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Multivessel coronary revascularization and outcomes in kidney transplant recipients

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Summary

Coronary artery disease is a major cause of morbidity and mortality in the kidney transplant population. We compared the long-term outcomes of coronary artery bypass graft (CABG) surgery with percutaneous coronary intervention (PCI) for multivessel coronary disease in a contemporary cohort of US kidney transplant recipients. From the U.S. Renal Data System, we identified all adult kidney transplant patients with ≥6 months of Medicare A+B undergoing first recorded multivessel coronary revascularization from 1997 to 2009. The associations of CABG *versus* PCI with death and the composite of death or myocardial infarction (MI) were compared using proportional hazards regression. Of the 2272 patients included in the study, 1594 underwent CABG and 678 underwent PCI. The estimated 5-year survival rate was 55% [95% confidence interval (CI) 53% to 57%] following coronary revascularization, with no significant association between revascularization type and death [adjusted hazard ratio (aHR) = 1.08; CI 0.94–1.23] or the composite of death or MI (aHR = 1.07; CI 0.96–1.18). Separate propensity score-matched analyses yielded similar results. In this analysis of kidney transplant recipients undergoing multivessel coronary revascularization, we found no difference between CABG and PCI in terms of survival or the composite of death and MI.

Introduction

Kidney transplantation is the best treatment for end-stage renal disease (ESRD) for survival and quality of life [1,2]. However, kidney transplant recipients have a reduced life expectancy compared with the general population [3]. Cardiovascular disease is the leading cause of death and accounts for almost as many deaths as infection and malignancy combined [4]. Contributing factors to this high cardiovascular risk include an overrepresentation of traditional risk factors such as hypertension and diabetes mellitus and nontraditional risk factors such as allograft dysfunction and systemic inflammation [5,6].

Kidney transplant recipients are at particularly high risk of coronary artery disease with a cumulative incidence of myocardial infarction (MI) of over 11% in the 3 years following successful transplant [7]. In randomized trials of non-ESRD patients with multivessel coronary artery disease, treatment with coronary artery bypass grafting (CABG) is superior to percutaneous coronary intervention (PCI) in terms of lower rates of repeat revascularization and cardiovascular events [8,9]. However, none of these trials included patients with ESRD. Observational studies of patients with ESRD on maintenance dialysis have shown a survival benefit associated with CABG over PCI [10,11], but data in the kidney transplant population are limited. The largest study, of U.S. transplant recipients from the 1990s undergoing coronary revascularization, found no difference in long-term survival, but did show a reduced risk of AMI and cardiac death associated with CABG compared with PCI [12]. However, that study and other smaller studies [13,14] pre-date important changes in revascularization practices and in the demographics and management of kidney transplant patients [4,15].

Coronary artery disease management in kidney transplant recipients remains a major challenge, given the large

evidence gap comparing CABG and PCI for the management of multivessel coronary disease in this population. We therefore sought to test the hypothesis that multivessel CABG would be associated with improved survival and cardiovascular morbidity compared with multivessel PCI in a contemporary kidney transplant population.

Materials and methods

Study population

We identified all patients in the United States Renal Data System (USRDS) who received a first documented CABG (ICD-9 procedure codes 36.1x) or PCI (ICD-9 procedure codes 36.00, 36.01, 36.02, 36.07, 36.06, 36.07, 36.09, or 00.66) after developing ESRD between 1997 and 2009 (Fig. 1). The hospital admission date was defined as the index date. We then required patients to have a functioning renal transplant on the index date and excluded patients on maintenance dialysis, patients with unknown mode of renal replacement therapy, or patients undergoing kidney transplant during the index hospitalization.

