analyses note that those with a prior history of CVD are more likely to develop ESRD, and all-cause mortality when combined with the CVD outcome, thus failure to ascertain outcomes after ESRD events may lead to underestimates of the risks associated with a history of CVD. Finally, we lack data on albuminuria as well as on immunologic related factors such as HLA type, donor age, and treatment for rejection episodes. Future studies should include these variables.

In conclusion, in a large, population of stable KTRs, we have identified an association between CVD history and CVD risk factors with ESRD and mortality outcomes. Further research is needed to evaluate strategies to help modify this risk.

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Table 1. Baseline characteristics stratified by eGFR category

	Total	eGFR >75	eGFR 60-<75	eGFR 45-<60	eGFR 30-<45	eGFR <30	p-value
	n = 3721	n = 297	n = 577	n = 1130	n = 1243	n= 474	
Age	51.64 (9.4)	49.8 (9.2)	51.1 (9.7)	51.5 (9.4)	52.1 (9.4)	52.5 (9)	<0.001
Women	1378 (37)	99 (32.3)	185 (32.1)	383 (33.9)	496 (39.7)	218 (46)	<0.001
Race							<0.001
White	2832 (76.1)	193 (65)	420 (72.8)	884 (78.2)	962 (77.4)	373 (78.7)	
Black	657 (17.7)	81 (27.3)	113 (19.6)	181 (16)	212 (17.1)	70 (14.8)	
Other	232 (6.2)	23 (7.7)	44 (7.6)	65 (5.8)	69 (5.6)	31 (6.5)	
Location							0.001
United States	2711 (72.9)	225 (75.8)	399 (69.2)	810 (71.7)	930 (74.8)	347 (73.2)	
Canada	401 (10.8)	22 (7.4)	57 (9.9)	104 (9)	142 (11.4)	76 (16.0)	
Brazil	609 (16.4)	50 (16.8)	121 (21)	216 (19.1)	171 (13.8)	51 (10.8)	
Graft vintage (median and IQR)	5.43 (4.97)	4.50 (4.69)	4.94 (4.93)	5.23 (4.82)	5.71 (5.02)	6.37 (5.17)	<0.001
Deceased Donor	57.8%	65.3%	56.5%	52.8%	58.3%	65%	<0.001
Smoking							0.4
Never	1818 (48.9)	142 (47.8)	276 (47.8)	561 (49.7)	623 (50.1)	216 (45.6)	
Current	415 (11.2)	33 (11.1)	60 (10.4)	106 (9.4)	157 (12.6)	59 (12.5)	
Former	1488 (40)	122 (41.1)	241 (41.8)	463 (41)	463 (37.3)	199 (42)	
SBP (mmHg)	136.14 (19.8)	133.26 (19.1)	135.60 (18.9)	136.31 (20)	136.28 (19.7)	137.83 (20.8)	0.03
DBP (mmHg)	78.65 (12.3)	79.07 (11.5)	79.05 (11.7)	79.16 (12.5)	78.22 (12.4)	77.84 (12.8)	0.2
BMI (SD) kg/m^2	29.18 (6.2)	28.35 (6.4)	28.31 (5.8)	29.03 (6.2)	29.38 (6.1)	30.58 (6.5)	<0.001
BMI category (kg/m^2)							<0.001
Less than 18.5	29 (0.78)	3 (1)	8 (1.4)	10 (0.9)	7 (0.6)	1 (0.2)	
18.5-24.9	957 (25.7)	94 (31.6)	174 (30.2)	289 (25.6)	314 (25.3)	86 (18.1)	
25-29.9	1328 (35.7)	105 (35.3)	200 (15.1)	416 (36.8)	435 (35.0)	172 (36.3)	
>30	1407 (37.81)	95 (32.0)	195 (34.7)	415 (36.7)	487 (39.2)	215 (45.4)	
Total Cholesterol (mg/dL)	184.8(44)	178.6 (39.5)	183.5 (39.8)	185 (43.9)	184.8 (43.9)	190 (50.9)	0.01
HDL (mg/dL)	46.2 (14)	46.8 (12.9)	48.1 (14.4)	46.5 (13.9)	45.6 (13.66)	44.7 (15)	<0.001
LDL (mg/dL)	101.2 (34.1)	98.1 (31.4)	101.1 (30.9)	101.7 (34)	100.7(35)	103.1(39.4)	0.4
Triglycerides (mg/dL)	199.2(185.3)	175.6(112)	177.4(116.1)	192.4(128.0)	204.8 (150)	242.6 (380.8)	<0.001
Serum creatinine (mg/dL)	1.6 (0.5)	1.2 (0.3)	1.3 (0.3)	1.5 (0.3)	1.8 (0.4)	2.2 (0.5)	<0.001
eGFR, (ml/min/173m^2)	48.9 (17.6)	87.7 (10.5)	66.5 (4.2)	52 (4.3)	37.8 (4.2)	24.9 (4.0)	
DM	1504 (40.4)	125 (42.1)	233 (40.4)	455 (40.3)	505 (40.6)	186 (39.2)	1.0
CVD	768 (20.6)	52 (17.5)	111 (19.2)	218 (19.3)	264 (21.2)	123 (26)	0.02

Data reported as mean ± standard deviation,or frequency (percent). SBP is systolic blood pressure, DBP is diastolic blood pressure, DM is history of diabetes mellitus, CVD is prior history of CVD. *P-value comparisons across eGFR categories are based on chi-square for categorical variables, and analysis of variance for continuous variables.

Table 2. Baseline characteristics stratified by history of CVD

	Total	CVD history	No CVD history	p-value
	N=3,721	N=768	N= 2953	
Age (SD)	51.6 (9.4)	55.4 (9.0)	50.7 (9.2)	<0.001
Women (n, %)	1377(37.0)	306 (39.8)	780 (26.4)	<0.001
Race				0.18
White	2832 (76.1)	600 (78.1)	2232 (75.6)	
Black	657 (17.7)	119 (15.5)	538 (18.2)	
Other	232 (6.2)	49 (6.4)	183 (6.2)	
Location				0.006
United States	2711 (72.9)	592 (77.1)	2119 (71.8)	
Canada	401 (10.8)	62 (8.1)	339 (11.5)	
Brazil	609 (16.4)	114 (14.8)	495 (16.8)	
Graft vintage (years)	5.4 (4.9)	5.2 (4.5)	5.5 (5.1)	0.10
Deceased Donor	2151 (57.8)	478 (62.2)	1671 (56.6)	0.005
Smoking				0.06
Current	415 (11.1)	84 (10.9)	331 (11.2)	
Former	1488 (40.0)	386 (50.3)	1102 (37.3)	
Never	1818 (48.9)	298 (38.8)	1520 (51.5)	
SBP (mmHg)	136.1 (19.8)	137.9 (20.9)	135.7 (19.4)	0.005
DBP (mmHg)	78.7 (12.3)	76.3 (12.8)	79.3 (12.1)	<0.001
BMI (SD) kg/m^2	29.2 (6.2)	29.4 (5.7)	29.1 (6.3)	0.29
BMI category (kg/m^2)				0.29
18.5-24.9	957 (25.7)	169 (21.9)	788 (26.7)	
less than 18.5	29 (0.8)	4 (0.5)	25 (0.8)	
25-29.9	1328 (35.7)	288 (37.5)	1040 (35.2)	
>30	1407 (37.8)	307 (40.0)	1100 (37.3)	
Total Cholesterol (mg/dL)	184.8 (44.0)	177.1 (41.6)	186.8 (44.3)	<0.001
HDL (mg/dL)	42.2 (14.0)	43.7 (12.5)	46.9 (14.3)	<0.001
LDL (mg/dL)	101.2 (34.4)	95.3 (33.1)	102.7 (34.6)	<0.001
Triglycerides (mg/dL)	199.2(185.3)	201.6 (142.6)	198.6 (194.9)	0.69
Serum creatinine (mg/dL)	1.63 (0.5)	1.7 (0.5)	1.6 (0.5)	0.005
eGFR, ml/min/1.73m^2	48.89 (17.6)	47.0 (16.8)	49.4 (17.8)	<0.001
eGFR >75	297 (8.0)	52 (6.8)	245 (8.3)	
eGFR 60- <75	577 (15.5)	111 (14.5)	466 (15.8)	
eGFR 45 - <60	1130 (30.4)	218 (28.4)	912 (30.9)	
eGFR 30 - <45	1243 (33.4)	264 (34.4)	979 (33.2)	
eGFR <30	474 (12.7)	123 (16.0)	351 (11.9)	
DM	1504(40.4)	449 (58.5)	1054 (35.7)	<0.001
ESRD Outcome	296 (8.0)	71 (9.2)	225 (7.6)	0.14
Mortality Outcome	440 (11.8)	158 (20.6)	282 (9.5)	<0.001
Composite Outcome	666 (17.9)	200 (26.0)	466 (15.8)	<0.001

Data reported as mean ± standard deviation,or frequency (percent). SBP is systolic blood pressure, DBP is diastolic blood pressure, DM is history of diabetes mellitus. *P-value comparisons across baseline CVD categories are based on chi-square for categorical variables, and analysis of variance for continuous variables.

Table 3. Outcomes by eGFR category (events per 1000 person years)

eGFR range	**Total**	**eGFR >75**	**eGFR 60-<75**	**eGFR 45-<60**	**eGFR 30-<45**	**eGFR <30**
	n=3721	**n=297**	**n=577**	**n=1130**	**n=1243**	**n=474**
ESRD						
Events	296 (8.0%)	12 (4%)	22 (3.8%)	42 (3.7%)	117 (9.4%)	103 (21.7%)
Total follow up (years)	13,750	1,152	2,186	4,316	4,512	1,583
Event rate (per 1,000 patient- years)	21.5	10.4	10.1	9.7	25.9	65.1
Mortality						
Events	440 (11.8%)	29 (9.8%)	51 (8.8%)	105 (9.3%)	160 (21.9%)	95 (20.04%)
Total follow up (years)	15.049	1,233	2,325	4,644	4,997	1,848
Event rate (per 1,000 patient- years)	29.2	23.5	21.9	22.6	32.0	51.4
Composite						
Events	666 (17.9%)	38 (12.8%)	68 (11.8%)	140 (12.4%)	250 (20.1%)	170 (35.9%)
Total follow up (years)	14,664	1,223	2,308	4,576	4,847	1,706
Event rate (per 1,000 patient- years)	45.3	31.1	29.4	30.6	51.6	99.6

Data reported as mean ± standard deviation for years. *P-value comparisons across eGFR categories are based on analysis of variance.

Table 4. Outcomes by baseline CVD history (events per 1000 person years)

	Overall	**Baseline CVD**	**No CVD**
	n=3721	**n= 768**	**n= 2953**
ESRD			
Events	296 (8.0%)	71 (9.2)	225 (7.6%)
Total follow up (years)	13,750	2,693	11,057
Event rate (per 1,000 patient- years)	21.5	27.2	20.2
Mortality			
Events	440 (11.8%)	158 (20.6%)	282 (9.5%)
Total follow up (years)	15.049	3,049	12,000
Event rate (per 1,000 patient- years)	29.2	51.8	23.5
Composite			
Events	666 (17.9%)	200 (26.0%)	466 (15.8%)
Total follow up (years)	14,664	2,715	11,949
Event rate (per 1,000 patient- years)	45.3	67.5	39.8

Data reported as mean ± standard deviation for years. *P-value comparisons across eGFR categories are based on analysis of variance.

Table 5. Univariate Analysis per characteristic for ESRD, Mortality, and Composite Outcome

