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Kidney Transplant List Status and Outcomes in the ISCHEMIA-CKD Trial

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Abstract

Background: Patients with chronic kidney disease (CKD) and coronary artery disease frequently undergo preemptive revascularization before kidney transplant listing.

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Clinical Trial Registration: ClinicalTrials.gov (NCT01985360)

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Tweet: Patients listed for kidney transplant in ISCHEMIA-CKD trial had similar outcomes with a conservative or invasive strategy

Objectives: In this post-hoc analysis from ISCHEMIA-CKD, we compared outcomes of patients not listed versus those listed according to management strategy.

Methods: In ISCHEMIA-CKD (n=777), 194 patients (25%) with chronic coronary syndromes and at least moderate ischemia were listed for transplant. The primary (all-cause mortality or nonfatal myocardial infarction [MI]) and secondary (death, nonfatal MI, hospitalization for unstable angina, heart failure, resuscitated cardiac arrest, or stroke) outcomes were analyzed using Cox multivariable modeling. Heterogeneity of randomized treatment effect between listed versus not listed groups was assessed.

Results: Compared with those not listed, listed patients were younger (60 versus 65 years), less likely of Asian race (15% versus 29%), more likely on dialysis (83% versus 44%), had fewer anginal symptoms, and more likely to have coronary angiography and coronary revascularization irrespective of treatment assignment. Among patients assigned to an invasive strategy versus conservative strategy, the adjusted hazard ratios (aHR) (95% confidence interval [CI]) for the primary outcome were 0.91 (0.54–1.54) and 1.03 (0.78–1.37) for those listed and not listed, respectively ($p_{interaction}$=0.68). Adjusted HR for secondary outcomes were 0.89 (0.55–1.46) in listed and 1.17 (0.89–1.53) in those not listed ($p_{interaction}$=0.35).

Conclusions: In ISCHEMIA-CKD, an invasive strategy in kidney transplant candidates did not improve outcomes compared with conservative management. These data do not support routine coronary angiography or revascularization in patients with advanced CKD and chronic coronary syndromes listed for transplant.

Condensed Abstract

In this post-hoc analysis from ISCHEMIA-CKD (n=777), we compared patients listed for kidney transplant (n=194 [25%]) versus those not listed. The primary outcome was all-cause mortality or nonfatal myocardial infarction. Heterogeneity of randomized treatment effect between listed versus not listed groups was assessed. We found that an invasive strategy did not improve outcomes compared with conservative management regardless of kidney transplant candidacy. These data do not support routine coronary angiography or revascularization in patients with chronic kidney disease and myocardial ischemia on stress testing listed for transplant.

Keywords

chronic kidney disease; kidney transplantation; ischemic heart disease; coronary angiography; coronary revascularization; medical therapy

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Candidates for kidney transplant are often at high risk for adverse cardiovascular events, including perioperative myocardial infarction (MI). Screening for occult coronary artery disease (CAD) is a primary component of pre-kidney transplant evaluation. The support for this strategy consists of one small randomized controlled trial conducted 3 decades ago, observational studies, and consensus statements primarily focused on correlating risk of cardiovascular events post-kidney transplant with pre-transplant cardiac risk stratification (including coronary angiography).(1–6) In the one trial, Manske et al. examined preemptive coronary revascularization compared with medical therapy in 26 candidates for kidney transplant with insulin-dependent diabetes mellitus and >75% stenosis in at least 1 epicardial

coronary artery. The study was stopped early (median follow-up 8.4 months) for benefit in the revascularization arm for the primary composite endpoint of unstable angina, myocardial infarction, or cardiac death. Despite the rapidly evolving and improving medical armamentarium for the management of chronic coronary disease, there have been no further randomized controlled trials conducted to confirm Manske et al.'s findings supporting preemptive coronary revascularization in kidney transplant candidates.

ISCHEMIA-CKD (International Study of Comparative Health Effectiveness of Medical and Invasive Approaches–Chronic Kidney Disease) is the only randomized trial to prospectively compare an initial invasive strategy of coronary angiography and revascularization plus optimal medical therapy versus an initial conservative strategy of optimal medical therapy alone in patients with advanced CKD and stable coronary disease.(7) There was no evidence of benefit for the invasive strategy on the primary outcome of all-cause death or nonfatal MI at 3 years. The ISCHEMIA-CKD study did not specifically seek patients being evaluated for kidney transplant; however eligibility criteria were such that patients undergoing pre-transplant evaluation were included in the trial. This report describes the subset of patients in ISCHEMIA-CKD who underwent cardiac stress testing prior to randomization as part of their evaluation for kidney transplant listing.

METHODS

Patient Population

The rationale and design of ISCHEMIA-CKD (NCT01985360) have been published.(8) A total of 802 participants were recruited between April 29, 2014 and January 31, 2018. Of these, 777 were randomized at 118 participating sites in 30 countries.(7,8) Principal inclusion criteria included end-stage renal disease on dialysis or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, chronic coronary syndromes with well-controlled angina or silent ischemia, and at least moderate or severe myocardial ischemia as determined by the site investigators. Major exclusion criteria included known left main disease or non-obstructive CAD, LVEF ≤35% or NYHA class III or IV heart failure, acute coronary syndromes within 2 months or unacceptable level of angina despite maximal medical therapy. The study protocol was approved by institutional review boards at participating sites and all patients provided written informed consent.

