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The Impact Of Donor And Recipient Renal Dysfunction On Cardiac Allograft Survival: Insights Into Reno-Cardiac Interactions

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Insights into Reno-Cardiac Interactions

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By Olga Laur

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The Impact of Donor and Recipient Renal Dysfunction on Cardiac Allograft Survival: Insights into Reno-Cardiac Interactions. Olga Laur, Meredith A. Brisco, and Jeffrey M. Testani. Section of Cardiology, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT

Background: Renal dysfunction (RD) is a potent risk factor for death in patients with cardiovascular disease. This relationship may be causal since experimentally induced RD produces findings such as myocardial necrosis and apoptosis in animals. Cardiac transplantation provides an opportunity to investigate this hypothesis in humans; if direct myocardial damage is principally responsible for the substantial risk associated with RD, this risk should be transferable from a donor with RD to the recipient via the allograft.

Methods: Cardiac transplantations from the UNOS registry were studied (n=23,056). RD was defined as an estimated glomerular filtration rate < 60 ml/min/1.73m.^{2}

Results: RD was present in 17.9% of donors and 39.4% of recipients. Donor characteristics that could theoretically result in myocardial damage such as longer ischemic time, older age, diabetes, hypertension, and cigarette use were associated with increased graft failure ($p \leq 0.007$ for all). However, donor RD was not associated with graft failure (age-adjusted HR=1.00, 95% CI 0.94-1.07, p=0.92). Moreover, in recipients with RD the highest risk for graft failure occurred immediately post-transplant (0-30 day HR=1.8, 95% CI 1.54-2.02, $p<0.001$) with subsequent attenuation of the risk over time (30-365 day HR=0.92, 95% CI 0.77-1.09, p=0.33).

Conclusions: The risk associated with RD does not appear to be transferrable from donor to recipient via the cardiac allograft and the risk associated with recipient RD is greatest immediately following transplant. These observations suggest that the non-myocardial aspects of cardio-renal dysfunction are of particular importance in the risk associated with RD.

Acknowledgements:

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Introduction:

Renal dysfunction (RD) is common in patients with cardiovascular disease and is strongly associated with increased morbidity and mortality.[1-7] Notably, this association persists after extensive adjustment for potential confounders, such as diabetes or hypertension, raising the possibility of a causal relationship. One potential mechanism by which RD may directly worsen outcomes is via direct myocardial damage.[8-12] Support for this possibility is derived from animal studies where experimentally induced RD results in pathology such as necrosis, apoptosis, fibrosis, arteriolar thickening, decreased capillary density, and contractile dysfunction.[13-19] Remarkably, some of these findings have also been reported following only brief exposures to RD in the setting of experimental acute kidney injury (AKI).[20]

Whether RD can cause direct myocardial damage in humans with enough severity to influence outcomes is unknown and represents a difficult hypothesis to test. In addition to potential direct myocardial effects, the epidemiologic signal for adverse outcomes associated with RD could also be driven by non-myocardial/peripheral factors intrinsic to the RD milieu, which are difficult to measure. These factors could take the shape of systemic myocardial depressant factors (i.e., “uremic toxins”) effects on the vasculature and other organs, in addition to unmeasured confounding factors (i.e., underutilization of beneficial therapies due to the RD or unmeasured disease severity).

Cardiac transplantation provides an opportunity to begin to investigate the importance of myocardial vs. peripheral effects of RD since the heart is being

transplanted into and out of the RD environment. When a heart is removed from a donor with RD, the peripheral RD environment will remain with the donor. However, any RD-induced myocardial damage will travel to the recipient with the graft. Thus, if significant myocardial damage occurs with RD we would expect this injury to travel with the heart and result in reduced post-transplant graft survival in recipients (Figure 1).[21] In essence, this finding would be similar to the concept that the myocardial damage induced by factors such a longer graft ischemic time or from advanced donor age results in worsened post-transplant outcomes (despite the rigorous graft selection process that seeks to avoid these exposures).

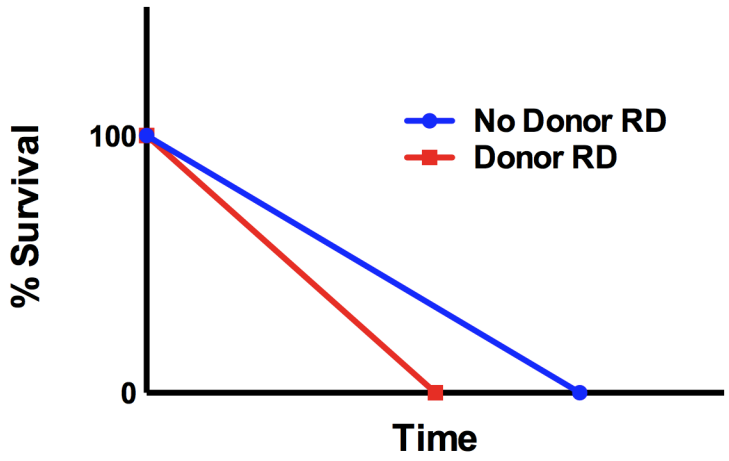

Figure 1. Hypothetical effect of donor RD on graft survival in recipients under assumption that donor RD causes direct myocardial damage

Similarly, transplanting a healthy heart into a recipient with RD would be expected to result in a progressive increase in risk over time after enough myocardial damage accumulates from the RD to begin to impact clinical outcomes(Figure 2).

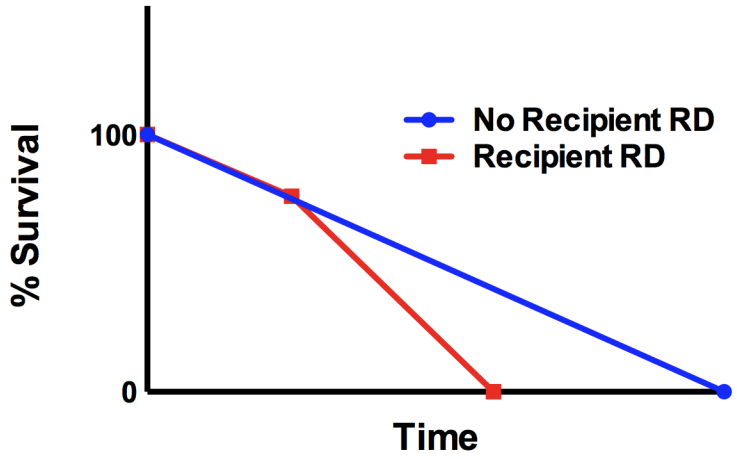

Figure 2. Hypothetical effect of recipient RD on graft survival in recipients under assumption that RD causes myocardial damage which accumulates in a time-dependent manner

However, if the risk associated with RD is primarily driven by the host's peripheral RD environment (i.e., systemic myocardial depressant factors), we would expect to see limited risk from donor RD but a significant up-front risk associated with transplant of a healthy donor heart into the environment of recipient RD. That is, we would expect the rate of graft failure to be accelerated post-transplantation in a group of recipients with RD followed by stabilization in the rate of graft failure between the two groups following a critical period of time (Figure 3).

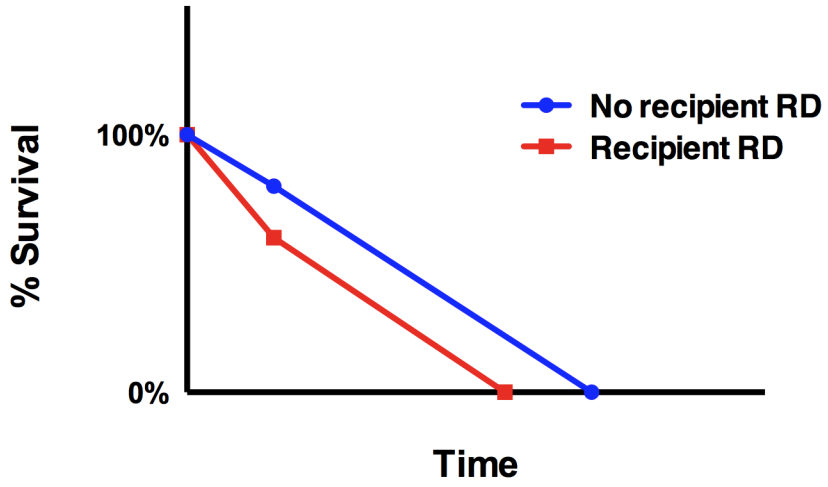

Figure 2.