	ESRD (n=296)			Mortality(n=440)			Composite (n= 666)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age per 10 years	0.8	(0.70, 0.90)	<0.001	1.64	(1.49, 1.81)	<0.001	1.22	(1.13, 1.32)	<0.001
Women	0.88	(0.69, 1.11)	0.3	0.94	(0.78, 1.15)	0.6	0.92	(0.78, 1.08)	0.3
Race									
White	ref			ref			ref		
Black	1.59	(1.22, 2.09)	<0.001	1.07	(0.83, 1.36)	0.6	1.29	(1.07, 1.56)	0.008
Other	1.19	(0.74, 1.93)	0.5	0.97	(0.65, 1.45)	0.9	1.07	(0.77, 1.48)	0.7
Location									
United States	ref			ref			ref		
Canada	0.82	(0.56, 1.20)	0.3	0.78	(0.56, 1.09)	0.1	0.86	(0.66, 1.11)	0.2
Brazil	0.45	(0.26, 0.79)	0.005	0.83	(0.58, 1.19)	0.3	0.72	(0.54, 0.98)	0.04
Graft vintage	1.02	(1.00, 1.04)	0.03	1.01	(0.99, 1.03)	0.2	1.02	(1.01, 1.03)	0.007
Deceased Donor	1.56	(1.22, 2.00)	<0.001	1.83	(1.48, 2.25)	<0.001	1.62	(1.37, 1.91)	<0.001
Smoking									
Never	ref			ref			ref		
Current	1.73	(1.24, 2.40)	<0.001	1.64	(1.23, 2.19)	<0.001	1.65	(1.31, 2.07)	<0.001
Former	1.04	(0.81, 1.34)	0.8	1.46	(1.20, 1.79)	<0.001	1.25	(1.06, 1.47)	0.009
SBP per 10 (mm Hg)	1.18	(1.12, 1.25)	<0.001	1.13	(1.08, 1.18)	<0.001	1.14	(1.10, 1.19)	<0.001
DBP per 10 (mm Hg)	1.12	(1.02, 1.24)	0.02	0.87	(0.80, 0.95)	0.001	0.98	(0.92, 1.05)	0.6
BMI category (kg/m^2)									
less than 18.5	0.51	(0.07, 3.69)	0.5	0.29	(0.04, 2.10)	0.2	0.20	(0.03, 1.40)	0.1
18.5-24.9	ref			ref			1		
25-29.9	1.08	(0.79 , 1.46)	0.6	0.85	(0.67, 1.09)	0.2	0.92	(0.76, 1.12)	0.4
>30	1.14	(0.85, 1.54)	0.4	0.96	(0.76, 1.21)	0.7	0.96	(0.79, 1.17)	0.7
Chole/20 (mg/dL)	1.06	(1.01, 1.12)	0.02	0.99	(0.95, 1.04)	0.9	1.02	(0.99, 1.06)	0.2
HDL/20 (mg/dL)	0.78	(0.66, 0.94)	0.007	0.83	(0.72, 0.96)	0.01	0.8	(0.71, 0.90)	<0.001
LDL/20 (mg/dL)	1.07	(1.01, 1.14)	0.04	0.96	(0.90, 1.01)	0.1	1.01	(0.97, 1.06)	0.7
TG/50 (mg/dL)	1.02	(1.01, 1.03)	0.005	1.02	(1.006, 1.03)	0.003	1.02	(1.01, 1.03)	<0.001
Creatinine (mg/dL)	4.07	(3.36, 4.94)	<0.001	1.6	(1.34, 1.92)	<0.001	2.4	(2.09, 2.76)	<0.001
eGFR/5 ml/min/1.73m^2	0.78	(0.75, 0.82)	<0.001	0.92	(0.89, 0.95)	<0.001	0.88	(0.85, 0.90)	<0.001
DM	1.33	(1.06, 1.67)	0.02	2.14	(1.77, 2.59)	<0.001	1.71	(1.45, 1.99)	<0.001
CVD	1.39	(1.07, 1.82)	0.02	2.22	(1.83, 2.70)	<0.001	1.71	(1.45, 2.02)	<0.001
MI	1.48	(1.21, 1.82)	<0.001	1.71	(1.48, 1.99)	<0.001	1.53	(1.34, 1.74)	<0.001
CA revasc	1.14	(0.89, 1.45)	0.3	1.49	(1.27, 1.74)	<0.001	1.3	(1.13, 1.50)	<0.001
stroke	1.41	(1.11, 1.81)	0.006	1.23	(0.99, 1.53)	0.06	1.21	(1.01, 1.45)	0.04
AAA	1.23	(0.51, 2.96)	0.6	2.07	(1.32, 3.24)	0.002	1.61	(1.02, 2.53)	0.04
RA revasc	0.8	(0.42, 1.53)	0.5	1.36	(0.98, 1.88)	0.07	1.15	(0.85, 1.56)	0.4
Amputation	1.08	(0.56, 2.08)	0.8	1.47	(0.97, 2.22)	0.07	1.3	(0.90, 1.87)	0.2
Caro revasc	1.36	(0.75, 2.47)	0.3	2.16	(1.61, 2.91)	<0.001	1.79	(1.35, 2.37)	<0.001
Study Group	0.88	(0.70, 1.11)	0.3	1.01	(0.84, 1.22)	0.9	0.96	(0.82, 1.11)	0.6

Univariate Analyses exploring the association between risk factors and ESRD, Mortality, and Composite outcomes. Hazard Ratio (HR) for age per 10 years, Chole; total cholesterol/20 mg/dL increase;l, LDL and HDL cholesterol per 20 mg/dL increase; TG/50 is triglycerides per 50 mg/dL increase, systolic and diastolic blood pressure per 10 mmHg increase; eGFR per 5mL/min/1.73m^2, vintage per year increase. DM; history of diabetes mellitus. CVD; baseline CVD history. MI; history of myocardial infarction. CA revasc; history of coronary revascularation. Stroke; baseline history of stroke. AAA; baseline history of abdominal aortic aneurysm. RA revasc; baseline history of renal artery revascularization. Amputation; prior history of lower extremity amputation. Caro revasc; baseline history of carotid revascularization..Study Group is the treatment variable in the parent study.

Table 6. Multivariable adjusted Models of ESRD

	Model 1	Model 2	Model 3	Model 4	Model 5
Age, per 10 years	0.79 (0.70, 0.90)	0.75 (0.66, 0.85)	0.74 (0.65, 0.85)	0.72 (0.63, 0.82)	0.68 (0.59, 0.78)
Women	0.87(0.68, 1.10)	0.77 (0.60, 0.97)	0.77 (0.60, 0.98)	0.79 (0.62, 1.01)	0.86 (0.67, 1.12)
Race					
White	ref	ref	ref	ref	ref
Black	1.58 (1.20, 2.07)	1.73 (1.31, 2.27)	1.66 (1.26, 2.20)	1.68 (1.27, 2.22)	1.62 (1.21, 2.15)
Other	1.21 (0.75, 1.97)	1.36 (0.84, 2.21)	1.37 (0.85, 2.23)	1.40 (0.87, 2.28)	1.48 (0.91, 2.41)
Location					
United States	ref	ref	ref	ref	ref
Canada	0.88 (0.60, 1.30)	0.77 (0.52, 1.13)	0.74 (0.50, 1.09)	0.74 (0.50, 1.10)	0.77 (0.52, 1.15)
Brazil	0.41 (0.24, 0.72)	0.50 (0.29, 0.86)	0.55 (0.32, 0.96)	0.54 (0.31, 0.94)	0.42 (0.23, 0.76)
Study Group	0.88 (0.71, 1.11)	0.94 (0.75, 1.18)	0.94 (0.75, 1.18)	0.94 (0.75, 1.18)	0.92 (0.73, 1.15)
eGFR, per 5 ml/min/173m^2		0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.74, 0.82)	0.79 (0.75, 0.82)
DM					1.34 (1.05, 1.72)
CVD				1.45 (1.10, 1.92)	1.33 (0.98, 1.73)
Graft vintage			1.01 (0.99, 1.04)	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)
Deceased Donor			1.48 (1.15, 1.90)	1.45 (1.13, 1.86)	1.40 (1.09, 1.81)
Smoking					
Never					ref
Current					1.42 (1.02, 1.99)
Former					1.16 (0.90, 1.51)
SBP/10 mmHg					1.19 (1.11, 1.27)
DBP/ 10 mmHg					0.99 (0.86, 1.13)
BMI category (kg/m^2)					
less than 18.5					0.81 (0.11, 5.90)
18.5-24.9					ref
25-29.9					0.97 (0.71, 1.33)
>30					0.81 (0.59, 1.12)
Chole/20 mg/dL					1.10 (0.96, 1.25)
HDL/20 mg/dL					0.78 (0.63, 0.95)
LDL/20 mg/dL					0.96 (0.83, 1.12)
TG/50 mg/dL					0.99 (0.97, 1.02)
Likelihood Ratio	37.33	192.3	203.2	209.8	261.9
Df	7	8	10	11	23
C-statistic	0.61	0.75	0.75	0.75	0.77

Table 4. Hazard Ratio (HR) for age per 10 years, LDL and HDL; Chole; cholesterol per 20 mg/dL higher; TG; triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year higher. DM; history of diabetes mellitus. CVD; baseline CVD history. ..Study Group is the treatment variable in the parent study.Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG.

Table 7. Multivariable adjusted Models of Mortality Outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Age/10 years	1.65 (1.50, 1.83)	1.64 (1.48, 1.81)	1.62 (1.46, 1.79)	1.54 (1.38, 1.70)	1.52 (1.35, 1.70)
Women	0.93 (0.77, 1.13)	0.90 (0.74, 1.10)	0.91 (0.75, 1.11)	0.98 (0.81, 1.20)	1.01 (0.82, 1.26)
Race					
White	ref	ref	ref	Ref	ref
Black	1.11 (0.86, 1.42)	1.18 (0.92, 1.51)	1.10 (0.85, 1.42)	1.11 (0.86, 1.43)	1.12 (0.86, 1.44)
Other	0.99 (0.67, 1.50)	1.04 (0.70, 1.43)	1.05 (0.70, 1.58)	1.05 (0.70, 1.59)	1.03 (0.68, 1.55)
Location					
United States	ref	ref	ref	Ref	ref
Canada	0.74 (0.53, 1.03)	0.69 (0.50, 0.97)	0.65 (0.47, 0.92)	0.68 (0.49, 0.96)	0.74 (0.53, 1.04)
Brazil	0.97 (0.68, 1.38)	1.01 (0.70, 1.43)	1.12 (0.78, 1.60)	1.12 (0.78, 1.60)	1.19 (0.81, 1.76)
Study Group	1.00 (0.83, 1.21)	1.03 (0.85, 1.24)	1.02 (0.85, 1.24)	1.03 (0.85, 1.24)	1.02 (1.01, 1.05)
eGFR, per 5 ml/min/1.73m^2		0.92 (0.89, 0.95)	0.92 (0.90, 0.95)	0.93 (0.90, 0.96)	0.93 (0.91, 0.96)
DM					1.90 (1.54, 2.33)
CVD				1.77 (1.44, 2.16)	1.51 (1.23, 1.85)
Graft vintage			1.01 (0.99, 1.03)	1.02 (0.99, 1.04)	1.03 (1.01, 1.05)
Deceased Donor			1.70 (1.38, 2.11)	1.67 (1.35, 2.06)	1.57 (1.27, 1.94)
Smoking					
Never					ref
Current					1.70 (1.26, 2.29)
Former					1.23 (1.02, 1.55)
SBP/10 mmHg					1.11 (1.05, 1.17)
DBP/ 10 mmHg					0.90 (0.81, 0.99)
BMIcategory (kg/m^2)					
less than 18.5					0.42 (0.06, 3.05)
18.5-24.9					ref
25-29.9					0.66 (0.51, 0.85)
>30					0.66 (0.51, 0.85)
Chole/20 mg/dL					1.17 (1.04, 1.31)
HDL/20 mg/dL					0.82 (0.68, 0.98)
LDL/20 mg/dL					0.86 (0.76, 0.98)
TG/50 mg/dL					0.99 (0.96, 1.03)
Likelihood Ratio	101.2	130.3	158.9	187.7	281.1
Df	7	8	10	11	23
C-statistic	0.643	0.657	0.675	0.689	0.72

Table 5. Analyses were censored at development of Mortality. Hazard Ratio (HR) for age per 10 years, LDL and HDL; Chole; cholesterol per 20 mg/dL higher; TG;triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year higher. DM; history of diabetes mellitus. CVD; baseline CVD history. ..Study Group is the treatment variable in the parent study. Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG

Table 8. Multivariable adjusted Models of Composite outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Age/10 years	1.22 (1.13, 1.33)	1.19 (1.10, 1.30)	1.18 (1.09, 1.29)	1.14 (1.05, 1.24)	1.11 (1.02, 1.22)
Women	0.91 (0.77, 1.06)	0.85 (0.73, 1.00)	0.86 (0.73, 1.01)	0.90 (0.76, 1.06)	0.97 (0.81, 1.15)
Race					
White	ref	ref	Ref	ref	ref
Black	1.32 (1.09, 1.59)	1.42 (1.18, 1.73)	1.37 (1.13, 1.66)	1.38 (1.14, 1.68)	1.38 (1.13, 1.69)
Other	1.09 (0.79, 1.51)	1.11 (0.88, 1.54)	1.19 (0.86, 1.65)	1.21 (0.87, 1.67)	1.26 (0.91, 1.74)
Location					
United States	ref	ref	Ref	ref	ref
Canada	0.86 (0.66, 1.12)	0.78 (0.60, 1.018)	0.75 (0.57, 0.97)	0.76 (0.59, 0.99)	0.81 (0.62, 1.05)
Brazil	0.76 (0.56, 1.02)	0.82 (0.60, 1.11)	0.91 (0.67, 1.23)	0.90 (0.66, 1.22)	0.83 (0.59, 1.15)
Study Group	0.96 (0.82, 1.11)	0.99 (0.85, 1.15)	0.99 (0.85, 1.15)	0.99 (0.85, 1.15)	0.98 (0.84, 1.14)
eGFR, per 5 ml/min/1.73m^2		0.87 (0.85, 0.90)	0.88 (0.85, 0.90)	0.88 (0.86, 0.90)	0.88 (0.86, 0.91)
DM					1.62 (1.37, 1.91)
CVD				1.50 (1.26, 1.78)	1.32 (1.11, 1.58)
Graft vintage			1.02 (1.00, 1.03)	1.02 (1.00, 1.03)	1.03 (1.01, 1.04)
Deceased Donor			1.52 (1.29, 1.80)	1.49 (1.26, 1.77)	1.41 (1.19, 1.67)
Smoking					
Never					ref
Current					1.54 (1.22, 1.95)
Former					1.16 (0.98, 1.38)
SBP/10 mmHg					1.13 (1.08, 1.18)
DBP/ 10 mmHg					0.94 (0.86, 1.03)
BMIcategory (kg/m^2)					
less than 18.5					0.30 (0.04, 2.14)
18.5-24.9					ref
25-29.9 kg/m^2					0.76 (0.62, 0.93)
>30 kg/m^2					0.69 (0.56, 0.84)
Chole/20					1.14 (1.04, 1.25)
HDL/20 mg/dL					0.76 (0.66, 0.88)
LDL/20 mg/dL					0.91 (0.82, 1.01)
TG/50 mg/dL					0.99 (0.97, 1.02)
Likelihood Ratio	37.41	152.9	183.7	204	314.4
Df	7	8	10	11	23
C-statistic	0.57	0.65	0.66	0.67	0.69

Table 6. Analyses were censored at development of ESRD or Mortality. Hazard Ratio (HR) for age per 10 years, LDL and HDL Chole; cholesterol per 20 mg/dL higher;TG; triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year increase. DM; history of diabetes mellitus. CVD; baseline CVD history. ..Study Group is the treatment variable in the parent study. Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG.