For the current post-hoc analysis, we categorized patients by their transplant list status at baseline. Patients listed for kidney transplant (n=179) were identified from the study database, which included patients both previously listed and those having a stress test to qualify for listing. In addition, patients identified during follow-up as having received a kidney transplant (n=15) post-randomization without indication of transplant list status at baseline were considered to be on the transplant list at enrollment. The final transplant list analysis cohort thus consisted of 194 participants (25% of the total ISCHEMIA-CKD cohort); median duration of follow-up for listed participants was 2.4 years (25th, 75th percentiles [1.6, 3.1]).

Clinical Outcomes

The primary outcome was a composite of all-cause death or nonfatal MI. The secondary outcome was a composite of death, nonfatal MI, stroke, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest (For the present analysis, stroke was included in the secondary outcome).(8) Among other renal endpoints, receipt of a kidney transplant was queried at each study visit.

Statistical Methods

Descriptive statistics of patient characteristics at baseline were analyzed by kidney transplant list status (not listed versus listed). We assessed associations of patient characteristics with list status using the chi-squared test for categorical variables and the Wilcoxon test for continuous variables. For categorical variables involving 2-by-2 comparisons, we substituted Fisher's exact test if the expected cell size was less than 5. We estimated cumulative event rates of the primary and secondary outcomes using the Kaplan-Meier method.

Multivariable Cox proportional hazards models were used to examine the association of each outcome with list status, adjusting for the following patient characteristics at baseline: age at randomization, sex, dialysis status, eGFR, ejection fraction, diabetes status, and treatment strategy. eGFR was controlled for only among non-dialysis patients by including an indicator for no dialysis at baseline (equal to 1 if a participant was not on dialysis, and 0 otherwise) and an interaction term between no dialysis at baseline and eGFR at baseline. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) were estimated. To examine whether the treatment effect differed by list status, we estimated the models adding an interaction between treatment and list status. Continuously measured variables were modeled as restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentiles. Proportional hazards assumptions were checked by inspecting the Schoenfeld residuals and testing the null hypothesis of no interaction of time with transplant list status and treatment strategy. For outcomes subject to competing risks, we used cause-specific hazard models.

All analyses were conducted using SAS 9.4 software (SAS Institute, Inc., Cary, NC) and R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a 2-tailed $p<0.05$ denoted statistical significance.

RESULTS

Baseline Characteristics

Baseline characteristics of ISCHEMIA-CKD participants not listed (n=583) and listed (n=194) for transplant are presented in Table 1. Fifty-one patients (26%) in the listed group received a kidney transplant during the course of the trial. Compared with those not listed, patients listed for transplant were younger, less likely of Asian race, less likely to have cerebrovascular or peripheral artery disease, more likely receiving dialysis, had a lower proportion with severe ischemia on stress testing, had less angina and better functional status based on the Seattle Angina Questionnaire and Canadian Cardiovascular Society Angina Class, had lower New York Heart Association class, and were more likely to undergo an imaging stress test.

Baseline characteristics of participants by kidney transplant list status and treatment strategy are presented in Table 2. Balance of measured baseline covariates between treatment strategies in each listing group was maintained, with the exception of the slightly younger age of those in the invasive strategy not listed for transplant. Supplemental Tables 1a and 1b present baseline and follow-up physiologic measurements, risk factors, and medications by list status and treatment strategy. Both not listed and listed patients had improved attainment of risk factor goals (systolic blood pressure <140 mm Hg; 55% increasing to 69% in those not listed and 56% to 68% in those listed) and greater medication adherence (62% to 70% in not listed and 70% to 84% in listed) from baseline to last study visit.

Coronary Angiography and Revascularization by List Status

In ISCHEMIA-CKD, the estimated 3-year cumulative incidence (accounting for competing risk of death) of coronary angiography and coronary revascularization was 31.6% and 19.6% in the conservative strategy group and 85.2% and 50.2% in the invasive strategy group. The cumulative incidence of coronary angiography and revascularization are presented in Figures 1a–b and Supplemental Figures 1a–b. There was greater use of coronary angiography and revascularization in patients listed for transplant, regardless of treatment strategy, compared with those not listed. Among patients assigned to the conservative strategy, the estimated 1-year cumulative incidence of coronary angiography and coronary revascularization was 15.9% and 10.7% for those not listed and 33.3% and 16.2% for those listed. For patients assigned to the invasive strategy, the 1-year cumulative incidence of coronary angiography and coronary revascularization was 80.9% and 45.6% for those not listed and 84.0% and 51.1 % for those listed.

The indications for coronary angiography and revascularization in the conservative strategy group at 3 years are presented in Supplemental Figure 2; 59% of angiograms and 46% of revascularizations were not protocol-specified. In the conservative strategy, 4.2% of those not listed for transplant had angiography for non–protocol-specified indications compared with 29.2% of listed patients—an approximately 7-fold difference.

Clinical Outcomes by Kidney Transplant List Status and Treatment Strategy

In an unadjusted analysis, the primary outcome of all-cause mortality or nonfatal MI at 3 years was not significantly different between those not listed and listed for kidney transplant, 38.1% versus 32.1%, respectively (log rank p=0.15) (Figure 2a). In a Cox proportional hazards adjusted model, listed participants demonstrated a lower hazard for the primary outcome compared with those not listed (adjusted HR [aHR] 0.72, 95% CI 0.53–1.00; p=0.048) (Figure 2b).