We excluded patients receiving both CABG and PCI during the same hospitalization and restricted the cohort to patients undergoing documented multivessel procedures (identified using ICD-9 procedure codes for 36.12, 36.13, 36.14, or 36.16 for multivessel CABG; 36.05 before October 2005; 00.66 and either an ICD-9 code of 00.41, 00.42, 00.43 or a CPT code of 92981, 92984, or 92996 after October 2005 for multivessel PCI). Among patients undergoing CABG, we excluded patients undergoing concomitant ventricular reconstruction or pericardial or valve surgery (ICD-9: 35.xx, 37.31, 37.32, 37.35, 37.4, or 37.5). We further excluded patients who had a history of CABG or PCI not based on procedure codes (ICD-9 diagnosis codes V45.81 or V45.82.)

We included patients revascularized between January 1, 1997 and December 31, 2009 and required patients to have continuous Medicare Part A and B coverage as primary payer for 6 months prior to the index date to ensure a uniform period in which to ascertain comorbid conditions and past healthcare utilization.

Follow-up and outcomes

The primary outcome of interest was death from any cause, ascertained from the USRDS "patient" file, which derives information on patient deaths irrespective of Medicare coverage status.

The secondary outcome was a composite of first MI or death from any cause. We defined MI as an ICD-9 diagnosis code of 410.xx as a primary hospitalization diagnosis code or 410.x1 in any secondary diagnosis code position. An MI occurring during the index hospitalization was not considered an outcome, as it may have occurred prior to, and led to, the revascularization.

Follow-up for the primary outcome was until January 1, 2010. Because ascertainment of MI required hospitalization information, for the composite outcome of death or MI we followed patients until death, the first time that Medicare Part A and B coverage ended, or January 1, 2010.

Covariates

We obtained data on age, sex, race (white, black and other), duration of ESRD, and cause of ESRD from the USRDS patient and treatment history files. We also obtained transplant-related characteristics such as number of years with current kidney transplant, transplant type (living donor, standard deceased donor, or expanded criteria donor), whether the current transplant was a preemptive transplant,

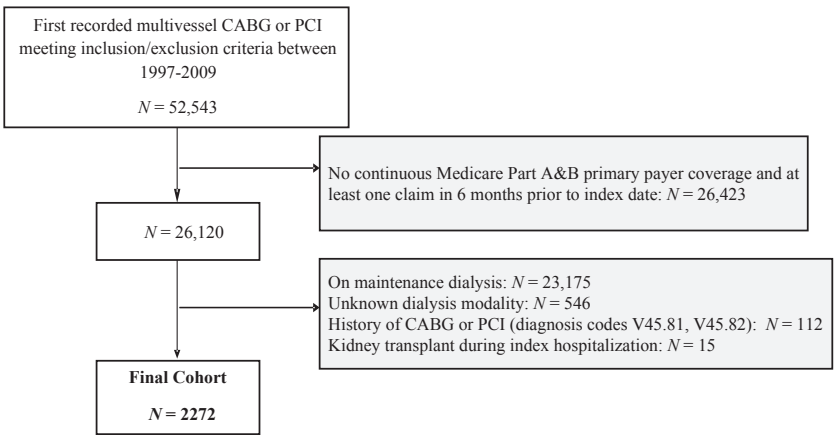

Figure 1 Cohort assembly of patients with functioning kidney transplant at the time of first recorded multivessel coronary revascularization.

and previous failed kidney transplant from the USRDS transplant files.

We defined comorbid conditions using ICD-9 codes and procedure codes from ≥1 inpatient or ≥2 outpatient encounters separated by at least 1 day in the 6 months prior to (but not including) the index date (Supporting Information Table S1). We identified the following comorbid conditions: MI, heart failure, hypertension, cerebrovascular disease, valve disease, peripheral vascular disease, diabetes mellitus, chronic lung disease, systemic cancer, tobacco use, and alcohol abuse. We identified an MI on index presentation by presence of an ICD-9 code of 410.xx in the primary diagnosis code position or 410.x1 in any secondary diagnosis code position.

To adjust for differences in prior healthcare utilization, we identified the number of non-nephrology outpatient visits, number of hospitalized days, and patients who had any nursing home stay in the 6 months prior to the index date.