Table 9. Comparison of analyzed versus missing cohort

	Analyzed	Missing	global p
	N=3,721	**N= 389**	
Age (SD)	51.6 (9.4)	53.3 (9.9)	0.002
Women (n, %)	1377 (37.0)	151 (38.8)	0.5
Race (n, %)			0.01
White	2832 (76.1)	233 (69.1)	
Black	657 (17.7)	68 (20.2)	
Other	232 (6.2)	36 (10.7)	
Location (n, %)			<0.001
United States	2711 (72.9)	272 (74.9)	
Canada	401 (10.8)	88 (24.2)	
Brazil	609 (16.4)	3 (0.8)	
Graft vintage (years)	4.0 (1.7-7.4)	3.6 (1.5-7.4)	0.47
Deceased Donor	2151 (57.8)	245 (63.1)	0.05
Smoking (n, %)			
Current	415 (11.2%)	34 (10.7)	
Former	1488 (40%)	111 (35.0)	
Never	1818 (48.9%)	172 (54.2)	
SBP (mmHg)	136.1 (19.8)	135.4 (19.3)	0.52
DBP (mmHg)	78.7 (12.3)	76.4 (9.8)	<0.001
BMI (SD) kg/m^2	29.2 (6.2)	29.0 (6.6)	0.71
BMI category (kg/m^2)			0.71
18.5-24.9	957 (25.7%)	3 (1.0)	
less than 18.5	29 (0.8%)	93 (30.1)	
25-29.9	1328 (35.7%)	98 (31.7)	
>30	1407 (37.8%)	115 (37.2)	
Chole (mg/dL) (SD)	184.8 (44.0)	178.0 (43.0)	0.05
HDL (mg/dL) (SD)	42.2 (14.0)	45.8 (13.1)	0.68
LDL (mg/dL) (SD)	101.2 (34.4)	96.6 (34.2)	0.10
TG (mg/dL) (SD)	199.2 (185.3)	188.6 (112.2)	0.25
Serum creatinine (mg/dL) (SD)	1.63 (0.48)	1.6 (0.5)	0.70
eGFR, ml/min/1.73m^2 (SD)	48.9 (17.6)	47.7 (20.3)	0.66
DM (n, %)	1504 (40.4%)	165 (42.4)	0.48
CVD (n, %)	768 (20.6%)	73 (18.9)	0.42
ESRD Outcome (n, %)	296 (8.0%)	41 (11.3)	0.05
Mortality Outcome (n, %)	440 (11.8%)	48 (13.2)	0.45
Composite Outcome (n, %)	666 (17.9%)	78 21.5)	0.11

Data reported as mean ± standard deviation or frequency (percent). SBP is systolic blood pressure, DBP is diastolic blood pressure, DM is history of diabetes mellitus, CVD is prior history of CVD *P-value comparisons across categories are based on chi-square for categorical variables, and analysis of variance for continuous variables.

Table 10. Interaction tests of Age, Sex, Diabetes, and eGFR by baseline CVD for ESRD outcome

	Age interaction	**Sex interaction**	**Diabetes interaction**	**eGFR interaction**
Age per10 years	0.65 (0.55, 0.77)	0.68 (0.56, 0.78)	0.68 (0.59, 0.79)	0.68 (0.69, 0.78)
Women	0.86 (0.67, 1.12)	0.85 (0.64, 1.14)	0.87 (0.67, 1.12)	0.86 (0.67, 1.12)
eGFR, per 5 ml/min/1.73m^2	0.79 (0.75, 0.83)	0.79 (0.75, 0.82)	0.79 (0.75, 0.82)	0.79 (0.75, 0.83)
DM	1.34 (1.05, 1.72)	1.34 (1.05, 1.72)	1.27 (0.97, 1.02)	1.34 (1.05, 1.72)
CVD	0.54 (0.10, 2.86)	1.31 (0.94, 1.83)	1.17 (0.76, 1.80)	1.62 (0.72, 3.67)
Age*CVD	1.19 (0.87, 1.63)			
Sex * CVD		1.06 (0.58, 1.91)		
Diabetes *CVD			1.24 (0.71, 2.17)	
eGFR *CVD				0.99 (0.97, 1.02)

Appendix Table 2. Interaction tests of age, sex, eGFR by baseline CVD on ESRD outcome. Hazard Ratio (HR) for age per 10 years; eGFR per 5mL/min/1.73m^2, vintage per year increase. DM; history of diabetes mellitus. CVD; baseline CVD history.

Table 11. Univariate Analysis of CVD, CVD/ESRD, CVD/Mortality, and CVD/ESRD/Mortality

	CVD		CVD/ESRD		CVD/MORTALITY		CVD/ESRD/MORTALITY	
	N = 527 events		N= 732 events		N= 732 events		N= 914 events	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age per 10 years	1.49	(1.37, 1.62)	1.22	(1.14, 1.31)	1.56	(1.45, 1.67)	1.31	(1.24, 1.41)
Women	0.78	(0.65, 0.93)	0.80	(0.69, 0.93)	0.81	(0.70, 0.94)	0.83	(0.73, 0.94)
Race								
White	ref	ref	ref	ref	ref	ref	ref	ref
Black	0.91	(0.72, 1.13)	1.14	(0.96, 1.36)	0.97	(0.81, 1.17)	1.14	(0.97, 1.33)
Other	0.83	(0.57, 1.20)	0.98	(0.73, 1.32)	1.01	(0.76, 1.34)	1.10	(0.86, 1.42)
Location								
United States	ref	ref	ref	ref	ref	ref	ref	ref
Canada	0.74	(0.56, 0.97)	0.82	(0.66, 1.02)	0.71	(0.56, 0.90)	0.81	(0.66, 0.98)
Brazil	0.59	(0.43, 0.82)	0.57	(0.43, 0.75)	0.61	(0.46, 0.77)	0.60	(0.47, 0.76)
Graft vintage	1.00	(0.99, 1.02)	1.01	(1.00, 1.02)	1.01	(0.99, 1.02)	1.01	(1.00, 1.03)
Deceased Donor	1.40	(1.17, 1.66)	1.45	(1.25, 1.67)	1.43	(1.23, 1.65)	1.43	(1.25, 1.63)
Smoking								
Never	ref	ref	ref	ref	ref	ref	ref	ref
Current	1.36	(1.05, 1.76)	1.50	(1.22, 1.85)	1.48	(1.19, 1.84)	1.56	(1.29, 1.88)
Former	1.31	(1.10, 1.56)	1.22	(1.05, 1.42)	1.40	(1.21, 1.62)	1.29	(1.13, 1.47)
SBP/10(mm Hg)	1.16	(1.11, 1.20)	1.16	(1.13, 1.20)	1.12	(1.08, 1.16)	1.14	(1.10, 1.17)
DBP/10 (mm Hg)	0.85	(0.79, 0.92)	0.95	(0.89, 1.01)	0.85	(0.80, 0.91)	0.93	(0.88, 0.99)
BMI category(kg/m^2)								
less than 18.5	1.03	(0.38, 2.79)	0.68	(0.25, 1.84)	0.66	(0.25, 1.78)	0.50	(0.19, 1.35)
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	1.17	(0.94, 1.46)	1.05	(0.88, 1.26)	0.99	(0.82, 1.18)	0.94	(0.80, 1.11)
greater than 30	1.14	(0.92, 1.42)	1.10	(0.92, 1.31)	0.99	(0.83, 1.19)	0.97	(0.83, 1.14)
Chole/20 (mg/dL)	0.96	(0.92, 0.99)	1.00	(0.96, 1.03)	0.97	(0.94, 1.00)	1.00	(0.97, 1.03)
HDL/20 (mg/dL)	0.79	(0.67, 0.89)	0.78	(0.70, 0.87)	0.76	(0.68, 0.85)	0.76	(0.69, 0.84)
LDL/20 (mg/dL)	0.93	(0.88, 0.98)	0.97	(0.93, 1.02)	0.94	(0.90, 0.98)	0.99	(0.94, 1.02)
TG/50 (mg/dL)	1.01	(1.00, 1.02)	1.02	(1.01, 1.03)	1.02	(1.01, 1.03)	1.02	(1.01, 1.02)
Creatinine (mg/dL)	1.51	(1.29, 1.77)	2.23	(1.96, 2.54)	1.46	(1.27, 1.67)	1.99	(1.77, 2.23)
eGFR/5 ml/min/1.73m^2	0.93	(0.91, 0.96)	0.90	(0.88, 0.92)	0.94	(0.92, 0.96)	0.91	(0.89, 0.93)
DM	2.96	(2.50, 3.51)	2.10	(1.83, 2.41)	2.44	(2.12, 2.81)	1.95	(1.73, 2.21)
CVD	3.10	(2.63, 3.65)	2.32	(2.01, 2.68)	2.70	(2.34, 3.10)	2.22	(1.95, 2.52)
Study Group	0.99	(0.84, 1.17)	0.95	(0.83, 1.09)	0.94	(0.82, 1.08)	0.91	(0.81, 1.03)

Univariate Analyses exploring the association between risk factors and CV/ESRD, CV/Mortality, and CV/ESRD/Mortality outcomes. Hazard Ratio (HR) for age per 10 years, Chole; total cholesterol per 20 mg/dL increase;, LDL and HDL cholesterol per 20 mg/dL increase; TG/50 is triglycerides per 50 mg/dL increase, systolic and diastolic blood pressure per 10 mmHg increase; eGFR per 5mL/min/1.73m^2, vintage per year increase. DM; history of diabetes mellitus.

Table 12. Multivariable adjusted Models of CVD outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Age, per 10 years	1.49 (1.37, 1.63)	1.49 (1.36, 1.63)	1.48 (1.35, 1.62)	1.35 (1.23, 1.48)	1.29 (1.16, 1.43)
Women	0.76 (0.64, 0.91)	0.73 (0.61, 0.87)	0.71 (0.60, 0.86)	0.81 (0.67, 0.97)	0.85 (0.70, 1.04)
Race					
White	ref	ref	ref	ref	ref
Black	0.94 (0.75, 1.00)	0.96 (0.76, 1.21)	0.92 (0.73, 1.17)	0.94 (0.74, 1.19)	0.84 (0.66, 1.08)
Other	0.86 (0.60, 1.25)	0.89 (0.62, 1.29)	0.90 (0.62, 1.31)	0.91 (0.63, 1.32)	0.95 (0.64, 1.39)
Location					
United States	ref	ref	ref	ref	ref
Canada	0.68 (0.52, 0.90)	0.68 (0.52, 0.90)	0.65 (0.49, 0.86)	0.70 (0.53, 0.93)	0.81 (0.60, 1.09)
Brazil	0.67 (0.48, 0.92)	0.71 (0.52, 0.98)	0.75 (0.54, 1.03)	0.74 (0.53, 1.02)	0.76 (0.54, 1.09)
Study Group	0.99 (0.84, 1.16)	1.00 (0.85, 1.19)	1.01 (0.85, 1.19)	1.02 (0.86, 1.20)	0.98 (0.82, 1.16)
eGFR, per 5 ml/min/1.73m^2		0.94 (0.91, 0.96)	0.94 (0.92, 0.96)	0.94 (0.92, 0.96)	0.95 (0.92, 0.97)
DM					2.33 (1.92, 2.82)
CVD				2.56 (2.14, 3.04)	2.09 (1.74, 2.52)
Graft vintage			1.00 (0.98, 1.02)	1.01 (0.99, 1.02)	1.02 (1.00, 1.03)
Deceased Donor			1.31 (1.10, 1.57)	1.25 (1.05, 1.50)	1.20 (1.00, 1.45)
Smoking					
Never					ref
Current					1.38 (0.97, 1.98)
Former					1.18 (0.93, 1.50)
SBP/10 mmHg					1.17 (1.11, 1.23)
DBP/ 10 mmHg					0.89 (0.80, 0.98)
BMI category (kg/m^2)					
less than 18.5					1.97 (0.72, 5.37)
18.5-24.9					ref
25-29.9					0.84 (0.66, 1.06)
greater than 30					0.73 (0.58, 0.93)
Chole/20 mg/dL					1.13 (0.98, 1.31)
HDL/20 mg/dL					0.79 (0.66, 0.93)
LDL/20 mg/dL					0.90 (0.77, 1.06)
TG/50 mg/dL					0.98 (0.93, 1.03)
Likelihood Ratio	108.5	139.9	151.1	253.4	381.4
Df	7	8	10	11	23
C-statistic	0.63	0.64	0.65	0.69	0.74

Appendix Table 4. Total of 527 CV events. Hazard Ratio (HR) for age per 10 years, LDL and HDL; Chole; cholesterol per 20 mg/dL higher; TG; triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year higher. DM; history of diabetes mellitus. CVD; baseline CVD history. Study Group is the treatment variable in the parent study.Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG.