There was no statistical evidence of an interaction between treatment strategy and list status for the primary composite (p=0.68) or secondary outcomes (p=0.35) (Supplemental Figure 3). Among participants not listed, the primary outcome was observed in 96/294 (33%) patients in the invasive-strategy group and 99/289 (34%) in the conservative-strategy group (aHR 1.03, 95% CI 0.78–1.37) (Table 3). Among those listed for transplant, the primary outcome occurred in 27/94 (28%) participants in the invasive strategy group and 30/100 (30%) in the conservative-strategy group (aHR 0.91, 95% CI 0.54–1.54) (Central

Illustration). The estimated cumulative incidence for the primary outcome by list status and treatment strategy is presented in Figures 3a–b.

The proportion of patients with the composite secondary outcome (all-cause death, nonfatal MI, hospitalization for unstable angina, heart failure, resuscitated cardiac arrest, or stroke) by treatment strategy is presented in Table 3. As with the primary outcome, no significant difference in event rates was seen between the invasive and conservative strategies, regardless of list status. Figures 3c–d illustrate the estimated cumulative incidence for the secondary outcome by list status and treatment strategy. Table 3 and Supplemental Table 2 provide additional data on primary and secondary outcomes by randomized group and kidney transplant list status.

Two sensitivity analyses were performed: 1. exclusion of the 15 transplanted participants assumed to have been listed (but not indicated in the database at baseline), and 2. assignment of the same 15 transplanted participants to the not listed group. There was no change in the primary outcome based on these sensitivity analyses (data not shown).

DISCUSSION

In this post-hoc analysis of 194 patients listed for kidney transplant in the ISCHEMIA-CKD trial, we found no evidence of a difference in either the primary or secondary outcome at 3 years by treatment strategy (invasive versus conservative), similar to the results from the overall trial.(7) Nor was a significant interaction between assigned treatment strategy and transplant list status observed. After adjustment for baseline covariates, patients listed for transplant had a better outcome than those not listed—a finding supporting the impact of potential selection bias for healthier patients in the process of identifying kidney transplant candidates.

We believe the findings of the present study and those of the overall ISCHEMIA-CKD trial should prompt a reexamination of the current clinical practice of preemptive noninvasive assessment and coronary revascularization of potential kidney transplant recipients with chronic coronary disease, particularly those with asymptomatic myocardial ischemia and those without left main CAD.

The results of this analysis differ from the prior, smaller study of Manske et al. that set the foundation for pre-emptive revascularization among potential kidney transplant recipients with stable CAD.(1) In the present study and the overall ISCHEMIA-CKD trial, the invasive and conservative strategies were equally efficacious; however, a crucial feature of the trial was the implementation of optimal medical therapy in both groups, including intensive treatment of dyslipidemia, with high treatment goal achievement.(7) In Manske et al., reflecting decades-old medical practice, medical therapy included only short-acting nifedipine and aspirin without statin therapy, angiotensin-receptor blockers/angiotensin converting enzyme inhibitors, or beta blockers, a regimen that would now be considered sub-standard.(9,10) Of note, patients with advanced CKD and stable coronary disease are often undertreated, with less frequent use of guideline-based medical therapy.(11,12)

Other studies that supported preemptive revascularization among potential kidney transplant recipients or patients with advanced CKD were observational and often single-center experiences with no comparator group.(12–15) Lentine et al. examined Medicare claims of patients undergoing kidney transplant.(16) Among those at high risk for cardiovascular events, cardiac evaluation (stress testing or angiography) was associated with a higher likelihood of post-transplant acute MI; however, only 10% of all high-risk patients undergoing cardiac evaluation actually received surgical or percutaneous coronary revascularization (a finding consistent with Konig et al (17)). The authors concluded that clinical risk status was the strongest predictor of post-transplant MI, regardless of evaluation or intervention. A more recent single-center study had similar findings, placing greater weight on clinical risk stratification than abnormal cardiac stress testing or extent and severity of stenoses on coronary angiography.(4)

A meta-analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), and FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trials found no convincing advantage of coronary revascularization compared with optimal medical therapy in patients with CKD.(18) Furthermore, in CARP (Coronary Artery Revascularization Prophylaxis) trial and the DECREASE-V (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo-V) pilot study, a strategy of pre-emptive coronary artery revascularization with percutaneous coronary intervention or coronary artery bypass grafting before elective high-risk vascular surgery was not beneficial.(3,19,20) In both studies, pre-emptive revascularization compared with optimal medical therapy alone was not associated with improved 30-day post-operative survival.

These findings highlight that screening to detect potentially critical coronary artery stenoses identifies kidney transplant candidates at especially high risk for adverse events, specifically during the perioperative period. However, whether an abnormal screening result warrants angiography and revascularization to reduce risk appears unlikely from the present study, at least in patients with well-controlled symptoms and without heart failure. Given the similar risk profiles of vascular surgery and kidney transplantation coupled with recent improvements in medical therapy for CAD, the strategy of pre-transplant screening for occult CAD (and preemptive revascularization) needs to be re-evaluated.