Hypothetical effect of recipient RD graft survival in recipients under assumption that RD is a marker of patient disease severity rather then causes direct myocardial damage

Study aim:

As such, the primary purpose of this analysis was to evaluate the risk associated with donor RD on post-transplant outcomes and to determine the temporal pattern of cardiovascular risk associated with recipient RD following transplantation of healthy donor hearts. This was accomplished using heart transplant records from United Network for Organ Sharing (UNOS) database, which is a national database that collects recipient and donor heart transplant data via established questionnaires distributed to all of the transplant centers.

Hypothesis 1: It is unlikely that renal dysfunction exerts direct damaging effect on myocardium and thus transplantation of donor hearts with and without history of RD will yield similar recipient graft outcomes.

Hypothesis 2: It is unlikely that renal dysfunction exerts direct damaging effect on myocardium and thus transplantation of donor hearts with and without history of proteinuria will yield similar recipient graft outcomes.

Hypothesis 3: It is unlikely that renal dysfunction exerts direct damaging effect on myocardium and thus transplantation of donor heart into the recipient environment of RD will not result in a time-dependent acceleration in graft failure compared to donor graft transplantation into recipients with no history of RD. Instead, we would expect to see a significant up-front risk associated with transplant of a healthy donor heart into the environment of recipient RD.

Methods:

Patient Population:

Cardiac transplant donor and recipient data were obtained for adult cardiac transplants between January 2000 and March 2013 (N=28,513) from the United Network for Organ Sharing (UNOS) database. Patients receiving either heart-lung or heart-kidney transplants and those with missing data on donor and recipient serum creatinine, donor race, or graft outcomes were excluded. For patients who underwent re-transplantation (n=1,620), only data on the first transplant was retained. Overall, 23,056 patients met the inclusion criteria (Figure 4).

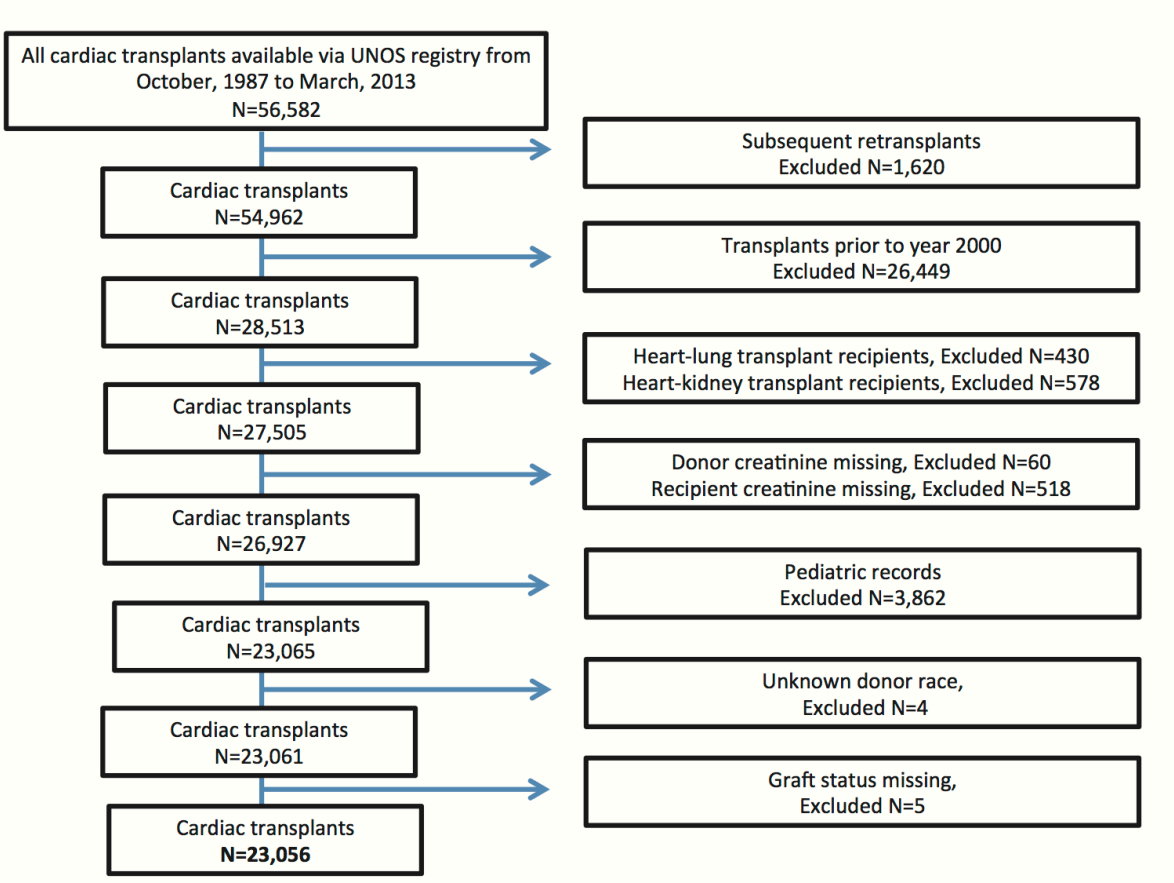

Figure 4. Consort diagram

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22] Terminal creatinine was used for donor eGFR calculation; serum creatinine at the time of transplant was used for recipient eGFR calculation. Subsequent recipient renal function was evaluated in a subset of patients with follow-up data available (n = 8,802). RD was defined as an eGFR < 60 ml/min/1.73m^2.[23, 24] Both donor and recipient groups were additionally stratified into National Kidney Foundation (NKF) stages of CKD severity (GFR ≥ 90

ml/min/1.73m^2, GFR 60-89 ml/min/1.73m^2, GFR 30-59 ml/min/1.73m^2, and GFR <30 ml/min/1.73m^2 where NKF stages 4 and 5 were combined).[23] Several donor or recipient dichotomous characteristics had a high degree of missingness (i.e., recipient cigarette use missing >30%) and there was prognostic information associated with the missing state of these variables. To ensure that the multivariable models captured as much risk as possible, these variables were coded using three levels (i.e., cigarette use yes, no, missing).

Statistical Analysis:

The primary focus of this analysis was (1) the association between donor RD and cardiac graft failure and (2) the time-dependent nature of the association between recipient RD and cardiac graft failure. A secondary analysis focused on the relationship between donor proteinuria and cardiac allograft failure. The primary endpoint of these analyses was recipient graft failure which was defined as retransplantation or recipient death during the study period. Values reported are mean ± SD or median (quartile 1 – quartile 4) for continuous variables, or percentile for categorical variables. Independent Student's t test was used to compare continuous variables. The Pearson chi-square test was used to evaluate associations between categorical variables. Correlation coefficients reported are Spearman's rho.