Table 13. Multivariable adjusted Models of CVD/ESRD outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Age, per 10 years	1.22 (1.13, 1.31)	1.19 (1.11, 1.29)	1.19 (1.11, 1.29)	1.12 (1.03, 1.21)	1.07 (0.98, 1.16)
Women	0.78 (0.68, 0.91)	0.73 (0.63, 0.84)	0.72 (0.62, 0.83)	0.78 (0.67, 0.90)	0.83 (0.70, 0.98)
Race					
White	ref	ref	ref	ref	ref
Black	1.17 (0.98, 1.39)	1.22 (1.02, 1.47)	1.19 (0.99, 1.43)	1.21 (1.00, 1.46)	1.12 (0.92, 1.36)
Other	1.01 (0.75, 1.36)	1.08 (0.80, 1.45)	1.07 (0.79, 1.45)	1.09 (0.81, 1.48)	1.15 (0.83, 1.59)
Location					
United States	ref	ref	ref	ref	ref
Canada	0.80 (0.64, 1.00)	0.77 (0.62, 0.97)	0.74 (0.59, 0.93)	0.76 (0.60, 0.96)	0.81 (0.63, 1.04)
Brazil	0.59 (0.45, 0.78)	0.65 (0.49, 0.86)	0.70 (0.53, 0.93)	0.68 (0.51, 0.91)	0.66 (0.48, 0.90)
Study Group	0.96 (0.83, 1.10)	0.99 (0.86, 1.13)	0.98 (0.85, 1.13)	1.00 (0.87, 1.15)	0.97 (0.84, 1.12)
eGFR, per 5 ml/min/1.73m^2		0.90 (0.88, 0.91)	0.90 (0.88, 0.92)	0.90 (0.89, 0.92)	0.91 (0.89. 0.92)
DM					1.85 (1.58, 2.17)
CVD				2.01 (1.72, 2.35)	1.75 (1.49, 2.06)
Graft vintage			1.01 (1.00, 1.02)	1.01 (0.99, 1.02)	1.02 (1.00, 1.03)
Deceased Donor			1.34 (1.15, 1.56)	1.30 (1.12, 1.52)	1.27 (1.08, 1.48)
Smoking					
Never					ref
Current					1.34 (1.06, 1.69)
Former					1.09 (0.93, 1.28)
SBP/10 mmHg					1.16 (1.11, 1.21)
DBP/ 10 mmHg					0.93 (0.86, 1.01)
BMI category (kg/m^2)					
less than 18.5					1.39 (0.51, 3.73)
18.5-24.9					ref
25-29.9					0.84 (0.69, 1.03)
greater than 30					0.76 (0.62, 0.93)
Chole/20 mg/dL					1.14 (1.03, 1.26)
HDL/20 mg/dL					0.77 (0.67, 0.89)
LDL/20 mg/dL					0.90 (0.81, 1.00)
TG/50 mg/dL					0.99 (0.96, 1.02)
Likelihood Ratio	60.29	170.1	190.8	265.6	400.8
Df	7	8	10	11	23
C-statistic	0.59	0.64	0.64	0.67	0.71

Appendix Table 5. There were 732 CVD and ESRD events. Hazard Ratio (HR) for age per 10 years, LDL and HDL; Chole; cholesterol per 20 mg/dL higher; TG; triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year higher. DM; history of diabetes mellitus. CVD; baseline CVD history. ..Study Group is the treatment variable in the parent study.Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG.

Table 14. Multivariable adjusted Models of CVD/Mortality outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Age, per 10 years	1.56 (1.45, 1.68)	1.55 (1.44, 1.67)	1.54 (1.43, 1.66)	1.44 (1.33, 1.55)	1.38 (1.27, 1.51)
Women	0.79 (0.69, 0.92)	0.76 (0.66, 0.89)	0.76 (0.66, 0.88)	0.84 (0.72, 0.98)	0.89 (0.76, 1.06)
Race					
White	ref	ref	ref	ref	ref
Black	1.01 (0.83, 1.21)	1.02 (0.84, 1.24)	0.98 (0.81, 1.20)	1.00 (0.82, 1.22)	0.89 (0.72, 1.10)
Other	1.06 (0.79, 1.41)	1.07 (0.80, 1.43)	1.09 (0.81, 1.46)	1.10 (0.82, 1.48)	1.17 (0.87, 1.59)
Location					
United States	ref	ref	ref	ref	ref
Canada	0.66 (0.52, 0.84)	0.66 (0.52, 0.83)	0.63 (0.49, 0.80)	0.67 (0.52, 0.86)	0.76 (0.59, 0.98)
Brazil	0.69 (0.53, 0.91)	0.73 (0.56, 1.96)	0.86 (0.65, 1.14)	0.77 (0.59, 1.01)	0.80 (0.60, 1.08)
Study Group	0.94 (0.82, 1.08)	0.96 (0.84, 1.11)	0.97 (0.84, 1.11)	0.98 (0.85, 1.12)	0.96 (0.83, 1.11)
eGFR, per 5 ml/min/1.73m^2		0.94 (0.92, 0.96)	0.94 (0.92, 0.96)	0.95 (0.93, 0.97)	0.95 (0.93, 0.97)
DM					2.06 (1.75, 2.42)
CVD				2.18 (1.89, 2.53)	1.84 (1.57, 2.16)
Graft vintage			1.01 (1.00, 1.02)	1.01 (1.00, 1.03)	1.02 (1.01, 1.04)
Deceased Donor			1.34 (1.15, 1.56)	1.29 (1.11, 1.50)	1.25 (1.07, 1.47)
Smoking					
Never					ref
Current					1.47 (1.16, 1.85)
Former					1.19 (1.01, 1.40)
SBP/10 mmHg					1.12 (1.08, 1.17)
DBP/ 10 mmHg					0.90 (0.83, 0.98)
BMI category (kg/m^2)					
less than 18.5					1.28 (0.42, 3.45)
18.5-24.9					ref
25-29.9					0.72 (0.59, 0.88)
greater than 30					0.66 (0.54, 0.81)
Chole/20 mg/dL					1.17 (1.05, 1.31)
HDL/20 mg/dL					0.75 (0.64, 0.87)
LDL/20 mg/dL					0.88 (0.78, 1.00)
TG/50 mg/dL					0.98 (0.95, 1.02)
Likelihood Ratio	174.6	209	223.9	320.9	458.8
Df	7	8	10	11	23
C-statistic	0.64	0.65	0.65	0.68	0.72

Appendix Table 6. There were 732 CVD and Mortality events. Hazard Ratio (HR) for age per 10 years, LDL and HDL; Chole; cholesterol per 20 mg/dL higher; TG; triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year higher. DM; history of diabetes mellitus. CVD; baseline CVD history. ..Study Group is the treatment variable in the parent study.Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG.

Table 15. Multivariable adjusted Models of CV/ESRD/Mortality outcome

	Model 1	Model 2	Model 3	Model 4	Model 5
Age, per 10 years	1.32 (1.24, 1.41)	1.30 (1.21, 1.39)	1.29 (1.21, 1.39)	1.22 (1.14, 1.31)	1.18 (1.09, 1.27)
Women	0.81 (0.71, 0.92)	0.76 (0.66, 0.87)	0.75 (0.66, 0.86)	0.81 (0.71, 0.93)	0.87 (0.75, 1.02)
Race					
White	ref	ref	ref	ref	ref
Black	1.17 (1.00, 1.37)	1.22 (1.04, 1.44)	1.19 (1.01, 1.41)	1.21 (1.02, 1.43)	1.12 (0.94, 1.34)
Other	1.14 (0.89, 1.47)	1.20 (0.93, 1.55)	1.21 (0.93, 1.56)	1.23 (0.95, 1.59)	1.32 (1.01, 1.74)
Location					
United States	ref	ref	ref	ref	ref
Canada	0.78 (0.64, 0.95)	0.76 (0.62, 0.93)	0.72 (0.59, 0.89)	0.74 (0.60, 0.92)	0.80 (0.64, 1.00)
Brazil	0.64 (0.50, 0.82)	0.69 (0.54, 0.89)	0.75 (0.58, 0.96)	0.73 (0.57, 0.94)	0.71 (0.54, 0.94)
Study Group	0.91 (0.81, 1.03)	0.95 (0.84, 1.07)	0.95 (0.83, 1.07)	0.96 (0.84, 1.08)	0.94 (0.83, 1.08)
eGFR, per 5 ml/min/1.73m^2		0.91 (0.88, 0.93)	0.91 (0.90, 0.93)	0.92 (0.90, 0.93)	0.92 (0.90, 0.94)
DM					1.78 (1.55, 2.05)
CVD				1.88 (1.64, 2.16)	1.65 (1.43, 1.91)
Graft vintage			1.01 (1.00, 1.03)	1.02 (1.00, 1.03)	1.02 (1.01, 1.04)
Deceased Donor			1.33 (1.16, 1.52)	1.29 (1.13, 1.48)	1.26 (1.10, 1.45)
Smoking					
Never					ref
Current					1.42 (1.15, 1.74)
Former					1.15 (1.00, 1.33)
SBP/10 mmHg					1.13 (1.09, 1.18)
DBP/ 10 mmHg					0.93 (0.86, 1.00)
BMI category (kg/m^2)					
less than 18.5					1.00 (0.37, 2.70)
18.5-24.9					ref
25-29.9					0.74 (0.62, 0.89)
greater than 30					0.68 (0.57, 0.81)
Chole/20 mg/dL					1.16 (1.07, 1.27)
HDL/20 mg/dL					0.74 (0.64, 0.84)
LDL/20 mg/dL					0.89 (0.81, 0.98)
TG/50 mg/dL					0.99 (0.96, 1.01)
Likelihood Ratio	105.8	214.1	230.7	306.3	457.2
Df	7	8	10	11	23
C-statistic	0.59	0.64	0.64	0.66	0.70

Appendix Table 7. There were 914 CVD, ESRD and Mortality composite events Hazard Ratio (HR) for age per 10 years, LDL and HDL; Chole; cholesterol per 20 mg/dL higher; TG; triglycerides per 50 mg/dL higher, systolic and diastolic blood pressure per 10 mmHg higher; eGFR per 5mL/min/1.73m^2, vintage per year higher. DM; history of diabetes mellitus. CVD; baseline CVD history. ..Study Group is the treatment variable in the parent study.Model 1 was *a priori* adjusted for age, sex, race, country, and study treatment assignment. Model 2 adjusted for variables in Model 1 as well as eGFR, Model 3 adjusted for variables in Model 2 as well as transplant graft vintage and donor type. Model 4 adjusted for variables in Model 3 as well as history of CVD. Model 5 adjusted for factors in Model 4 as well as CVD risk factors including: history of diabetes, smoking status, SBP, DBP, BMI category, total cholesterol, HDL, LDL, and TG.

Figure 1. Flowchart of FAVORIT cohort members for this analysis

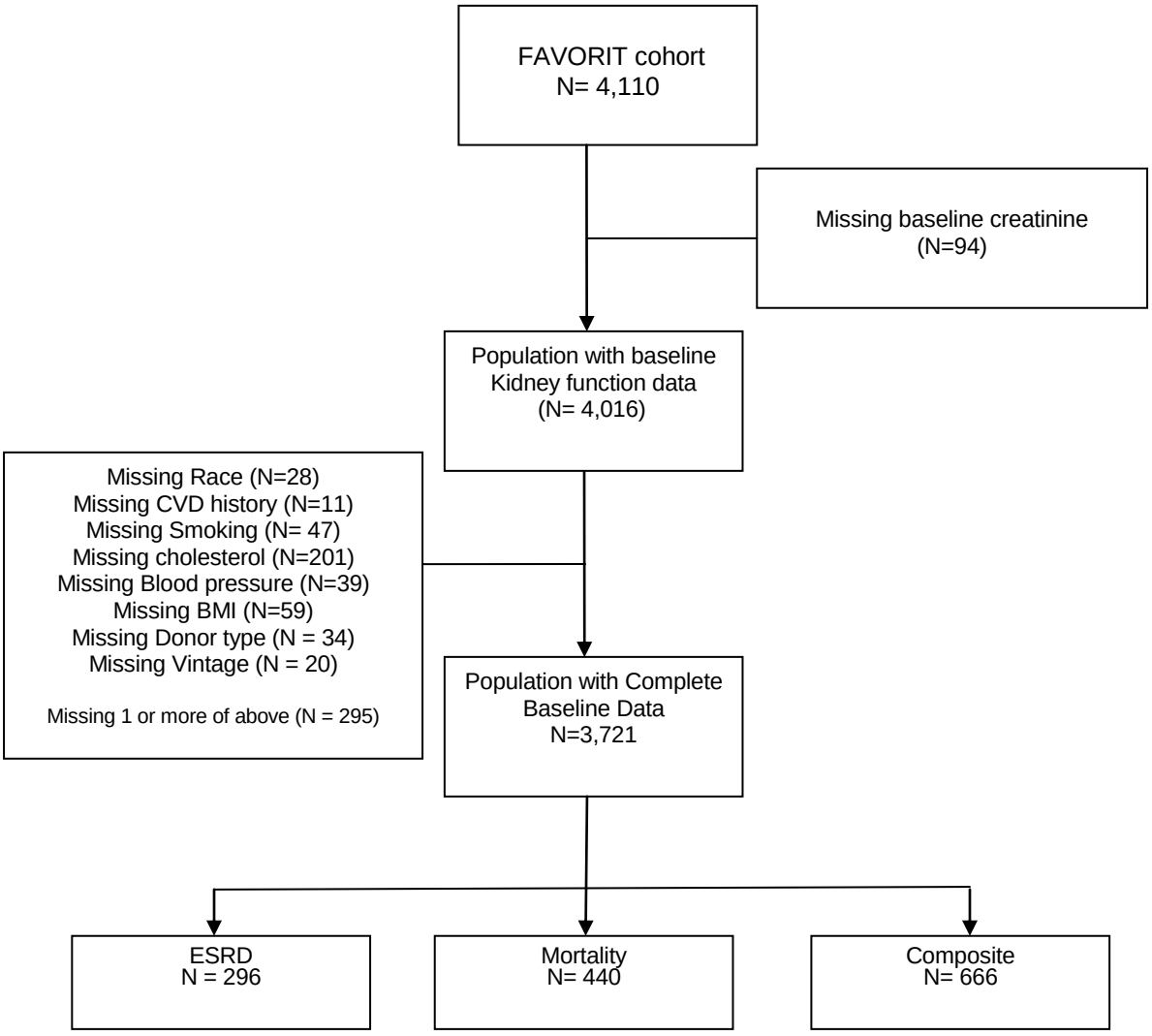
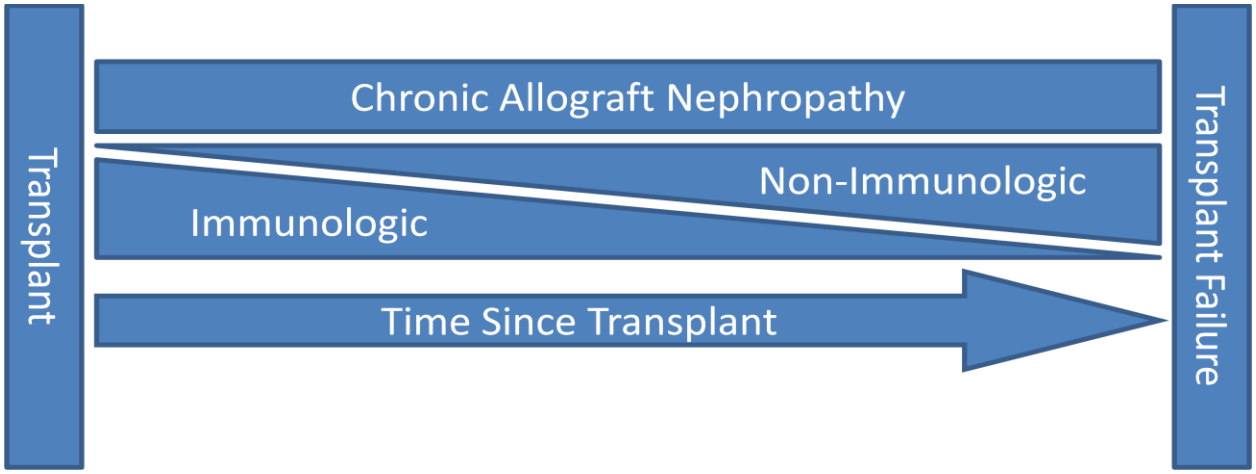