Although there is broader consensus among the kidney transplant community about the need for screening for asymptomatic CAD among those at high risk, there is significant heterogeneity in revascularization practices, which is likely a reflection of the lack of compelling evidence.(16,21,22) We believe our data support the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines and the American Heart Association/American College of Cardiology statement on evaluating and managing cardiac disease in candidates for kidney and liver transplantation. Both recommend that asymptomatic candidates with known CAD should not undergo routine coronary revascularization exclusively to reduce perioperative cardiac events, and that such therapy be reserved for high-risk anatomic subsets in whom revascularization confers survival benefits.(21,22) In a single-center observational study of 3698 patients evaluated for kidney

transplantation, coronary revascularization was associated with enhanced survival only in patients with 3-vessel disease (23).

Our study does not directly address the issue of whether kidney transplant candidates should be routinely screened for obstructive CAD before planned live donor transplant, wait-listing for deceased donor transplant, or as part of routine surveillance of patients previously listed for transplantation (the latter recommended in KDOQI [Kidney Disease Outcomes Quality Initiative] and societal guidelines(24,25)). The strategy of routine surveillance is the subject of the ongoing CARSK (Canadian-Australian Randomized trial of Screening Kidney transplant candidates for coronary artery disease) trial (26).

In the invasive strategy group in ISCHEMIA-CKD, the frequency of participants with coronary anatomy undergoing revascularization was lower than in the ISCHEMIA trial. This is attributable to suboptimal target vessels and “false positive” stress tests without pre-test computed tomographic angiography to exclude non-obstructive CAD. In addition, the majority of cardiac stress testing in ISCHEMIA-CKD employed nuclear scintigraphy (61.8%), which has been shown to have lower diagnostic accuracy in patients with end-stage kidney disease (27,28).

It is noteworthy that twice as many patients in the conservative strategy listed for transplant underwent angiography compared with those not listed (33% versus 16% at 1 year). We hypothesize that this may reflect a differing approach in the clinical management of listed patients randomized to the conservative strategy (i.e., rational, but unproven, lingering clinician concerns regarding non-intervention in waitlisted patients with evidence for inducible moderate or severe myocardial ischemia). This hypothesis is supported by the nearly 7-fold difference in non–protocol-specified indications for angiography in the conservative strategy in patients listed versus those not listed (and a greater proportion receiving revascularization).

The strategy of preemptive coronary revascularization in kidney transplant candidates is based on the unproven assumption of improved perioperative (and possibly long-term) post-transplant outcomes, and potentially improved outcomes of waitlisted patients (particularly those with prolonged waitlist times, which can easily extend to 5 years or more). The reduction in all-cause mortality associated with kidney transplant, as compared with waitlist status,(9) may be denied to those patients with extended waitlist times (i.e., they do not survive long enough to receive a kidney, and cardiovascular mortality is the most common cause of death). In the present study, we find no evidence to support the concept of improved waitlist survival from preemptive coronary revascularization. Only 51 patients underwent transplantation, preventing definitive comparison of the invasive versus conservative strategies for outcomes.

There are several important limitations to the present study. It is a post-hoc secondary analysis of a subset of 194 of 777 participants enrolled in ISCHEMIA-CKD. The modest sample size reduced the ability to detect a difference in outcomes related to treatment strategy in the kidney transplant-listed patients. Moreover, a substantial proportion of those listed for transplant randomized to the conservative strategy (cumulative incidence of 22% at

3 years) underwent coronary revascularization. The potential difference in outcome between the invasive and conservative strategies in this post-hoc analysis of listed patients could have been diluted by the fact that revascularization was only performed in 50% of invasive strategy participants, and further diluted by revascularization of 20% of conservative strategy participants. The follow-up time was relatively short (median 2.4 years), particularly when compared with waitlist times of many kidney transplant candidates, which often extends beyond 5 years.(29) In ISCHEMIA-CKD, noninvasive coronary computed tomography angiography to exclude left main disease was not performed. However, individual sites could exclude patients from study entry if the stress test results were concerning for left main disease, and only 2.5% of invasively managed patients in ISCHEMIA-CKD had left main disease. Conceivably, patients with large ischemic burdens not due to left main disease were not entered in the trial. Patients with a left ventricular ejection fraction <35%, recent acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass grafting within the past year, severe angina, and heart failure were excluded, so any conclusions do not apply to these patient subsets. Finally, due to the limitations of data collection, accrued waitlist time of the 194 listed patients in our study could not be determined, nor accrued time post-transplantation, and the effect of perioperative major adverse cardiac events on those patients who underwent transplantation could not be ascertained.

In conclusion, in patients with stable coronary disease and advanced chronic kidney disease listed for kidney transplant, our study found no overall difference in all-cause death or nonfatal MI between an initial invasive strategy and an initial conservative strategy. Our findings do not support routine coronary angiography or coronary revascularization in patients waitlisted for kidney transplant exclusively for the purposes of reducing cardiac events or mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BARI-2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
CAD	coronary artery disease
CARP	Coronary Artery Revascularization Prophylaxis Trial
CARSK	Canadian-Australian Randomized trial of Screening Kidney Transplant candidates for coronary disease
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial
DECREASE-V	Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo-V
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
ISCHEMIA-CKD	International Study of Comparative Health Effectiveness of Medical and Invasive Approaches-Chronic Kidney Disease Trial
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative

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Perspectives

Competency in Medical Knowledge:

In patients listed for kidney transplantation who have stable ischemic heart disease and inducible myocardial ischemia on stress testing, management with optimal medical therapy is associated with outcomes comparable to those with an invasive strategy of coronary angiography and revascularization along with optimal medical therapy.