Cox proportional hazards models were used to evaluate time-to-event associations between both donor RD and recipient RD with graft failure. Patients were censored if lost to follow-up or alive at the conclusion of the data collection period

(March 2013). Given the strong influence of donor age on graft survival and the strong influence of age on calculated eGFR, all models evaluating the association between eGFR and graft failure were adjusted for age unless otherwise specified.[21, 25] Covariates for multivariable models included all donor, recipient and graft-related factors with a univariate association with graft failure at $p<0.2$ or a theoretical basis for confounding (donor and graft covariates = gender, diabetes, hypertension, cigarette use, cause of death, CMV status, infection, inotrope use, ischemic time, and donor ejection fraction; recipient covariates = eGFR, age, gender, race, BMI, diabetes, hypertension, cerebrovascular disease, ischemic cardiomyopathy, cigarette use, UNOS status at listing, mechanical ventilation, inotrope, intra-aortic balloon pump, mechanical circulatory support use, recipient CMV status, and donor-recipient mismatch in gender). Kaplan-Meier survival curves were plotted for four groups of donor and recipient eGFR (eGFR ≥ 90, eGFR 60-89, eGFR 30-59, and eGFR <30 ml/min/1.73m^2). The x-axis was terminated when the number at risk was <10% and statistical significance was determined using the log-rank test. When evaluating the association between recipient eGFR and graft failure, our primary focus was how the effect of RD on graft outcomes changed over time. As such, we performed an extended adjusted cox model utilizing two Heaviside functions to examine the magnitude of the effect of RD on graft outcomes in the first 30 days and from 30 days to 1 year. For all analyses, a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Version 19 (IBM SPSS

Statistics, IBM Corporation, Armonk, New York) and Stata 13.0 (Statacorp, College Station Texas).

Coding analysis:

All coding necessary for UNOS database cleaning, donor and recipient eGFR estimation, univariate and multivariate cox regression analysis for donor RD, donor proteinuria, and recipient RD over the total length of the post-transplant follow-up was performed by me using SPSS software (see below). Adjusted extended cox model utilizing two Heaviside function was performed by Dr. Meredith Brisco via Stata software.

Coding for estimation of eGFR in donor and recipient:

```
**CKD EPI equation  race 1 = African American ; 0 = non African American**
Compute EPIsexMultiplier=$sysmis.
if Race_don eq 1 and gender_don eq "F" EPIsexMultiplier=166.
if Race_don eq 1 and gender_don eq "M" EPIsexMultiplier=163.
if Race_don eq 0 and gender_don eq "F" EPIsexMultiplier=144.
if Race_don eq 0 and gender_don eq "M" EPIsexMultiplier=141.
EXECUTE.

Compute EPIexponent=$sysmis.
if  gender_don eq "F" and creat_don LE 0.7 EPIexponent=-0.329.
if  gender_don eq "F" and creat_don gt 0.7 EPIexponent=-1.209.
if  gender_don eq "M" and creat_don LE 0.9 EPIexponent=-0.411.
if  gender_don eq "M" and Creat_don gt 0.9 EPIexponent=-1.209.
```

```
EXECUTE.

compute Episex=$sysmis.
if gender_don="F" Episex= 0.7.
if gender_don="M" Episex=0.9.
EXECUTE.

compute CKD_EPI_donor=$sysmis.
compute CKD_EPI_donor=
EPIsexMultiplier*((creat_don/EPIsex)**EPIexponent)*(0.993**age_don).
EXECUTE.
```

Coding for stratifying donor and recipient groups into stages:

```
COMPUTE CKD_EPI_donorstage=$sysmis.
if CKD_EPI_donor ge 90 CKD_EPI_donorstage= 0.
if CKD_EPI_donor ge 60 and CKD_EPI_donor lt 90 CKD_EPI_donorstage=1.
if CKD_EPI_donor ge 30 and CKD_EPI_donor lt 60 CKD_EPI_donorstage=2.
if CKD_EPI_donor ge 0 and CKD_EPI_donor lt 30 CKD_EPI_donorstage=3.
EXECUTE.

COMPUTE CKD_EPI_recipstage=$sysmis.
if CKD_EPI_recip ge 90 CKD_EPI_recipstage= 0.
```

```
if CKD_EPI_recip ge 60 and CKD_EPI_recip lt 90 CKD_EPI_recipstage=1.
if CKD_EPI_recip ge 30 and CKD_EPI_recip lt 60 CKD_EPI_recipstage=2.
if CKD_EPI_recip ge 0 and CKD_EPI_recip lt 30 CKD_EPI_recipstage=3.
EXECUTE.
```

Coding for unadjusted donor RD cox regression model:

```
COXREG time
  /STATUS=gfailure(1)
  /METHOD=ENTER CKD_EPI60donor age_doncox10
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

Coding for unadjusted donor proteinuria cox regression model:

```
COXREG time
  /STATUS=gfailure(1)
  /METHOD=ENTER prot_donor
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

Coding for donor RD cox regression model adjusted with donor and recipient risk factors:

```
   COXREG time
     /STATUS=gfailure(1)
     /CONTRAST (htn_recip1)=Indicator(1)
    /CONTRAST (cig_recip1)=Indicator(1)
  /CONTRAST (cmv_recip1)=Indicator(1)
/CONTRAST (allinotropes1)=Indicator(1)
   /METHOD=ENTER  CKD_epi60donor CKD_epirecipcox10 agecox10 gender_recip
gender_mismatch1 race_recip BMI_CALC  diab_recip htn_recip1  cereb_recip
cig_recip1
 ischCM  vent_recip inotropes_trr iabp_trr stat_recip ischtime LV_eject cmv_recip1
mech_circ_support  age_doncox10 gender_donor diab_donor htn_donor cig_donor
 cod_anoxia_donor  cmv_donor donor_infection allinotropes1
   /PRINT=CI(95)
     /PRINT=CI(95)
     /CRITERIA=PIN(.05) POUT(.20) ITERATE(20).
```

Coding for donor proteinuria cox regression model adjusted with donor and recipient risk factors:

```
   COXREG time
     /STATUS=gfailure(1)
      /CONTRAST (htn_recip1)=Indicator(1)
    /CONTRAST (cig_recip1)=Indicator(1)
  /CONTRAST (cmv_recip1)=Indicator(1)
```

```
 /CONTRAST (allinotropes1)=Indicator(1)
    /METHOD=ENTER  prot_donor CKD_epirecipcox10 agecox10 gender_recip
gender_mismatch1 race_recip BMI_CALC  diab_recip htn_recip1  cereb_recip
cig_recip1
 ischCM  vent_recip inotropes_trr iabp_trr stat_recip ischtime LV_eject cmv_recip1
mech_circ_support  age_doncox10 gender_donor diab_donor htn_donor cig_donor
 cod_anoxia_donor  cmv_donor donor_infection allinotropes1
    /PRINT=CI(95)
      /PRINT=CI(95)
      /CRITERIA=PIN(.05) POUT(.20) ITERATE(20).
```

Coding for recipient RD unadjusted Cox regression model:

```
COXREG time
  /STATUS=gfailure(1)
  /METHOD=ENTER CKD_EPI60recip agecox10
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

Coding for recipient RD cox regression model adjusted with donor and recipient risk factors:

```
    COXREG time
```

```
      /STATUS=gfailure(1)
      /CONTRAST (htn_recip1)=Indicator(1)
     /CONTRAST (cig_recip1)=Indicator(1)
   /CONTRAST (cmv_recip1)=Indicator(1)
 /CONTRAST (allinotropes1)=Indicator(1)
    /METHOD=ENTER  CKD_epi60recip CKD_epi_donorcox10 agecox10 gender_recip
gender_mismatch1 race_recip BMI_CALC  diab_recip htn_recip1  cereb_recip
cig_recip1
 ischCM  vent_recip inotropes_trr iabp_trr stat_recip ischtime LV_eject cmv_recip1
mech_circ_support  age_doncox10 gender_donor diab_donor htn_donor cig_donor
 cod_anoxia_donor  cmv_donor donor_infection allinotropes1
    /PRINT=CI(95)
      /PRINT=CI(95)
      /CRITERIA=PIN(.05) POUT(.20) ITERATE(20).
```

Coding provided by Dr. Meredith Brisco:

**FINAL MODEL evaluating Hazard ratio associated with recipient RD at 1 month post-transplantation and following 1 month post transplantation.