Statistical analysis

Differences in baseline characteristics among patients undergoing multivessel CABG versus multivessel PCI were compared using chi-square tests, *t*-tests, and nonparametric tests as appropriate. Unadjusted incidence rates, defined as the number of events over person-time observed, were calculated for each outcome.

We used multivariate Cox models, stratified by index year, to compute adjusted hazard ratios (HR) for each outcome, with PCI serving as the referent. We computed hazard ratios using two nested models: Model 1, adjusted for age, sex, and race; and, Model 2, additionally adjusted for the variables listed in Table 1. Transplant type was missing for 17% of patients, which was not missing completely at random. Because missingness was correlated with some of the variables, we assumed a missing at random mechanism. We applied multiple imputation techniques using a multivariate normal model (SAS PROC MI) to obtain five imputed datasets, applied the Cox regression model to each imputed dataset, and combined the results as described by Little and Rubin [16] (SAS PROC MIANALYZE). We performed two sensitivity analyses: one using a complete case analysis and one using ten imputed datasets. We hypothesized *a priori* that there could be effect modification by diabetes mellitus status, and therefore tested for interaction between the treatment modalities and diabetes mellitus as an extension of Model 2 using a multiplicative interaction term. Imputation was performed taking into account the interaction. In addition, given the rapid adoption of drug-eluting stents after their introduction into the U.S. market in April 2003, we tested for effect modification by stent era in an analogous fashion: 1997–2003 (bare metal stent era) and 2004–2009 (drug-eluting stent era).

Table 1. Baseline patient characteristics.

	Full Cohort		
	CABG *N* = 1594	PCI *N* = 678	*P*
Patient Demographics			
Age (years)	57.6 (11.0)	58.6 (10.6)	0.04
Female	30.8	34.7	0.07
Race			
White	84.1	84.2	0.9
Black	12.0	11.8	
Other	3.9	4.0	
Cause of ESRD			
Diabetes	42.9	41.2	0.3
Hypertension	16.4	15.6	
Glomerulonephritis	17.9	16.8	
Other	22.8	26.4	
Total years with ESRD, median (IQR)	8.5 (5.6–13.2)	8.3 (5.0–12.7)	0.1
Years with current transplant, median (IQR)	6.0 (3.0–9.9)	5.5 (2.9–9.5)	0.2
Transplant type			
Living donor	26.5	22.1	0.2
Standard deceased donor	53.8	55.0	
Expanded criteria donor	7.1	8.4	
Missing	17.6	14.5	
Preemptive current transplant	7.7	8.6	0.5
Had previous failed kidney transplant	12.9	10.0	0.05
Skilled Nursing Facility Utilization	2.6	3.5	0.2
Hospital days, median (IQR)	3 (1–9)	3 (1–7)	<0.0001
Non-nephrology clinic visits, median (IQR)	14 (8–22)	15 (9–23)	0.3
MI during index hospitalization	23.8	32.6	<0.0001
Comorbidities			
Myocardial infarction	6.7	6.3	0.7
Cerebrovascular disease	10.4	8.7	0.2
Valve disease	14.1	14.8	0.7
Heart failure	22.3	21.2	0.6
Peripheral vascular disease	16.5	15.8	0.7
Diabetes mellitus	60.8	59.9	0.7
Hypertension	76.9	74.5	0.2
Alcohol	0.5	0.6	0.8
Tobacco	3.6	2.8	0.3
Cancer	3.6	4.9	0.1
Chronic pulmonary disease	9.4	12.1	0.05

Given the baseline differences in patient characteristics between CABG and PCI recipients, we conducted a companion analysis using a propensity score-matched cohort [17] (Model 3). We used as predictors of receipt of CABG or PCI all of the baseline variables included in our multivariable adjusted models listed above. Given the missing data on transplant type, we also used multiple imputation, including all the variables used in Model 2, and the specified outcome (death and death or MI) to generate five imputed datasets. For each imputed dataset, we used a greedy matching algorithm [18] to match each patient who received a multivessel PCI with a patient who received a multivessel CABG with a difference in propensity scores of no greater than 0.01. We further required that the patients match by index year. We ran a Cox regression model on each matched dataset, and combined the results as above. Sensitivity analyses were performed to assess several different approaches to using propensity score analysis in the presence of missing data. Full details can be found in the Supporting Information Data S1.