Translational Outlook:

Further studies are needed to compare the outcomes after renal transplantation in patients managed with these two strategies for ischemic heart disease.

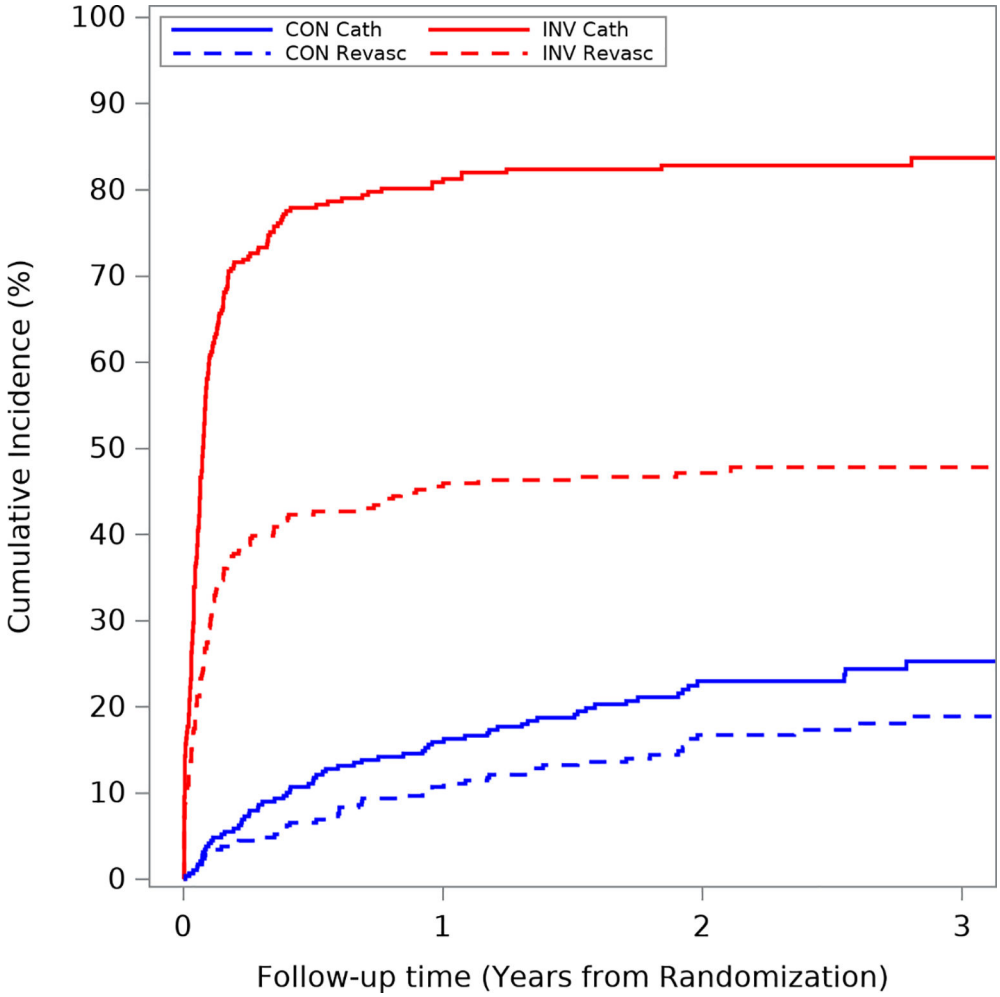


Figure 1a. Coronary angiography and revascularization in patients not listed for transplant.
Cumulative incidence of coronary angiography and revascularization by treatment arm in patients not listed for kidney transplant. The blue lines represent patients in the conservative arm and the red lines represent those in the invasive arm. The solid lines represent coronary angiography and the dashed lines represent revascularization. **Abbreviations:** CON cath=angiography/catheterization in conservative arm; CON revasc=revascularization in conservative arm; INV cath=angiography/catheterization in invasive arm; INV revasc=revascularization in invasive arm.