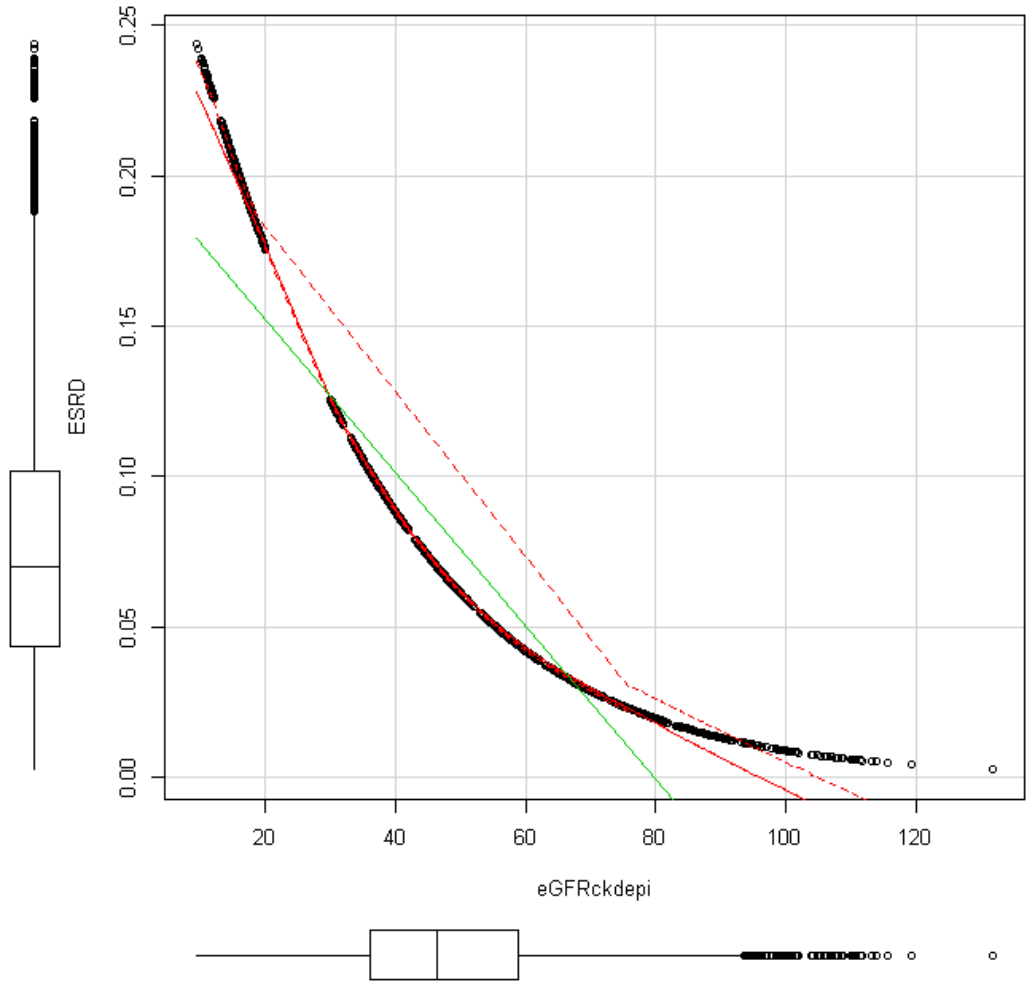
Figure 1. Derivation of the FAVORIT cohort for this analysis. CVD, cardiovascular disease; BMI, body mass index.

Figure 2. Kidney Disease Progression in Transplant Recipients



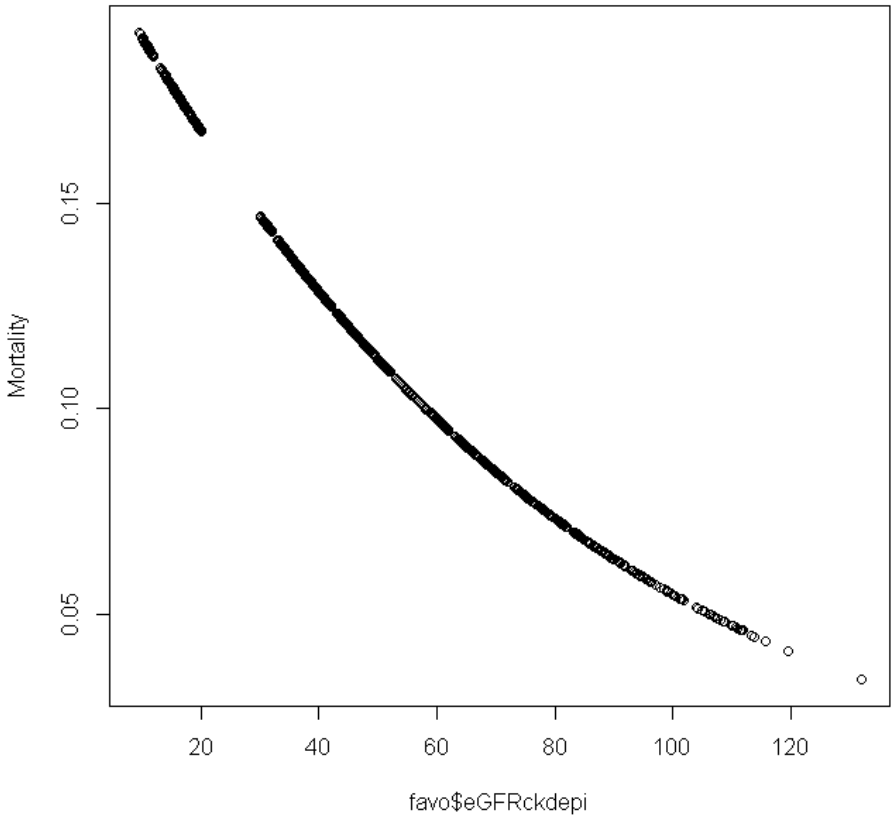
Schematic diagram of the interrelationship among transplant factors, time and transplant failure. Early after transplant, immunologic factors comprise the primary risk to allograft success while non-immunologic factors likely become paramount as the time since transplant increases, although at any time point both of these may result in transplant graft failure.

Appendix Figure 4. Exploration of eGFR as linear vs. non-linear variable for 3 outcomes
Appendix Figure 4a. eGFR as for ESRD outcome.



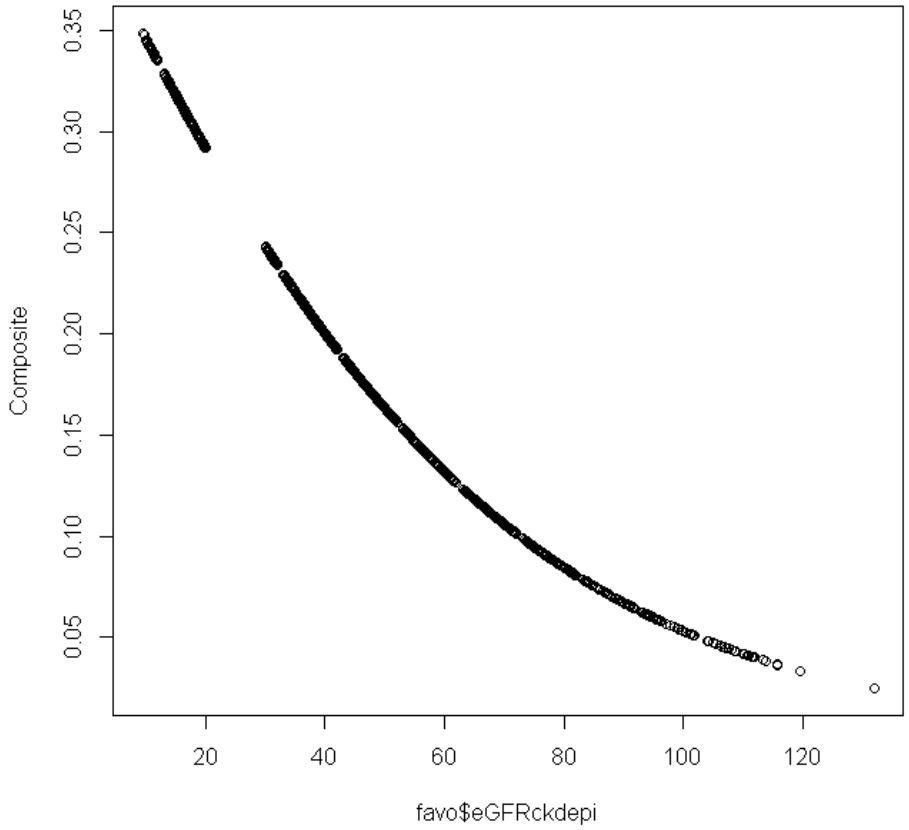
Nonlinear relationship between eGFR with the outcome of ESRD. For a higher eGFR the risk of developing ESRD is lower.

Figure 4b. eGFR with Mortality Outcome



Linear relationship between eGFR with the outcome of Mortality. For a higher eGFR the risk of Mortality is lower.

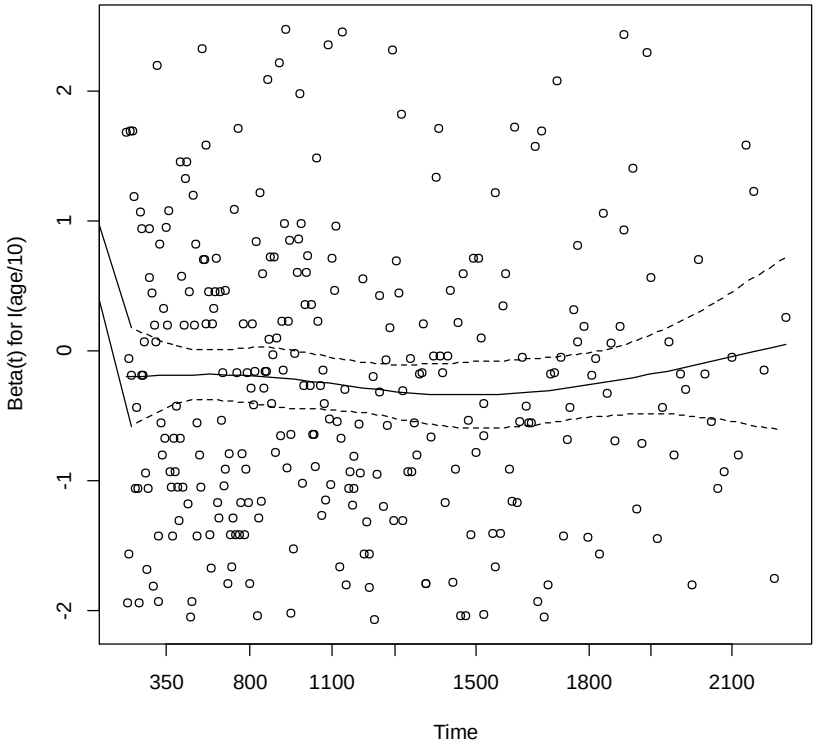
Figure 4c. eGFR with Composite outcome



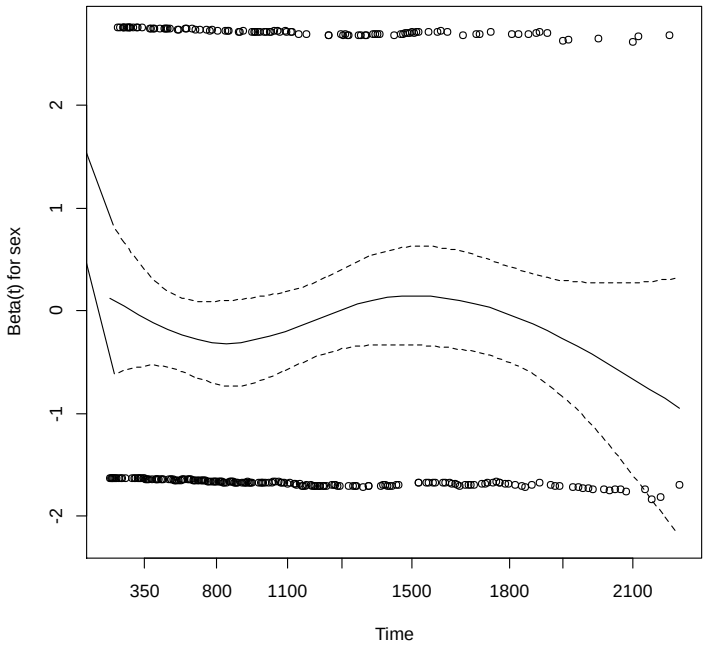
Linear relationship between eGFR with the composite outcome, For a higher eGFR the risk of developing either ESRD or Mortality is lower.