We calculated Kaplan–Meier survival rates using the matched cohort and repeated the Cox regression models for our outcomes of interest. We tested the proportional hazards assumption using log (-log) plots. The institutional review board of Stanford University approved the study. A waiver of informed consent was obtained because of the nature of the study. All analyses were conducted using SAS Enterprise Guide 4.3 (Cary, NC).

Results

Our final cohort consisted of 2272 patients with a functioning kidney transplant at the time of their first recorded multivessel coronary revascularization (Fig. 1). The proportion of patients undergoing CABG fell from 80% in 1997 to a nadir of 58% in 2006 (Fig. 2). After their introduction to the U.S. market in 2003, over 70% of patients undergoing PCI received a drug-eluting stent. Patients undergoing CABG tended to be younger, less often had a diagnosis of an MI during the index hospitalization, but were otherwise fairly well balanced compared with patients undergoing PCI (Table 1).

Patients undergoing CABG were followed up for a median of 3.6 years [interquartile range (IQR) 1.3–6.5 years], during which time there were 872 deaths. Patients undergoing PCI were followed up for a median of 3.2 years (IQR 1.2–5.5 years) during which time there were 313 deaths (Table 2). Although the crude incidence of death at 30 days was higher for patients undergoing CABG compared with PCI, the long-term crude incidence rates were similar in both groups at approximately 12 deaths/100 person-years. The majority of deaths were because of cardiovascular events (Table 2). Five-year survival rates were 55% (CI 53% to 57%) irrespective of revascularization type. In the propensity score-matched cohort, patients undergoing CABG had 30-day, two- and five-year survival rates of 95% (CI 93% to 96%), 76% (CI 72% to 79%), and 55% (CI 51% to 60%), respectively; 30-day, two- and five-year survival rates were similar for patients undergoing PCI (97%, CI 95% to 98%; 77%, CI 74% to 81%; and 58%, CI 54% to 63%; Fig. 3a).

We found no significant association of revascularization type with death in unadjusted or adjusted models (Fig. 4). Our results were not materially changed in sensitivity analyses using complete case analyses, ten imputed datasets, or in models using other propensity score and imputation techniques (Supporting Information Table S2). There was no evidence of effect modification by diabetes mellitus status or by stent era (P-interaction >0.1 in all models).

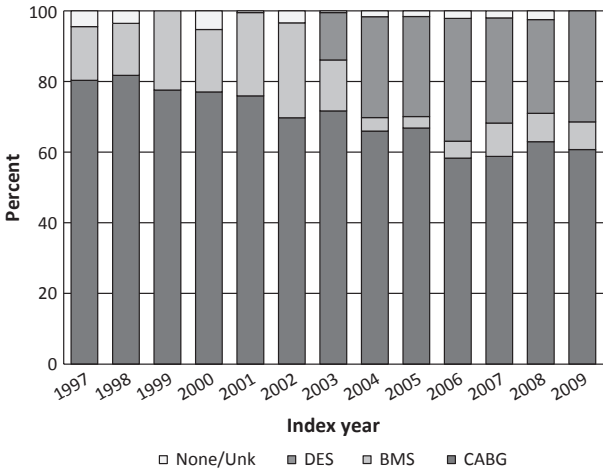

Figure 2 Distribution of revascularization method by index year. Unk, unknown; DES, drug eluting stent; BMS, bare metal stent; CABG, coronary artery bypass grafting.

Table 2. Outcomes and crude incidence rates in the full cohort.