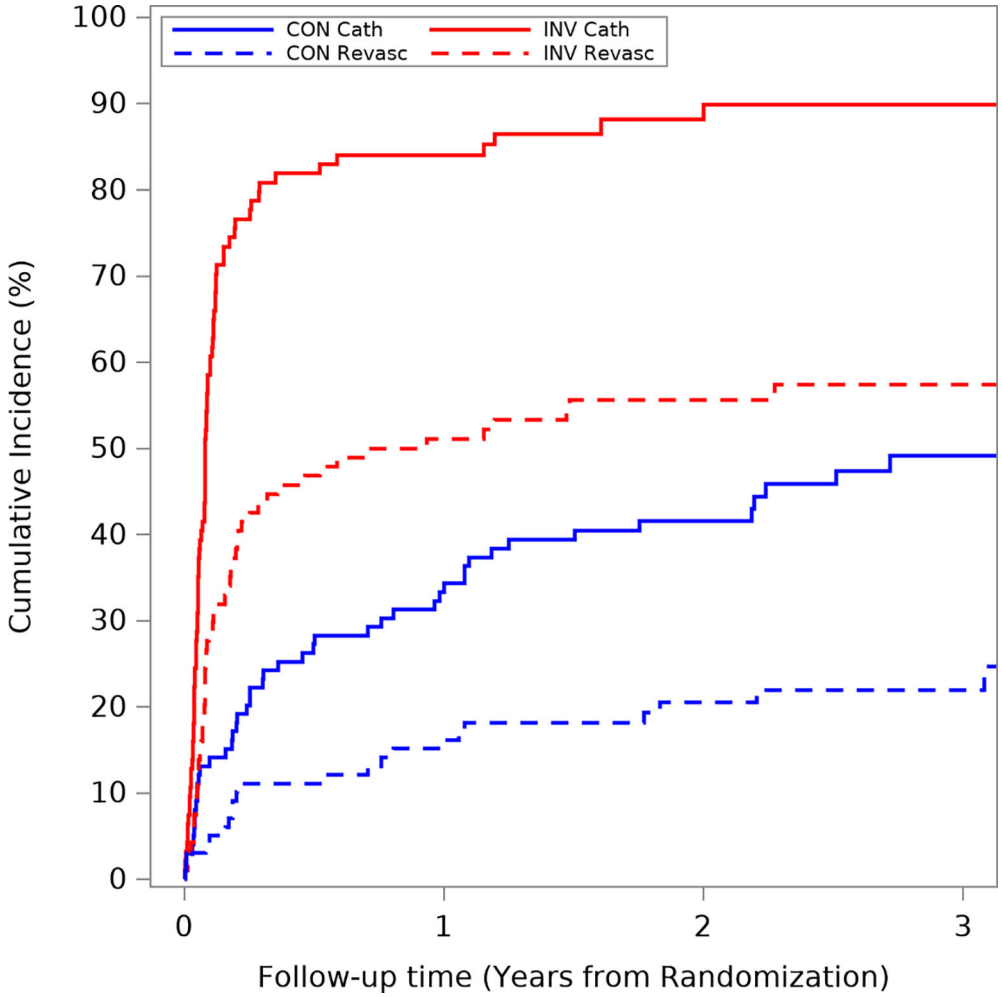


Figure 1b. Coronary angiography and revascularization in patients listed for transplant.
Unadjusted cumulative incidence of coronary angiography and revascularization in patients who are listed for kidney transplant. The blue lines represent patients in the conservative arm and the red lines represent those in the invasive arm. The solid lines represent coronary angiography and the dashed lines represent revascularization. **Abbreviations:** CON cath=angiography/catheterization in conservative arm; CON revasc=revascularization in conservative arm; INV cath=angiography/catheterization in invasive arm; INV revasc=revascularization in invasive arm.