Figure 5. Test of proportional hazards assumption.
Schoenfeld for ESRD

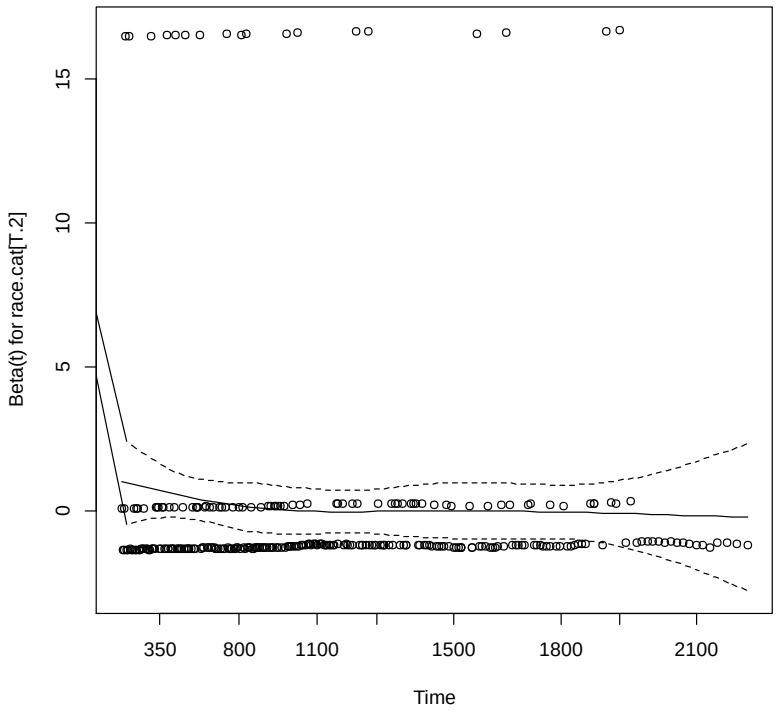
a. Age



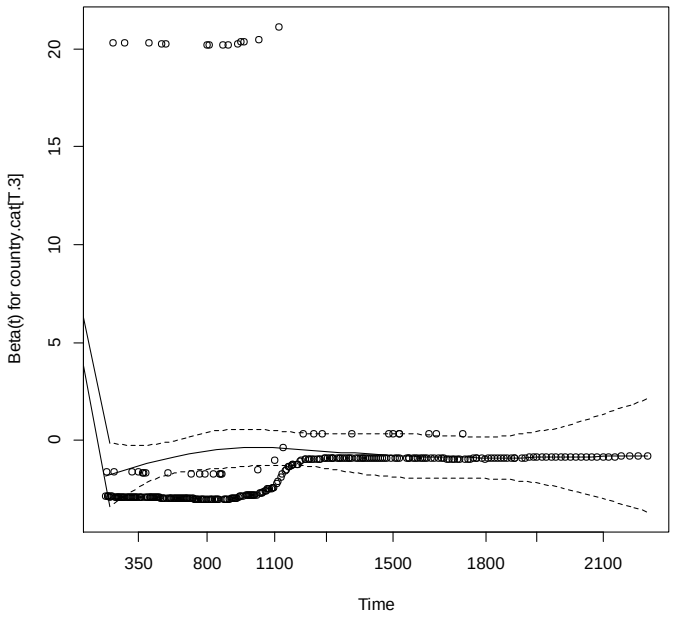
a. Sex



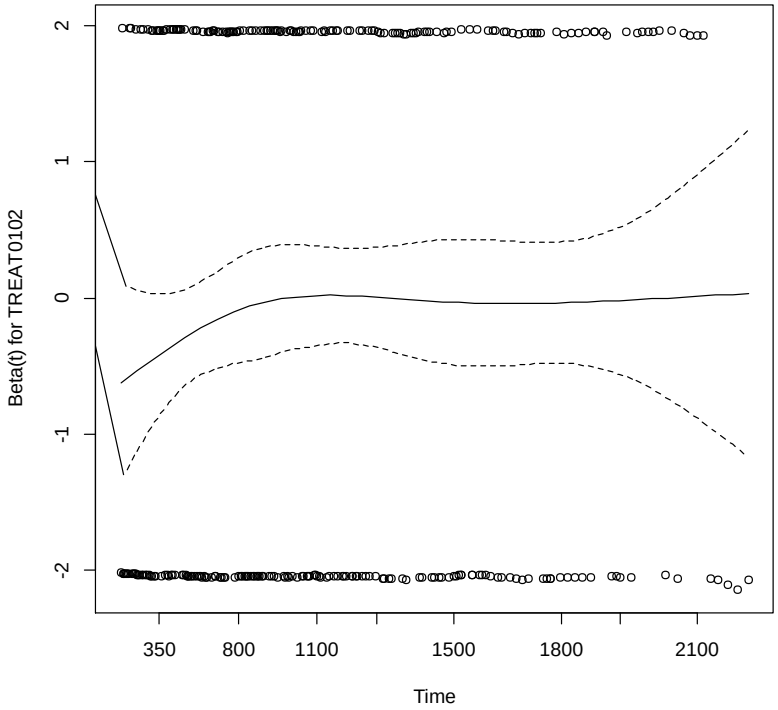
b. Race



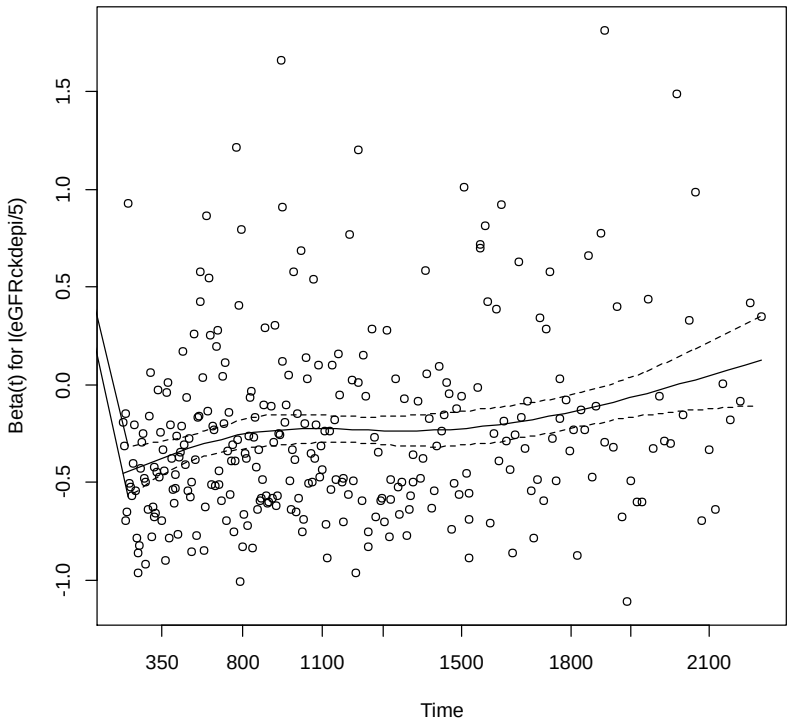
c. Country


Beta(t) for country.cat[T.3]
20
15
10
5
0
350
800
1100
1500
1800
2100
Time

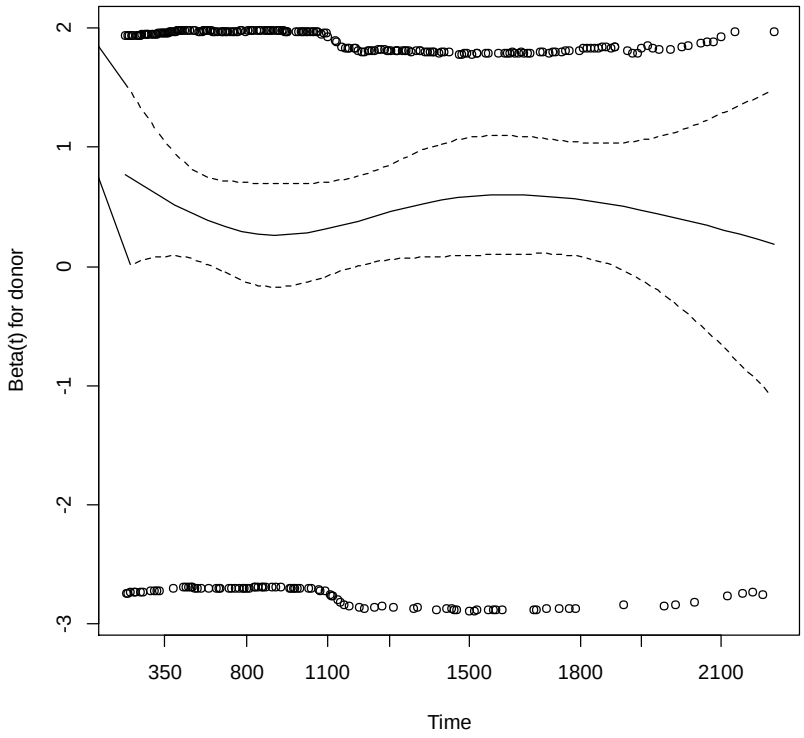
d. Treatment group



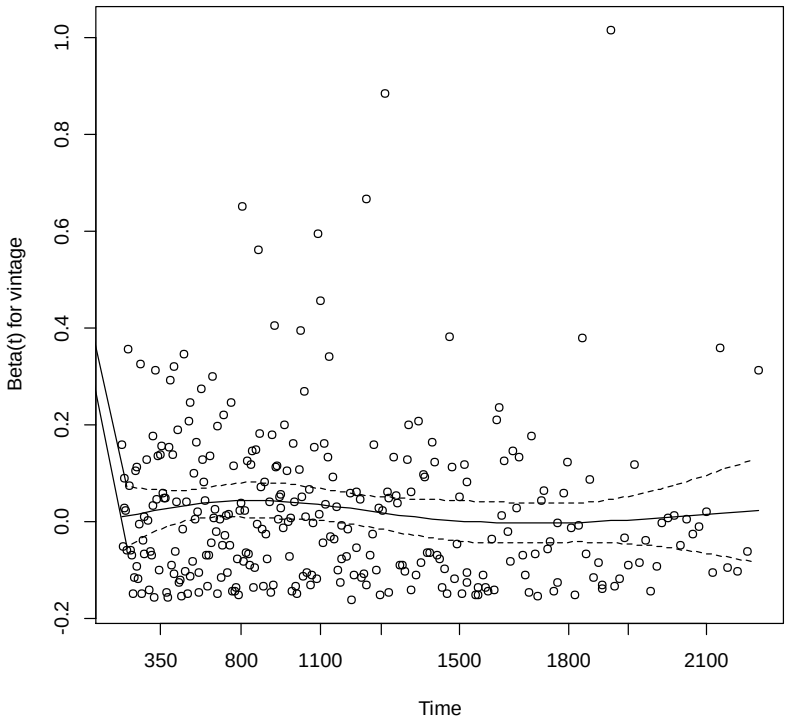
e. eGFR


Beta(t) for I(eGFRckdepi/5)
1.5
1.0
0.5
0.0
-0.5
-1.0
350
800
1100
1500
1800
2100
Time

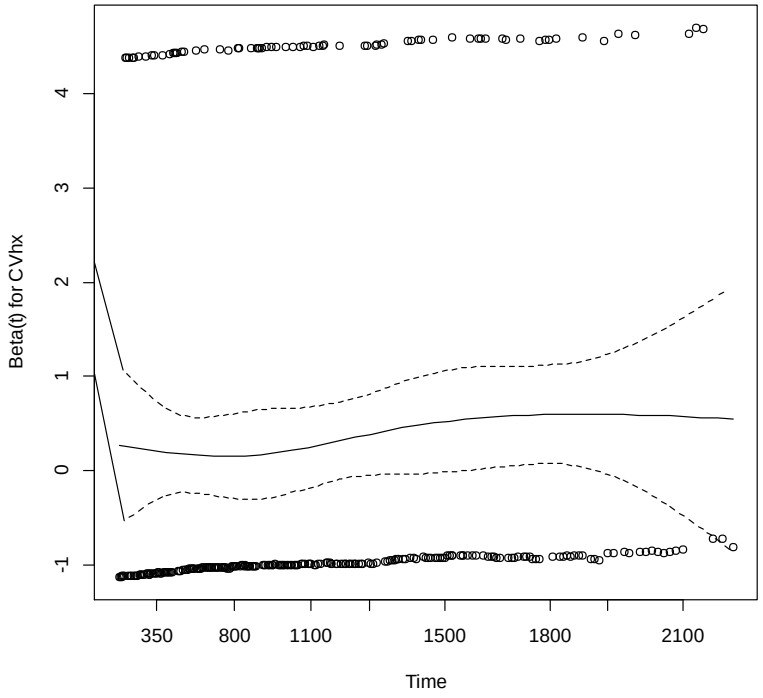
f. donor



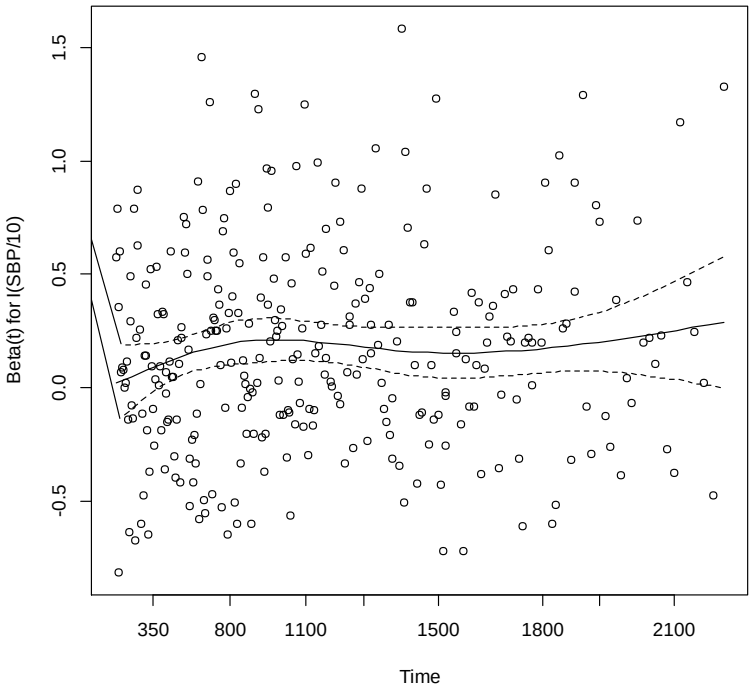
g. vintage


Beta(t) for vintage
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
350
800
1100
1500
1800
2100
Time