Outcome	CABG *N* = 1594	PCI *N* = 678
Death		
Events within 30 days	98	22
Total number of events	872	313
Person-time at risk (years)	6735	2537
Incidence rate (events/100 person-years)	12.6	12.3
Causes of death, *N* (%)		
Cardiovascular	292 (33.5)	85 (27.2)
Infection	75 (8.6)	30 (9.6)
Withdrawal from dialysis	18 (2.1)	6 (1.9)
Other/unknown	487 (55.9)	192 (61.3)
Death or Myocardial Infarction		
Number of events	1360	573
Person-time at risk (years)	5710	2102
Incidence rate (events/100 person-years)	23.8	27.3

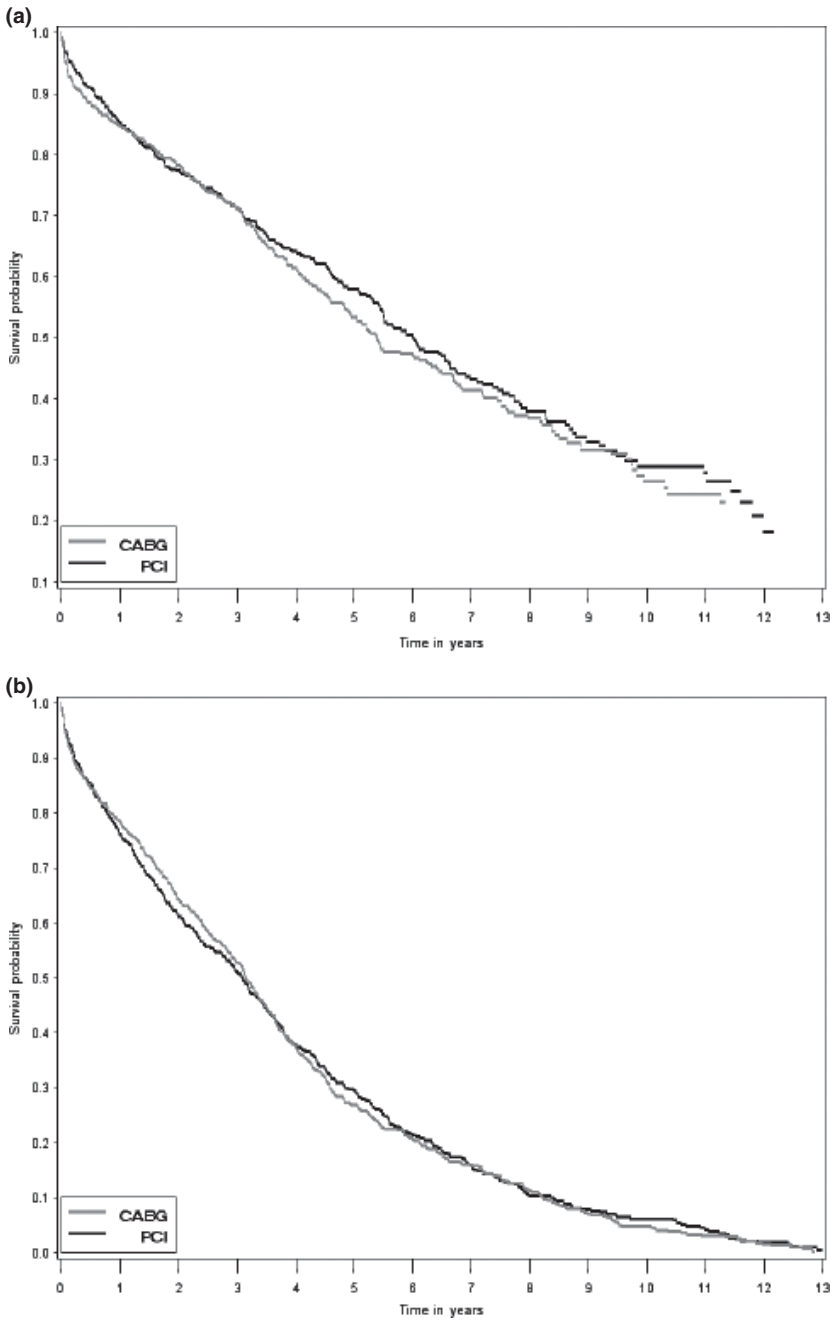

Figure 3 Survival curves for the propensity score-matched cohort for (a) death and (b) the composite of death or MI. Log-rank tests yielded $P = 0.48$ for the outcome of death (A) and $P = 0.79$ for the outcome of death or MI (B).

For the composite outcome of death or MI, there were 1360 events for patients receiving a CABG and 573 events for patients receiving a PCI (Table 2). We found no significant association of revascularization type with the composite outcome in unadjusted and adjusted models (Figs 3b and 4) and our results were not materially changed in any of our sensitivity analyses (Supporting Information Table S2).

Discussion