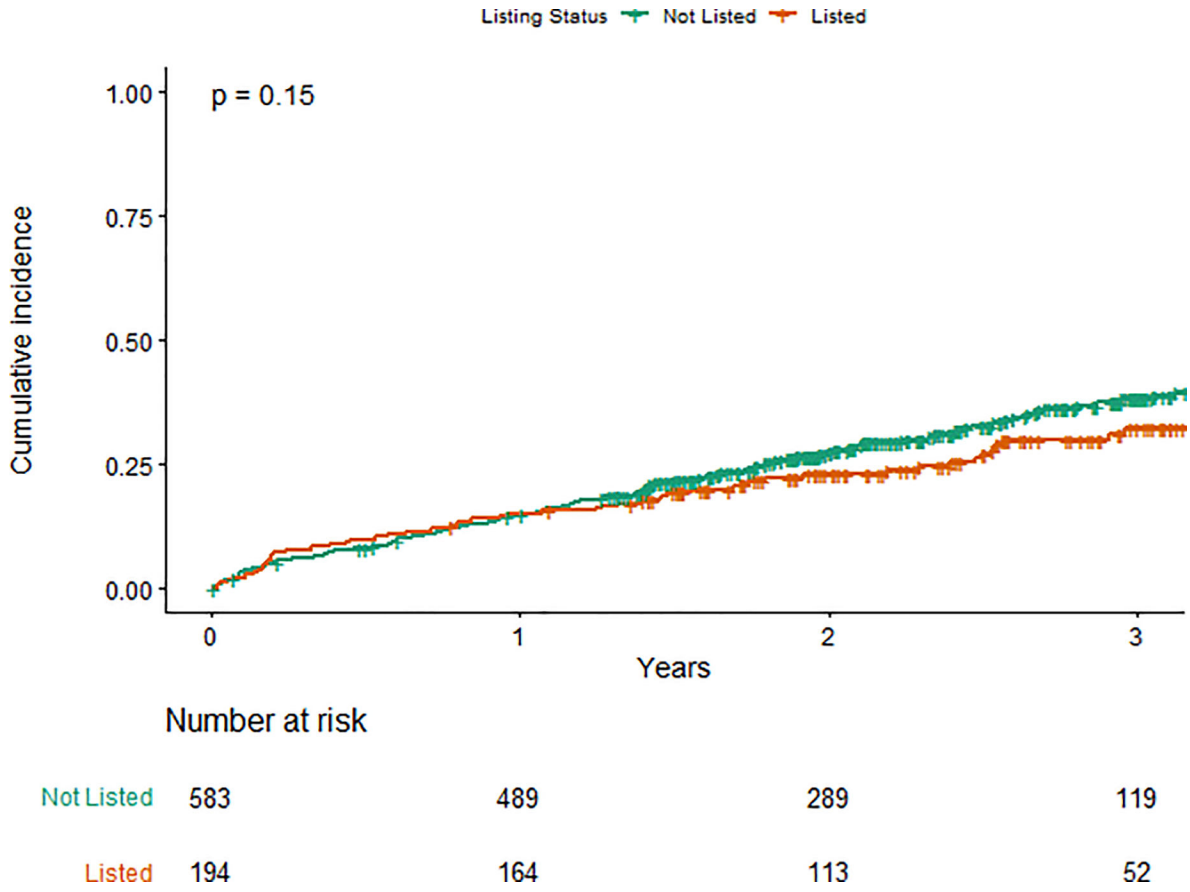


Figure 2a. Primary outcome by list status.

Cumulative incidence function for the primary outcome (all-cause mortality/non-fatal myocardial infarction) in patients not listed (green) and listed (orange) for kidney transplant at study enrollment; number at risk at each time point is listed beneath the graph.

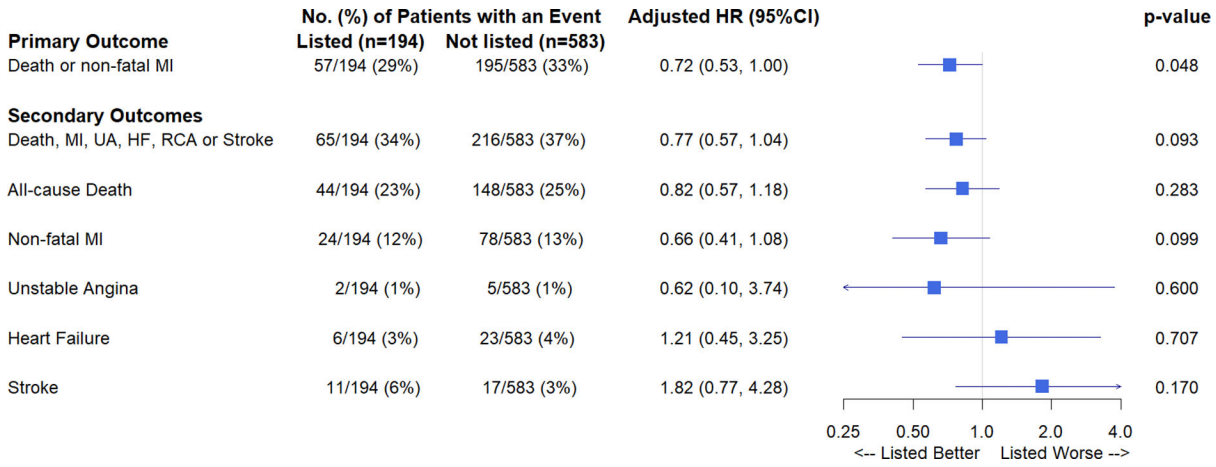


Figure 2b. Forest plot of outcomes by transplant list status.

Forest plot presenting adjusted hazard ratios for the primary outcome and individual secondary outcomes in patients listed and not listed for kidney transplant; $p<0.05$ was considered statistically significant. **Abbreviations:** CI=confidence interval; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; RCA=resuscitated cardiac arrest; UA=unstable angina.