```
stsplit rd, at(30)
gen rd1mo=CKD_EPI60recip*(rd==30)

xi: stcox CKD_EPI60recip rd1mo age_doncox10
```

xi: stcox CKD_EPI60recip rd1mo age_doncox10 CKD_EPI_donorcox10 agecox10 gender_recip gender_mismatch1 race_recip BMI_CALC ///
diab_recip i.htn_recip1 cereb_recip i.cig_recip1 ischCM vent_recip INOTROPES_TRR IABP_TRR stat_recip ischtime LV_EJECT i.cmv_recip1 ///
mech_circ_support gender_donor diab_donor htn_donor cig_donor cod_anoxia_donor cmv_donor donor_infection i.allinotropes1

Results:

Donor Characteristics:

In total, 23,056 patients met the inclusion criteria. Baseline donor characteristics stratified by presence of donor RD are presented in Table 1.

Table 1. Baseline donor characteristics stratified by presence or absence of donor renal dysfunction

Characteristic	Overall Cohort (n = 23,056)	Donor RD Present		P-value
		No (n = 18,919)	Yes (n = 4,137)	
Demographics				
Age, years	31.6 ± 12.2	30.9 ± 12.1	34.6 ± 11.9	<0.001
Age > 50 years	8.0%	7.5%	10.3%	<0.001
Female gender	28.6%	28.3%	30.1%	0.020
White race	85.9%	86.4%	83.5%	<0.001
BMI	26.6 ± 5.6	26.3 ± 5.5	28.1 ± 5.9	<0.001

Comorbidities				
Diabetes mellitus	2.6%	2.3%	4.2%	<0.001
Hypertension	13.1%	11.2%	21.5%	<0.001
Cigarette use	22.6%	22.3%	23.8%	0.030
Alcohol use	19.5%	19.0%	22.2%	0.013
CMV positive	61.3%	61.2%	61.8%	0.460
Suspected infection	7.0%	6.9%	7.6%	0.094
Donor cause of death				
Anoxia	13.3%	10.8%	25.1%	<0.001
Stroke	24.9%	24.2%	28.0%	<0.001
Head trauma	60.8%	63.9%	46.5%	<0.001
Cardiac allograft				
Ischemic time, hours	3.2 ± 1.0	3.2 ± 1.0	3.2±1.0	0.013
Ischemic time ≥ 4 hours	21.0%	20.8%	22.2%	0.050
LVEF, %	61.6 ± 7.6	61.5 ± 7.7	61.8 ± 7.6	0.047
LVEF ≤ 45%	2.2%	2.3%	1.9%	0.100
Inotropic support	61.9%	61.6%	63.3%	0.045
Laboratory values				
BUN, mg/dl	15.5 ± 12.4	12.7 ± 7.8	28.0 ± 19.7	<0.001
Creatinine, mg/dl	1.3 ± 1.2	0.9 ± 0.3	2.8 ± 2.1	<0.001
eGFR, ml/min/1.73m^2	92.2 ± 34.8	104.1 ± 25.0	37.7 ± 16.3	<0.001
Proteinuria	32.6%	28.8%	50.1%	<0.001

RD: renal dysfunction, BMI: body mass index, CMV: cytomegalovirus, LVEF: left ventricular ejection fraction, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate.

RD was present in 17.9% of donors with a mean eGFR that was significantly depressed at 37.7 ± 16.3 ml/min/1.73m^2 and an elevated creatinine at 2.8 ± 2.1 mg/dl. Donors with RD were older, with a substantially higher prevalence of diabetes, hypertension, and death from anoxic cause. However, measures of cardiac allograft function such as ejection fraction and inotrope use were generally similar between groups as was the graft ischemic time (Table 1).

Donor RD and graft failure:

Out of 23,056 recipients, 6,852 (29.7%) experienced graft failure during a median follow-up of 3.9 (IQR 1.1-7.0) years. Serving as a positive control, donor risk factors that could potentially induce myocardial damage such as older donor age, hypertension, diabetes, cigarette use, and longer ischemic time were all significantly associated with recipient graft failure (Figure 5 and Table 2).

Table 2. Donor and recipient characteristics and their associations with graft failure

	HR	95% CI	P-value
Donor Characteristics			
Age, per 10 year increase	1.11	1.09-1.14	<0.001
Age > 50 years	1.35	1.25-1.46	<0.001

Female gender	1.12	1.07-1.18	<0.001
Diabetes mellitus	1.22	1.05-1.41	0.007
Hypertension	1.13	1.06-1.22	<0.001
Cigarette use	1.18	1.11-1.24	<0.001
CMV positive	1.11	1.06-1.16	<0.001
Suspected infection (blood)	1.12	1.02-1.22	0.02
Donor inotropic support	1.07	1.01-1.13	0.02
Donor cause of death: anoxia	1.02	0.95-1.10	0.56
Donor renal function *			
eGFR, per 10 ml/min/1.73m^2 increase	1.00	0.99-1.01	0.96
eGFR < 90 ml/min/1.73m^2	1.02	0.97-1.07	0.44
eGFR < 60 ml/min/1.73m^2	1.00	0.94-1.07	0.92
eGFR < 45 ml/min/1.73m^2	1.00	0.93-1.09	0.96
eGFR < 30 ml/min/1.73m^2	0.92	0.83-1.03	0.14
Creatinine, per 1mg/dl increase	1.00	0.97-1.02	0.65
Creatinine > 1.5 mg/dl	1.01	0.95-1.08	0.71
Creatinine > 2.0 mg/dl	0.94	0.86-1.04	0.22
Creatinine > 2.5 mg/dl	0.99	0.89-1.10	0.78
Proteinuria	1.00	0.95-1.05	0.96
Cardiac Allograft Characteristics			
Ischemic time, hours	1.08	1.05-1.10	<0.001
Ischemic time ≥ 4 hours	1.22	1.15-1.29	<0.001

LVEF, %	1.00	1.00-1.00	0.62
LVEF ≤ 45%	1.12	0.96-1.29	0.15
Recipient Characteristics			
Age, per 10 year increase	1.00	0.98-1.02	0.76
Female gender	1.06	1.00-1.12	0.04
Gender mismatch	1.15	1.08-1.22	<0.001
Race	1.35	1.27-1.44	<0.001
BMI	1.01	1.00-1.02	<0.001
Diabetes mellitus	1.19	1.13-1.26	<0.001
Hypertension	1.17	1.11-1.24	<0.001
Cerebrovascular disease	1.18	1.07-1.30	0.001
Cigarette use	1.09	1.02-1.17	0.01
Ischemic cardiomyopathy	1.16	1.10-1.21	<0.001
CMV positive	1.10	1.04-1.16	<0.001
Inotropic support	1.05	1.00-1.10	0.07
IABP	1.22	1.10-1.34	<0.001
Mechanical circulatory support	1.14	1.07-1.22	<0.001
UNOS status 1A	1.13	1.08-1.19	<0.001
Mechanical ventilation	1.20	1.04-1.37	0.01
Recipient renal function *			
Recipient eGFR, per 10	0.95	0.94-0.96	<0.001
Recipient eGFR < 90 ml/min/1.73m^2	1.13	1.06-1.21	<0.001

Recipient eGFR < 60 ml/min/1.73m^2	1.28	1.21-1.34	<0.001
Recipient eGFR < 45 ml/min/1.73m^2	1.45	1.37-1.54	<0.001
Recipient eGFR < 30 ml/min/1.73m^2	1.80	1.60-1.94	<0.001

*All donor eGFR covariates were adjusted for donor age and recipient eGFR covariates were adjusted for recipient age. CMV: cytomegalovirus, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, RD: renal dysfunction, BMI: body mass Index, IABP: intra-aortic balloon pump, UNOS: United Network of Organ Sharing.

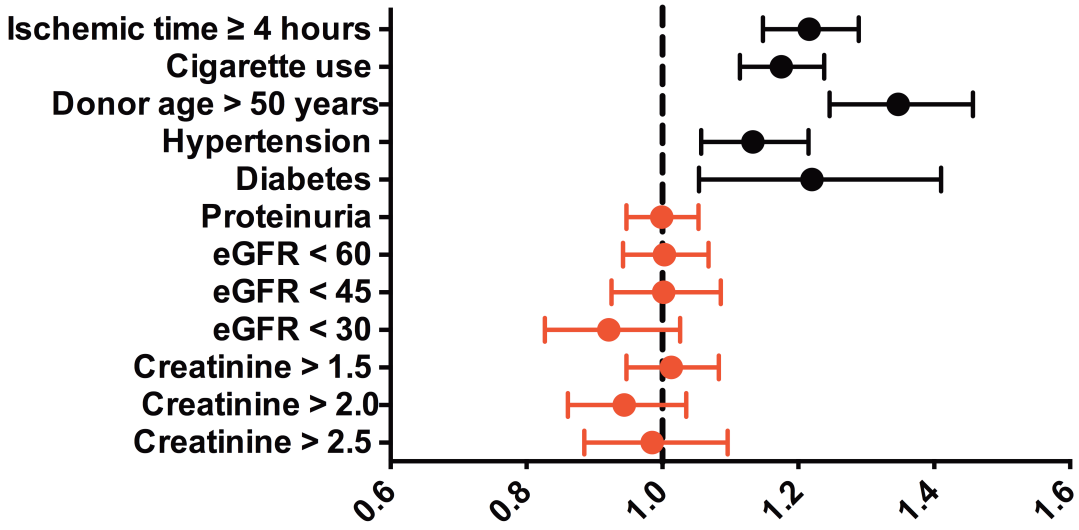