In our study of U.S. kidney transplant recipients undergoing first recorded revascularization for multivessel coronary artery disease, we observed significant changes in revascularization practices in the kidney transplant population over the study period with decreased CABG utilization and widespread adoption of drug-eluting stents. We found no

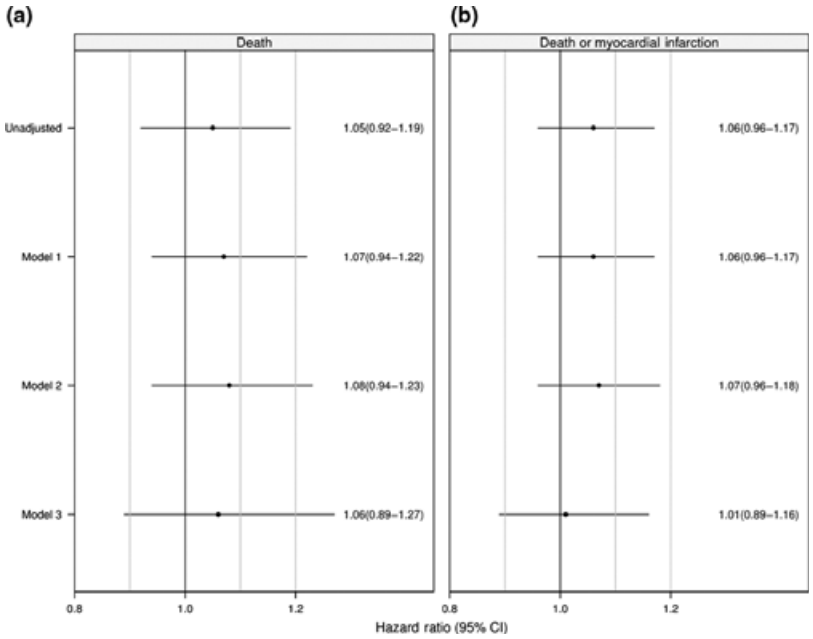

Figure 4 Unadjusted and adjusted hazard ratios for coronary artery bypass grafting compared with percutaneous coronary intervention (referent) for the outcomes of (a) death or (b) death or myocardial infarction. Model 1: Adjusted for age, sex, race. Model 2: Model 1 + adjustment for cause of ESRD, total years with ESRD, years with current transplant, transplant type, preemptive current transplant, previous failed transplant, skilled nursing facility utilization, hospital days, non-nephrology clinic visits, index myocardial infarction, and comorbid conditions: myocardial infarction, cerebrovascular disease valve disease, heart failure, peripheral vascular disease, diabetes mellitus, hypertension, alcohol, tobacco, cancer, chronic pulmonary disease. Model 3: Propensity score-matched cohort.

differences in the survival or the composite outcome of death or MI among patients undergoing CABG versus PCI, findings that were robust across a number of analytical approaches.