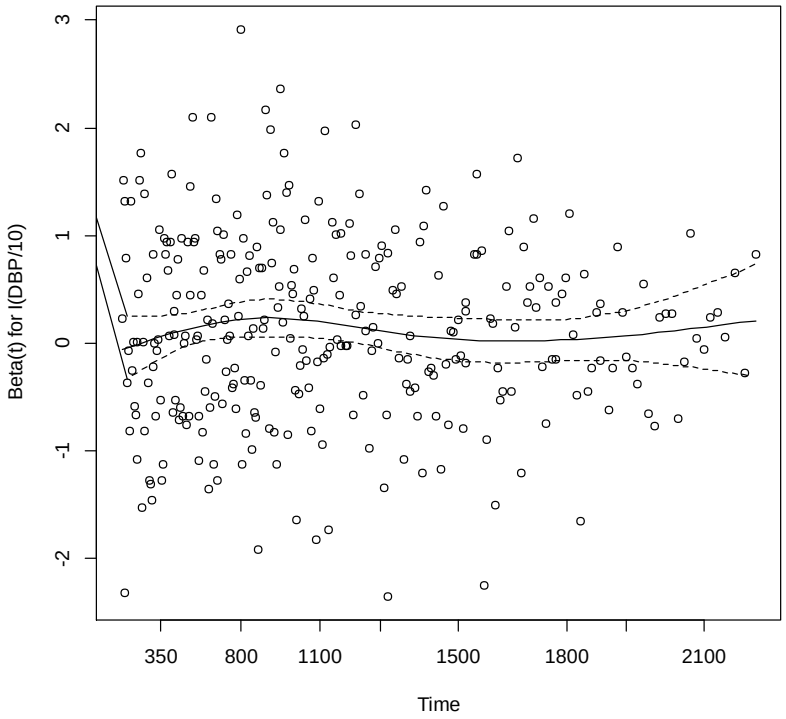
h. CVhx



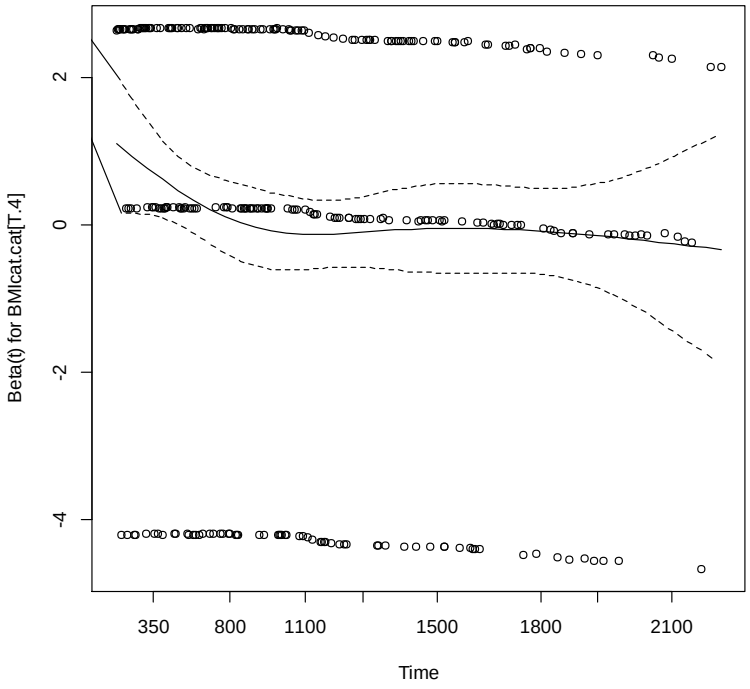
i. SBP


Beta(t) for I(SBP/10)
1.5
1.0
0.5
0.0
-0.5
350
800
1100
1500
1800
2100
Time

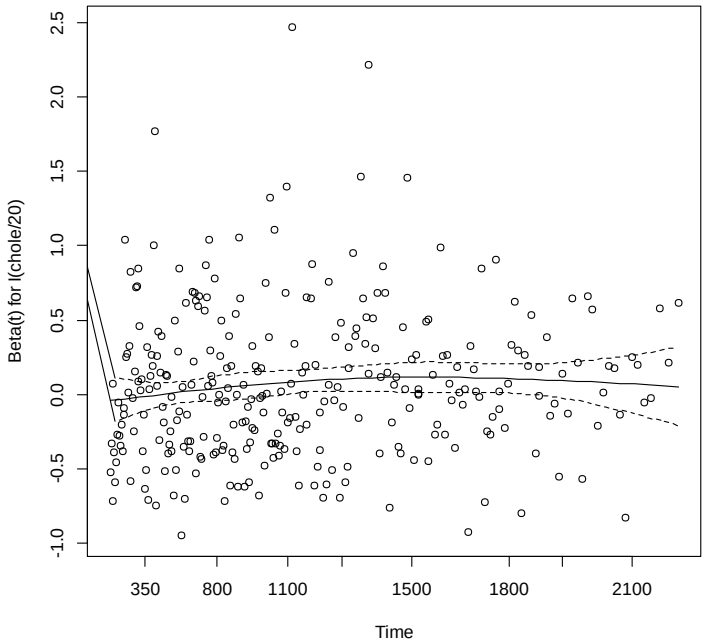
j. DBP



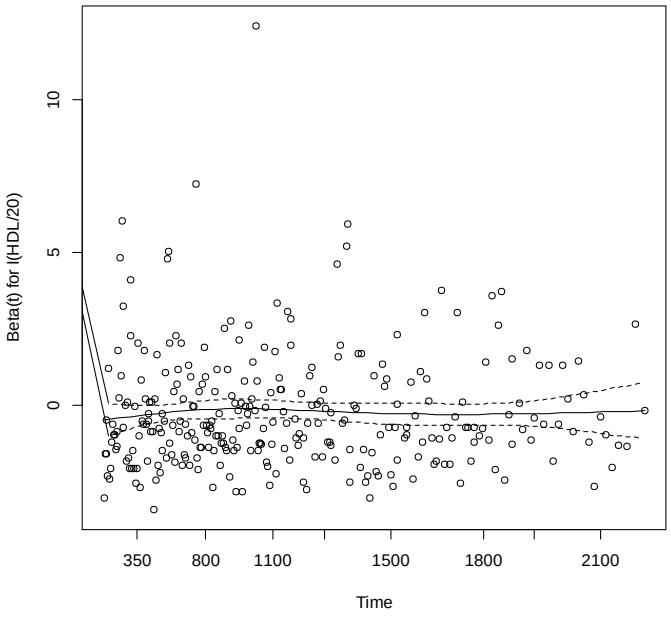
k. BMI



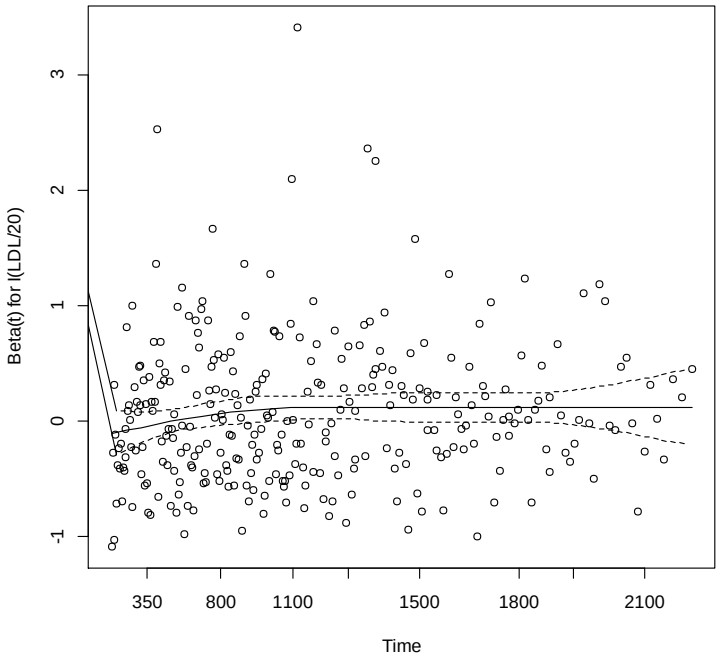
l. Cholesterol



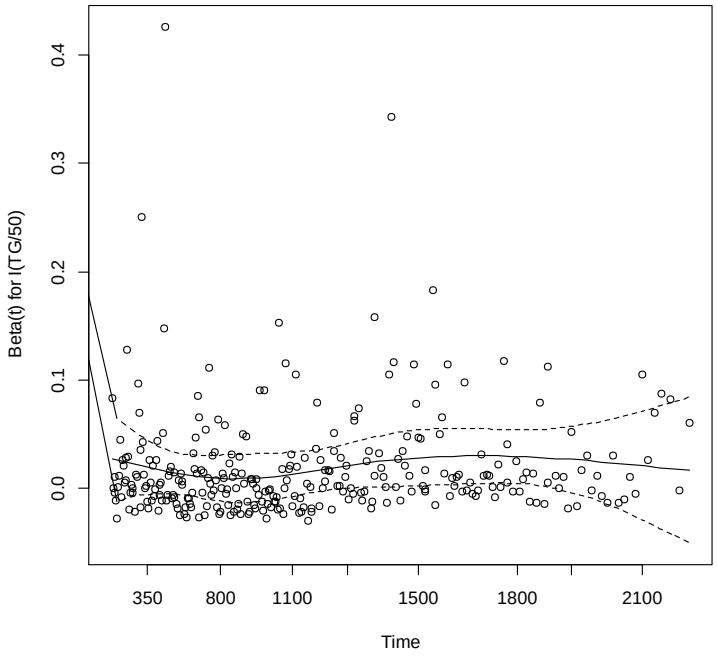
m. HDL



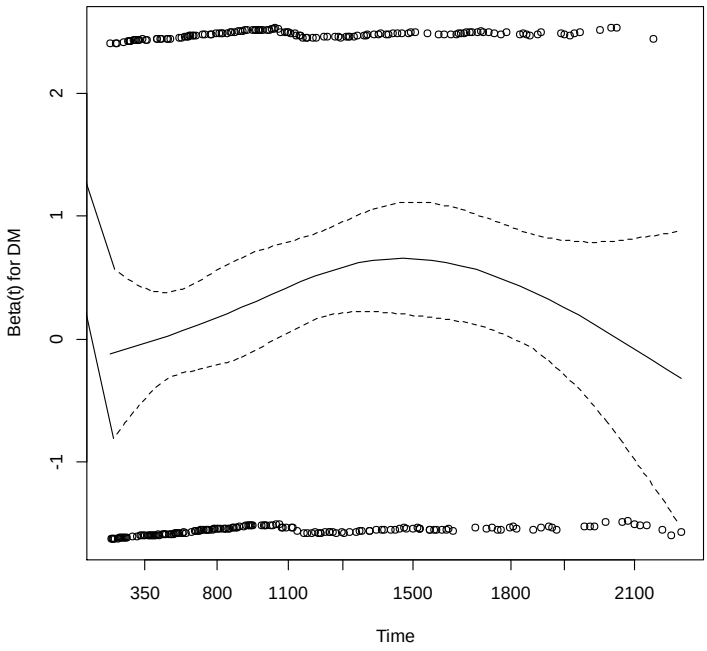
n. LDL



o. TG



p. DM



q. Smoking status

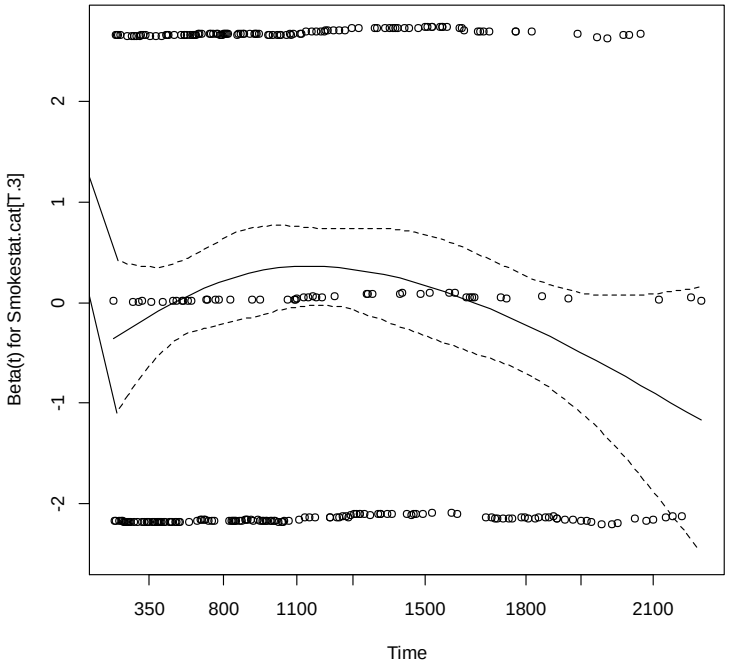


Figure 6. Kaplan Meier curves for each outcome (CVD/ESRD and CVD/Mortality and CVD)