Figure 5. Risk of graft failure from selected donor risk factors with theoretical direct deleterious effects on the myocardium. eGFR: estimated glomerular filtration rate. *Due to the dependence of eGFR on age, all eGFR categories were adjusted for donor age.

However, there was no significant relationship between donor RD and graft failure (HR=1.05 95% CI 0.98-1.12 p=0.14). Following adjustment for age, the hazard

ratio further approached unity (HR= 1.00, 95% CI 0.94-1.07, p=0.92). A similar lack of association between donor RD and graft failure was observed with larger reductions in eGFR and using creatinine-based cut points to define RD (Figure 5). Further adjustment for other donor characteristics (HR=0.99, 95% CI 0.92-1.06, p=0.76) or donor and recipient characteristics did not alter the lack of relationship between donor RD and graft survival (HR= 0.98, 95% CI 0.92-1.05, p=0.60, Table 3).

Table 3. Association between donor renal dysfunction and recipient graft failure adjusted for donor and recipient risk factors

	HR	95% CI	P-value
Donor Characteristics			
eGFR < 60 ml/min/1.73m2	0.98	0.92-1.05	0.60
Age, per 10 year increase	1.11	1.08-1.13	<0.001
Female gender	0.96	0.86-1.07	0.45
Diabetes mellitus	1.18	1.01-1.38	0.04
Hypertension	0.95	0.88-1.04	0.26
Cigarette use	1.07	1.00-1.14	0.03
CMV positive	1.1	1.05-1.17	<0.001
Suspected infection (blood)	1.10	1.00-1.22	0.06
Cause of death: anoxia	1.07	0.99-1.17	0.10
Inotropic support*	1.04	0.97-1.1	0.26
Cardiac Allograft Characteristics			
Ischemic time, hours	1.07	1.04-1.10	<0.001

LVEF, %	1.00	1.00-1.00	0.19
Recipient Characteristics			
Age (per 10 year increment)	0.93	0.90-0.95	<0.001
Female gender	1.14	1.05-1.24	0.003
Gender mismatch	1.18	1.04-1.33	0.01
Black race	1.40	1.31-1.50	<0.001
BMI	1.00	1.00-1.01	0.34
Diabetes mellitus	1.14	1.07-1.21	<0.001
Hypertension*	1.12	1.05-1.20	<0.001
Cerebrovascular disease	1.10	0.98-1.22	0.11
Cigarette use*	1.05	0.98-1.14	0.19
Ischemic cardiomyopathy	1.19	1.13-1.27	<0.001
CMV positive*	1.04	0.98-1.10	0.21
Inotrope use	1.02	0.96-1.07	0.59
IABP	1.08	0.97-1.22	0.17
Mechanical circulatory support	1.20	1.11-1.30	<0.001
UNOS status 1A	1.11	1.05-1.18	<0.001
Mechanical ventilation	1.19	1.02-1.38	0.03
eGFR, per 10 ml/min/1.73m2 increase	0.95	0.94-0.96	<0.001

*Missing data in these covariates was coded as a separate category due to its prevalence (9% for donor inotropic support; 50% for recipient hypertension; 36% for recipient history of cigarette use, 6% for recipient cmv positive status). The associated HR

specifically represents the risk of graft failure in a group with one of these risk factors vs. without. eGFR: estimated glomerular filtration rate, CMV: cytomegalovirus, LVEF: left ventricular ejection fraction, RD: renal dysfunction, BMI: body mass Index, IABP: intra-aortic balloon pump, UNOS: United Network of Organ Sharing.

A "dose-response" relationship between donor eGFR and graft failure was not apparent as progressively worse donor CKD stages (Figure 6) and eGFR as a continuous parameter (adjusted HR=1.00 per 10 ml/min/1.73m^2, 95% CI 1.00-1.01, p=0.37) were not associated with increased risk of graft failure.

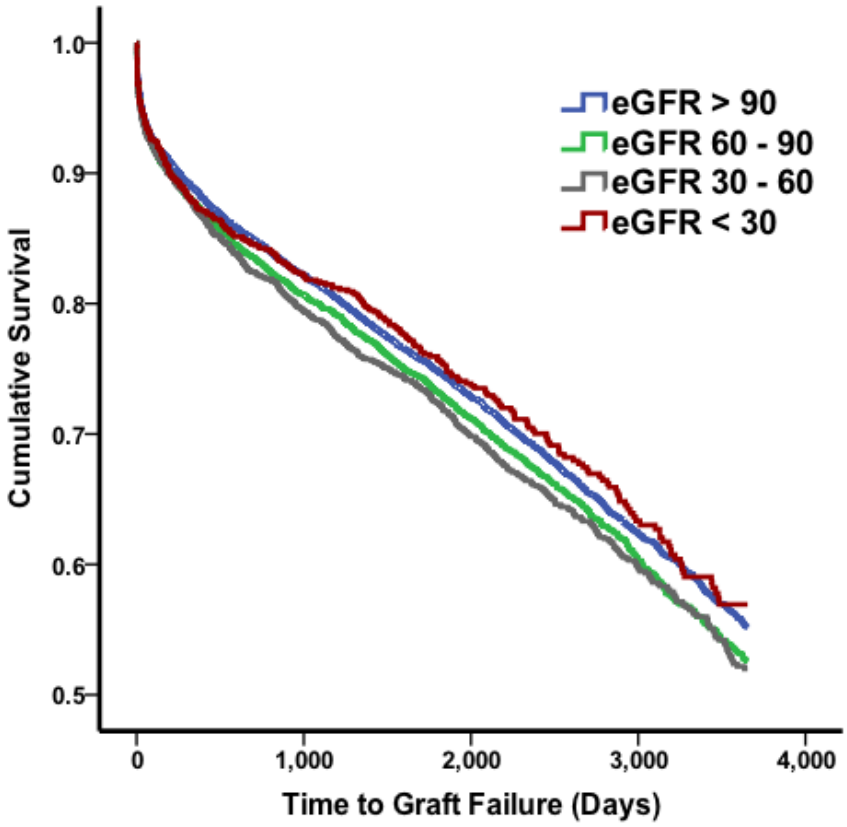

Figure 6. Kaplan-Meier survival plots stratified by donor eGFR categories. eGFR: estimated glomerular filtration rate in mL/min/1.73m^2.

Donor proteinuria and graft failure:

In total, 32.6% of donors (n=7,406) had proteinuria at the time of evaluation. Not surprisingly, proteinuria was more common in donors with hypertension (37.1% vs. 31.9%, p<0.001) and in donors with diabetes (41.2% vs. 32.3%, p<0.001). Donor proteinuria was not associated with decreased graft survival (HR=1.00, 95% CI 0.95-1.05, p=0.96, Figure 5), and this lack of association persisted with extensive adjustment for donor and recipient characteristics (HR=1.00, 95% CI 0.94-1.06, p=0.97, Figure 7).

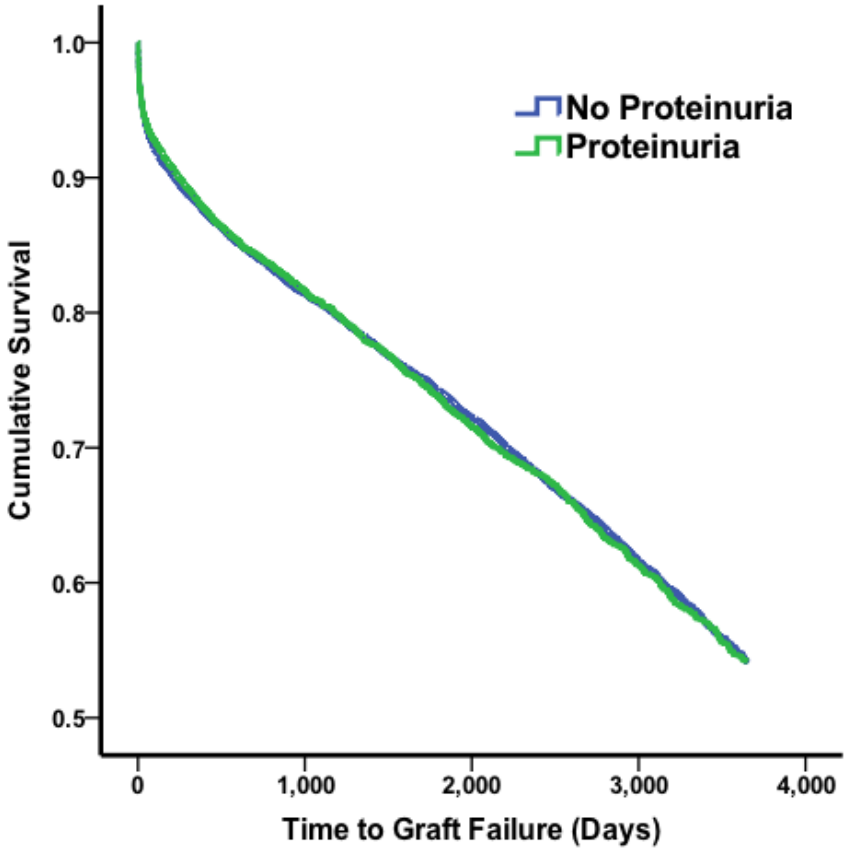

Figure 7. Kaplan-Meier survival plots stratified by donor proteinuria.

Recipient characteristics:

Baseline characteristics of recipients with and without RD are presented in Table 4.

Table 4. Baseline recipient characteristics stratified by presence or absence of recipient renal dysfunction

	Overall	Recipient RD present		P - value
Characteristic	**(n = 23,056)**	**No (n = 13,982)**	**Yes (n = 9,074)**	

Demographics				
Age, years	52.3 ± 12.3	49.3 ± 13.0	56.8 ± 9.7	<0.001
Female gender	24.4%	24.2%	24.7%	0.372
Gender mismatch	15.8%	16.3%	15.1%	0.017
White race	82.7%	80.9%	85.6%	<0.001
BMI	26.8 ± 4.8	26.5 ± 4.9	27.2 ± 4.6	<0.001
Comorbidities				
Diabetes mellitus	24.0%	21.0%	28.6%	<0.001
Hypertension	40.1%	38.2%	42.9%	<0.001
Peripheral vascular	3.4%	2.7%	4.5%	<0.001
Cerebrovascular disease	5.5%	5.2%	6.0%	0.011
Cigarette use	49.0%	48.1%	50.5%	0.005
Ischemic cardiomyopathy	38.4%	35.2%	43.4%	<0.001
CMV positive	62.1%	61.1%	63.6%	<0.001
Disease severity at				
Inotropes	43.0%	41.0%	45.9%	<0.001
IABP	5.3%	5.1%	5.7%	0.028
Mechanical circulatory	21.8%	24.1%	18.2%	<0.001
UNOS status 1A	44.2%	45.6%	42.1%	<0.001
Mechanical ventilation	4.1%	4.3%	3.9%	0.093
Cardiac allograft				
Ischemic time (hours)	3.2 ± 1.0	3.2 ±1.0	3.2 ±1.0	0.110

Ischemic time ≥ 4 hours	21.0%	20.7%	21.5%	0.137
LVEF	61.6 ± 7.6	61.7±7.6	61.4±7.7	0.008
LVEF ≤ 45%	2.2%	2.0%	2.5%	0.010
Laboratory values				
Creatinine, mg/dl	1.3 ± 0.7	1.0 ± 0.2	1.8 ± 0.8	<0.001
eGFR, ml/min/1.73m^2	69.9 ± 26.5	86.2 ± 20.1	44.7 ± 10.9	<0.001
Hemodynamics				
MPAP, mm/Hg	28.3 ± 10.2	27.9 ± 10.3	29.0 ± 10.0	<0.001
PCWP, mm/Hg	18.8 ± 8.8	18.5 ± 8.9	19.2 ± 8.6	<0.001
TPG, mm/Hg	9.6 ± 5.4	9.5 ± 5.5	9.8 ± 5.3	0.001