Kidney transplant recipients have a unique cardiovascular risk profile and are at high risk for coronary artery disease [4,7]. Compounding an excess of traditional risk factors, kidney transplant recipients are exposed to the enhanced risk of cardiovascular disease associated with reduced glomerular filtration rate (GFR) and ESRD, an effect magnified by lengthening transplant waiting lists and protracted dialysis requirements [19,20]. Transplantation, while improving GFR, also contributes additional cardiovascular risk, most notably through the adverse metabolic side-effects associated with current immunosuppressive medication [21]. These unique attributes distinguish the kidney transplant from the general, dialysis and nondialysis-dependent chronic kidney disease populations, and make it important that guidelines for management of cardiovascular disease are based on studies conducted within the kidney transplant population.

Our study of kidney transplant recipients undergoing multivessel coronary revascularization between 1997 and 2009 extends the results of an earlier study by Herzog *et al.* examining CABG or PCI between 1995 and 1999 [12]. Consistent with our results, that study also showed no difference in the risk of all-cause or cardiac death by revascularization type. When they examined a composite outcome of cardiac death or MI, they found a 43% (CI 24% to 58%) lower risk associated with CABG compared with angioplasty without stenting. However, while 25% of their population underwent angioplasty without stenting, only 2% of our patients had no stent placed at the time of PCI, reflective of contemporary practice patterns. Also, their study included patients with single-vessel disease, a condition with a more favorable prognosis usually treated by PCI, which may have biased their results toward the null. We restricted our analysis to patients undergoing multivessel revascularization only, thereby providing a more fair comparison of the relative benefits of CABG compared with PCI.

The five-year survival rates in our study of 55% irrespective of revascularization type are similar to those rates reported by Herzog *et al.* [12], indicating the lack of improvement in outcomes over the past decade, despite advancements in procedural technique and technology, and use of cardio-protective medications such as statins and platelet inhibitors. Although the five-year survival rates in this kidney transplant population exceed the dismal 22–25% five-year survival rates postmultivessel coronary revascularization in patients with ESRD on dialysis that we previously reported [10], they are still far lower than the 90% five-year survival rates seen in non-ESRD patients [9].

Our study has a number of strengths, including the use of a relatively large population of contemporary U.S. kidney transplant patients, enhancing the applicability of our results to current clinical practice. In addition, the important issue of handling missing data was recently highlighted in the literature [22], and we used several multiple imputation techniques rather than only complete case analysis as recommended to verify the robustness of our results [23]. However, our study also has limitations. As with all nonrandomized studies comparing two treatment strategies, our analysis could be affected by selection bias, despite adjustment for numerous baseline demographic and clinical characteristics. We also attempted to further mitigate potential selection bias by performing a companion propensity score-matched analysis and were reassured to find that our results were unchanged with this approach. In addition, because our analysis relies on diagnostic coding, we lacked data on a number of potentially clinically important factors including coronary anatomy, left ventricular ejection fraction, renal function, physical functioning, and medication use, all of which can influence the selection of revascularization type and outcomes.

In summary, in a large cohort of contemporary kidney transplant patients undergoing revascularization for multivessel coronary artery disease, we found no differences in survival or the composite of death or MI between patients treated with CABG or PCI. In the absence of a randomized controlled trial, our study represents the best available comparison of revascularization strategies in the kidney transplant population. Our data suggest that CABG and PCI are both good options for revascularization in multivessel coronary disease and that the decisions regarding choice of revascularization modality should be made on an individual patient basis. Our results underscore the need to focus future cardiovascular studies on patients with ESRD to improve outcomes.

Authorship

CRL, MMR, WCW and TIC: designed research/study. CL, MMR, WCW and TIC: performed research/study. WCW: collected data. MMR and TIC: analyzed data. CRL, MMR, WCW and TIC: wrote the manuscript. All authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Technical appendix.

Table S1. ICD-9 Codes used to identify comorbid conditions.

Table S2. Sensitivity analyses.

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