Figure 6a. CVD outcome by baseline CVD

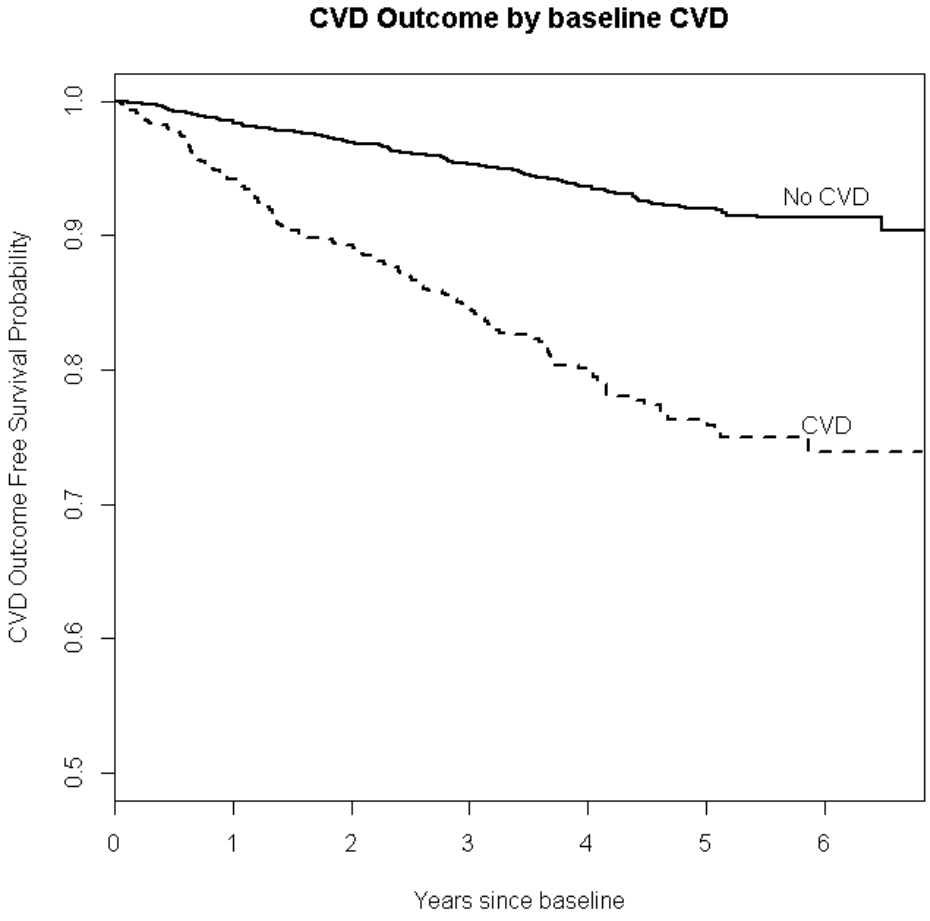


Figure 6b. CVD/ ESRD outcome by baseline CVD

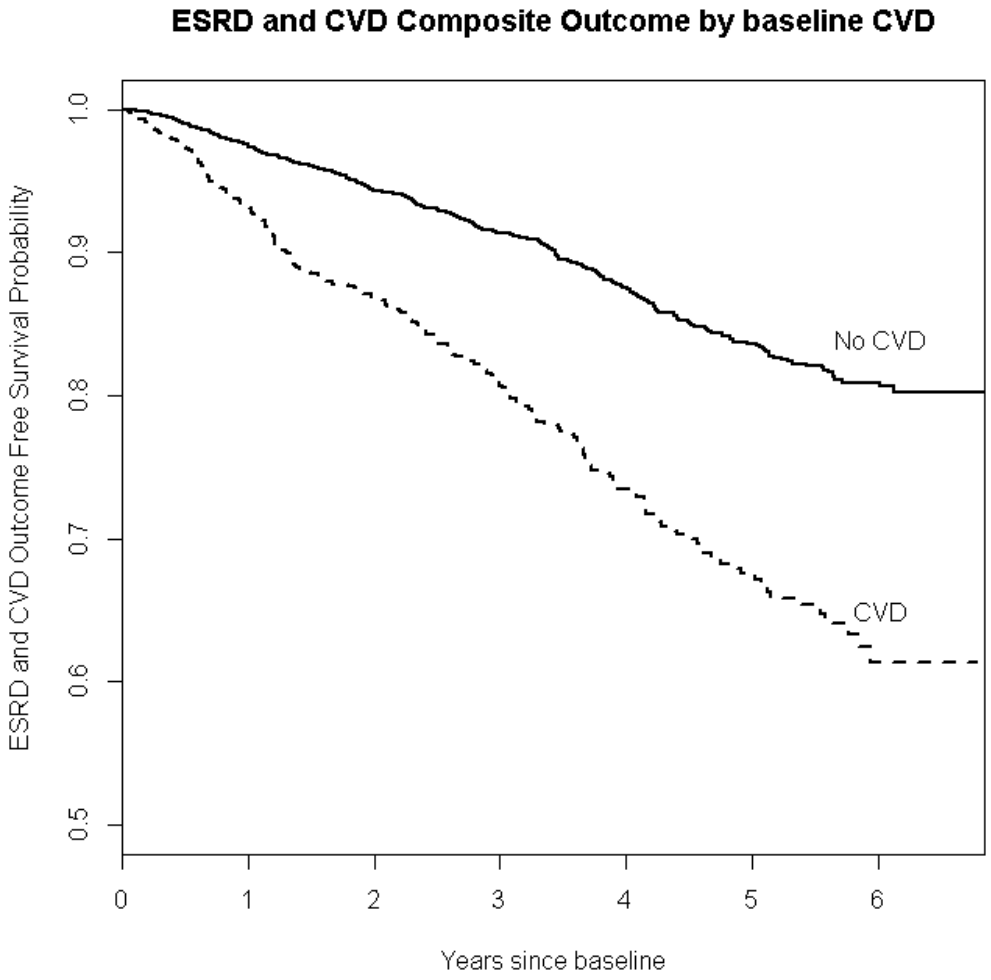


Figure 6c. CVD and all-cause Mortality by baseline CVD

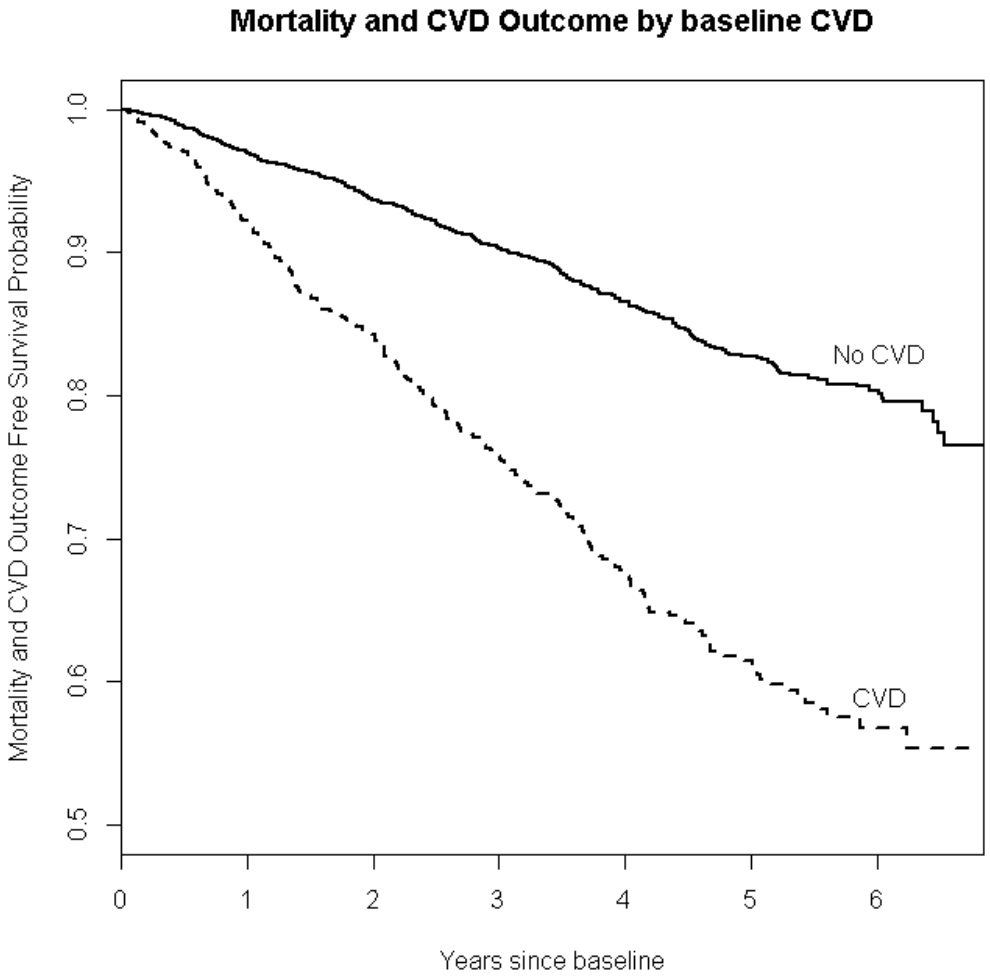


Figure 6d. CVD/ESRD/ all-cause Mortality by baseline CVD

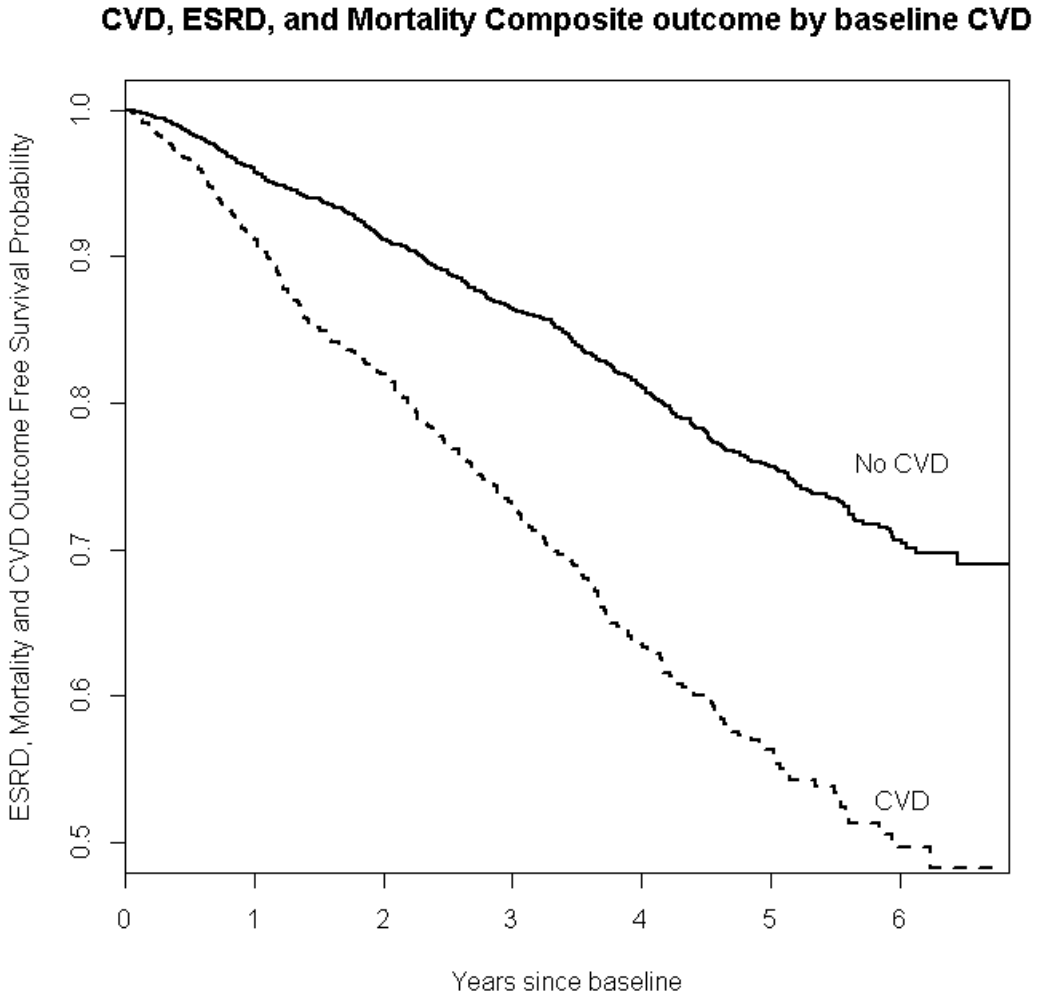


Figure 6. Kaplan-Meier plots for A) CVD, B) CVD/ESRD, C) CVD/all-cause mortality, D) CVD/ESRD/all-cause Mortality stratified by CVD baseline history. Figures depict estimates of the survival function. Analyses exclude participants with missing covariate data.