CO, L/min	4.5 ± 1.5	4.5 ±1.5	4.6 ±1.5	0.018
PVR, Wood units	2.4 ±2.0	2.4 ± 1.9	2.4 ± 2.0	0.324

RD: renal dysfunction, BMI: body mass Index, CMV: cytomegalovirus, IABP: intraaortic balloon pump, UNOS: United Network of Organ Sharing, LVEF: left ventricular ejection fraction, eGFR: estimated glomerular filtration rate, MPAP: mean pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure, TPG: transpulmonary gradient, CO: cardiac output, PVR: pulmonary vascular resistance.

The mean eGFR of the population was 69.9 ± 26.5 ml/min/1.73m^2 and RD was present in 39.4% of recipients. Amongst recipients with RD, the mean eGFR was 44.7 ± 10.9 ml/min/1.73m^2. Similar to donors, recipients with RD were older and more likely to have evidence of CVD in the form of ischemic cardiomyopathy and peripheral vascular disease. Additionally, recipients with RD exhibited several indices of increased HF-

disease severity including greater utilization of inotropes and intra-aortic balloon pumps and higher filling pressures. Pre-transplant allograft function was similar between recipients with and without RD. When only those recipients who received allografts from RD-free donors were examined (n=18,919), the observed similarities and differences between those recipients with and without RD were similar (data not shown).

Recipient RD and timing of graft failure:

Over the entire follow-up period, recipient RD was significantly associated with poor graft outcomes even following extensive adjustment for donor and recipient characteristics (Adjusted HR=1.27, 95% CI 1.20-1.34, p<0.001). However, there was a significant difference in the risk attributable to RD which varied over time (p time-dependent interaction = <0.001). Interestingly, the highest risk of graft failure associated with RD occurred immediately within the first 30 days post-transplant (adjusted HR=1.76, 95% CI 1.54-2.02, p<0.001). The risk associated with RD subsequently decreased as time went on such that the hazard associated with baseline RD from 30 days to 1 year no longer significantly impacted subsequent graft survival (HR=0.92, 95% CI 0.77-1.09, p=0.33, Table 5, Figure 8).

Table 5. Association between recipient renal dysfunction and recipient graft failure adjusted for donor and recipient risk factors

	HR	**95% CI**	**P-value**
Recipient Characteristics			
eGFR < 60 ml/min/1.73m2, within 1st month	1.76	1.54-2.02	<0.001

eGFR < 60 ml/min/1.73m2, 1 month to 1 year	0.92	0.77-1.09	0.33
Age, per 10 year increase	0.94	0.92-0.97	<0.007
Female gender	1.14	1.05-1.24	<0.001
Gender mismatch	1.17	1.03-1.33	0.015
Black race	1.39	1.30-1.49	<0.001
BMI	1.00	1.00-1.01	0.23
Diabetes mellitus	1.13	1.06-1.21	<0.001
Hypertension*	1.14	1.06-1.21	<0.001
Cerebrovascular disease	1.10	0.98-1.22	0.10
Cigarette use*	1.06	0.98-1.14	0.16
Ischemic cardiomyopathy	1.19	1.12-1.26	<0.001
CMV positive*	1.03	0.97-1.09	0.30
Inotrope use	1.03	0.97-1.09	0.31
IABP	1.06	0.94-1.20	<0.31
Mechanical circulatory support	1.16	1.07-1.27	<0.001
UNOS status 1A	1.12	1.05-1.18	<0.001
Mechanical ventilation	1.20	1.03-1.39	0.021
Cardiac Allograft Characteristics			
Ischemic time, hours	1.06	1.04-1.09	<0.001
LVEF, %	1.00	1.00-1.00	0.12
Donor Characteristics			
Age, per 10 year increase	1.11	1.08-1.14	<0.001

Female gender	0.96	0.86-1.07	0.43
Diabetes mellitus	1.15	0.97-1.35	0.11
Hypertension	0.96	0.88-1.04	0.31
Cigarette use	1.08	1.01-1.14	0.02
CMV positive	1.11	1.05-1.17	<0.001
Suspected infection (blood)	1.10	1.00-1.22	0.06
Cause of death: anoxia	1.08	0.99-1.18	0.08
Inotropic support*	1.04	0.98-1.11	0.23
eGFR, per 10 ml/min/1.73m2 increase	1.00	1.00-1.01	0.39

*Missing data in these covariates was coded as a separate category due to its prevalence (9% for donor inotropic support; 50% for recipient hypertension; 36% for recipient history of cigarette use, 6% for recipient cmv positive status). The associated HR specifically represents the risk of graft failure in a group with one of these risk factors vs. without. eGFR: estimated glomerular filtration rate, CMV: cytomegalovirus, LVEF: left ventricular ejection fraction, RD: renal dysfunction, BMI: body mass Index, IABP: intra-aortic balloon pump, UNOS: United Network of Organ Sharing.

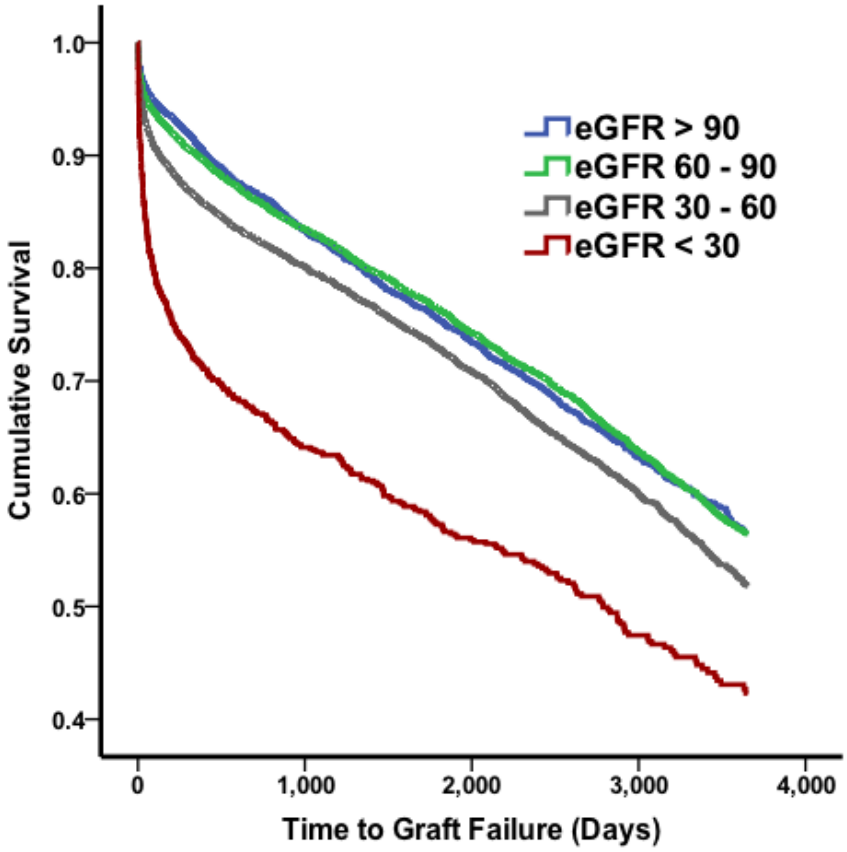

Figure 8. Kaplan-Meier survival curves stratified by recipient eGFR categories. eGFR: estimated glomerular filtration rate in mL/min/1.73m^2.

The attenuation in risk did not appear to be primarily driven by recovery in renal function; when patients with data on repeat renal function were evaluated (data available 37%, median time to follow-up creatinine = 6.0 years), eGFR in patients with RD did not meaningfully improve post-transplant (baseline eGFR 45.0 ± 10.5 ml/min/1.73m^2 vs. follow-up eGFR 47.3 ± 20.1 ml/min/1.73m^2). Similar findings of an early period of high risk followed by attenuation in risk was observed when examining only cardiac allografts from donors without RD (p interaction = 0.13).

Discussion:

Principal Findings of the Study:

The principal findings of this study are 1) RD in a cardiac donor, regardless of its severity, is not associated with worsened graft survival and 2) the risk of graft failure associated with recipient RD is substantial and most pronounced in the first 30 days following cardiac transplantation with subsequent attenuation in the risk over time. Thus RD-associated risk cannot be transferred between patients via the myocardium, but placement of a healthy myocardium into a host with RD results in immediate worsening in outcomes. The pattern of this risk is most consistent with the concept that the primary source of risk associated with RD is derived from the peripheral or non-myocardial aspects of the cardio-renal environment.

A large body of evidence from animal models has clearly demonstrated that significant adverse myocardial structural changes such as apoptosis, necrosis, and fibrosis occur with experimentally induced RD.[13-20] Given that these are known mediators of disease in humans, it is reasonable to believe if the above pathology also occurred in humans with RD it would result in worse outcomes. Importantly, despite significant pathologic changes, animal systolic function was only mildly or not impaired at all, suggesting that if this damage occurred in humans it would likely not be avoided during the allograft screening process.[16] Consistent with the above premises, it has previously been reported that factors which plausibly can cause direct myocardial damage such as older donor age, hypertension, and diabetes have been linked to

worsened post-transplant graft survival. These findings serve as "positive controls" that subclinical myocardial damage in the donor can be transmitted to the recipient despite the donor screening process.[21, 26-30] However, even with severe RD in the donor the risk associated with donor RD approached zero in a sample size of >23,000 patients. Although the graft selection process and complicated peri-transplant management of these patients may have attenuated the signals in this study, the complete lack of a detectable risk with donor RD argues that the peripheral RD environment is the dominant factor in RD-associated risk.

Further support for the above concept is provided by the findings with respect to recipient RD. Importantly, substantial acute systolic dysfunction has not been a predominant finding in animal models of experimentally induced RD and we could not detect any signal for worsened outcomes with donor RD, which was likely acute in the majority of cases.[16] As a result even if myocardial damage began to occur immediately following transplant of a healthy donor heart into a recipient with RD, myocardial dysfunction would not be expected to manifest itself in immediately worsened outcomes. Rather, only over months to years as myocardial damage accumulated would we expect to see worsened outcomes associated with recipient RD if the myocardial pathology was the dominant driver. To the contrary, we found that when donor hearts were placed into the environment of recipient RD the opposite pattern was apparent with substantially increased risk immediately following transplant, followed by attenuation of the risk over time. Unlike a delayed effect as myocardial injury accumulates from RD, the peripheral

aspects of RD such as unmeasured disease severity, underutilization of beneficial therapies (i.e, calcineurin inhibitors), and systemic myocardial depressant factors would be expected to be the most pronounced immediately after transplant. The finding of a substantially increased early risk associated with RD followed by subsequent attenuation is in line with the latter hypothesis.

The direct implication of this study is that transplantation of appropriately selected hearts from donors with even significant RD does not appear to worsen post-transplant outcomes. However, this analysis also may shed some light on potential therapeutic approaches toward cardio-renal dysfunction. If transplantation of a heart from a donor with RD was associated with worse post-transplant outcomes, this would indicate that once cardio-renal syndrome occurs, the damage is likely irreversible. However, the absence of a risk associated with donor RD and attenuation of the risk associated with recipient RD over time post-transplant suggests that the risk associated with cardio-renal dysfunction may be modifiable. Further research is necessary to better understand the non-myocardial determinants of RD associated risk and evaluate if strategies to improve these risk factors could improve outcomes in these patients.

Study Limitations:

This study is subject to limitations inherent to analyses of a retrospective post-hoc study, such as uncontrolled confounding and reliance on data from a large registry. It is unclear to what degree transplantation and subsequent treatment with nephrotoxic

medications such as calcineurin inhibitors may have influenced the RD-graft survival association. Furthermore, although RD is not a standard parameter that is considered in the organ selection process, we do not have data on how RD may have affected the organ refusal rate. Post-transplant decisions such as the choice of immunosuppression may have been influenced by recipient RD, potentially altering the post-transplant graft failure risk. Additionally, the graft failure outcome was primarily driven by recipient death, which could represent non-myocardial events such as infection or malignancy. Although renal function did not appear to improve post-transplant in the patients with serial creatinine values available, long-term changes in renal function were not available in the majority of patients, and when this data was available it was several years after the transplant. As a result, in some patients improvement in renal function may have occurred attenuating the risk associated with time of transplant RD at later time periods.

In conclusion, the risk associated with RD does not appear to be transferrable from donor to recipient via the cardiac allograft and the risk associated with recipient RD is greatest immediately following transplant. Overall these data support the safety of transplantation of appropriately selected allografts from donors with RD. Additionally, these data suggest that the non-myocardial aspects of cardio-renal dysfunction appear to be of particular importance in driving the risk associated with RD.

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Supplementary materials:

Abstract accepted at Amereican College of Cardiology conference 2014:

Donor and Recipient Renal Dysfunction and Post Cardiac Transplant Graft Survival - Insights Into Cardiorenal Interactions

Authors: Olga Laur, Meredith Brisco, Alexander Kula, Susan Cheng, Steve Coca, Abeel Mangi, Wilson Tang, Jeffrey Testani

Background: The major mode of death in patients with renal dysfunction (RD) is cardiovascular disease (CVD). Notably, there may be a causal effect of RD given that myocardial necrosis/apoptosis has been seen in animal models of RD. However, RD is also a marker of overall CVD severity. Cardiac transplantation provides an opportunity to study this as hearts are being transplanted in and out of the environment of RD: If irreversible myocardial damage occurs immediately with RD, as seen in animal models of acute kidney injury, transplantation of a heart from a donor with RD should yield reduced graft survival. However, if cardiac damage from RD develops gradually, transplantation of a healthy RD-free donor heart into a recipient with RD should yield an initial low risk period followed by high event rates months to years later.

Methods: Adult cardiac allograft recipients in the UNOS registry were studied (n=35,914). RD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2.

Results: RD was present in 17.2 % of donors and 39.4% of recipients with an overall worsening in eGFR over time in recipients ($p<0.001$). Donor characteristics known to cause or reflect myocardial damage such as ischemic time > 4 hours (adjusted HR 1.2,

p<0.001), age > 50 years (adjusted HR=1.3, p<0.001), or ejection fraction ≤ 45% (adjusted HR 1.2, p=0.03) were associated with reduced graft survival. To the contrary, the risk associated with RD did not follow the heart as transplantation from a donor with RD did not reduce graft survival (adjusted HR=0.98, p=0.44). RD-free donor hearts placed into a recipient with RD paradoxically had the highest risk of graft dysfunction in the first 30 post-operative days (Adjusted HR 1.6, p<0.001). Subsequently, the hazard attributable to recipient RD (adjusted HR 1.2, p<0.001) did not increase over time (p=0.8) as would be expected with slow accumulation of myocardial damage from RD. **Conclusion**: Transplantation of a heart in and out of the environment of RD was not associated with worsened outcomes in a manner consistent with a clinically meaningful direct effect of RD on the myocardium. These data provide additional support that RD primarily serves as a marker rather than a direct cause of CVD.

Abstract accepted at International Society for Heart and Lung transplantation conference in April 2014:

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Authors: Olga Laur, Meredith Brisco, Alexander Kula, Susan Cheng, Steve Coca, Abeel Mangi, Wilson Tang, Jeffrey Testani

Background: The major mode of death in patients with renal dysfunction (RD) is cardiovascular disease (CVD). Notably, there may be a causal effect of RD given that

myocardial necrosis/apoptosis has been seen in animal models of RD. However, RD is also a marker of overall CVD severity. Cardiac transplantation provides an opportunity to study this as hearts are being transplanted in and out of the environment of RD: If irreversible myocardial damage occurs immediately with RD, as seen in animal models of acute kidney injury, transplantation of a heart from a donor with RD should yield reduced graft survival. However, if cardiac damage from RD develops gradually, transplantation of a healthy RD-free donor heart into a recipient with RD should yield an initial low risk period followed by high event rates months to years later.

Methods: Adult cardiac allograft recipients in the UNOS registry were studied (n=35,914). RD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2.

Results: RD was present in 17.2 % of donors and 39.4% of recipients with an overall worsening in eGFR over time in recipients ($p<0.001$). Donor characteristics known to cause or reflect myocardial damage such as ischemic time > 4 hours (adjusted HR 1.2, $p<0.001$), age > 50 years (adjusted HR=1.3, $p<0.001$), or ejection fraction ≤ 45% (adjusted HR 1.2, $p=0.03$) were associated with reduced graft survival. To the contrary, the risk associated with RD did not follow the heart as transplantation from a donor with RD did not reduce graft survival (adjusted HR=0.98, $p=0.44$). RD-free donor hearts placed into a recipient with RD paradoxically had the highest risk of graft dysfunction in the first 30 post-operative days (Adjusted HR 1.6, $p<0.001$). Subsequently, the hazard attributable to recipient RD (adjusted HR 1.2, $p<0.001$) did not increase over time ($p=0.8$) as would be expected with slow accumulation of myocardial damage from RD.

Conclusion: Transplantation of a heart in and out of the environment of RD was not associated with worsened outcomes in a manner consistent with a clinically meaningful direct effect of RD on the myocardium. These data provide additional support that RD primarily serves as a marker rather than a direct cause of CVD.