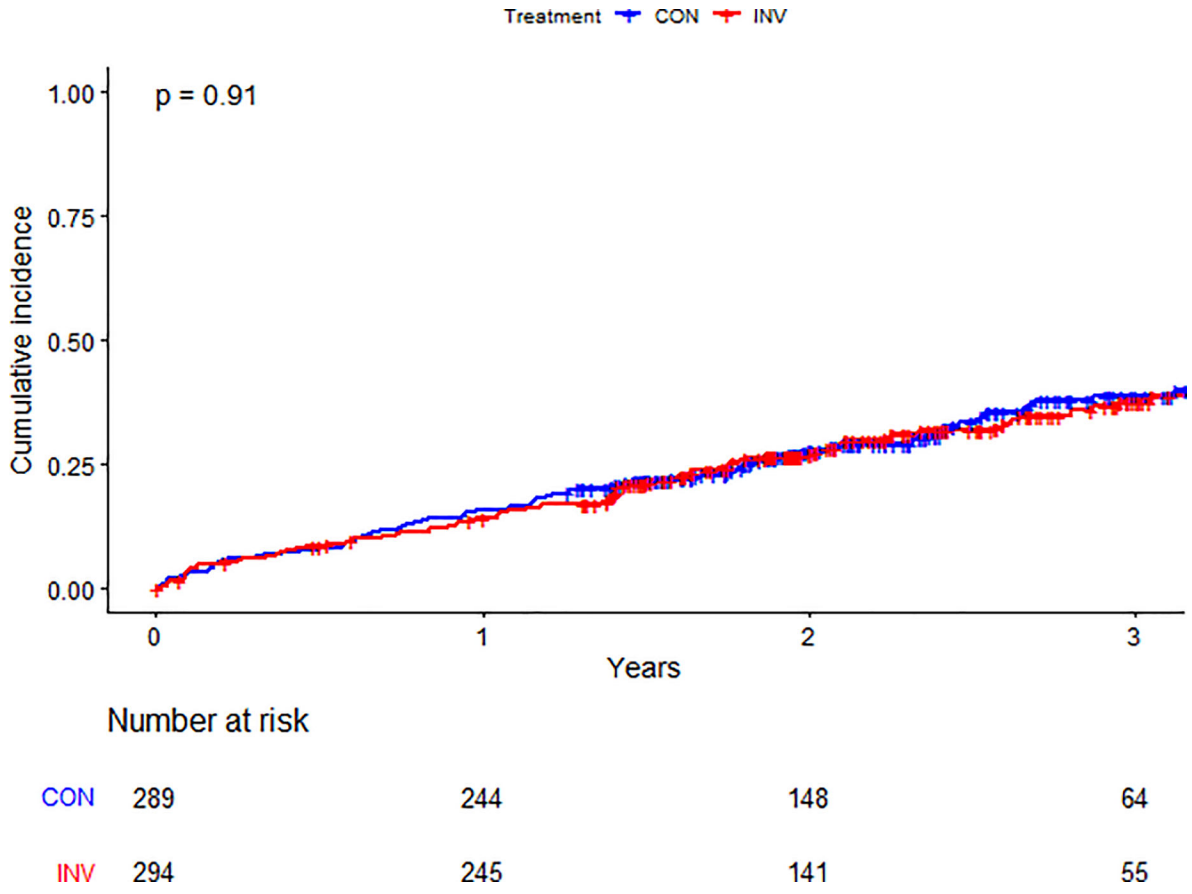


Figure 3a. Primary outcome by treatment arm in patients not listed.

Cumulative incidence of the primary outcome between randomized treatment arms in patients not listed for kidney transplant. The blue line represents those in the conservative arm; the red line represents those in the invasive arm. Number at risk at each time point is listed below the graph. **Abbreviations:** CON=conservative arm; INV=invasive arm.

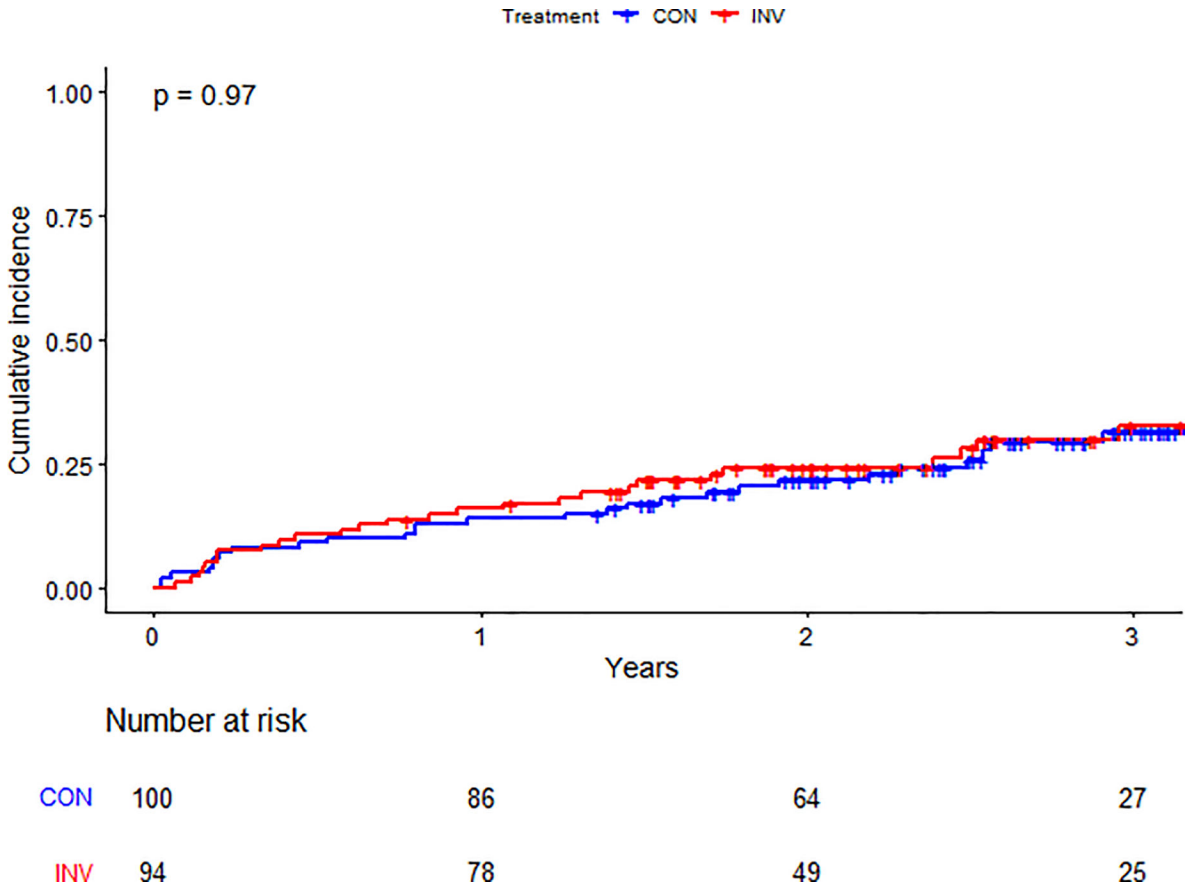


Figure 3b. Primary outcome by treatment arm in patients listed for transplant.

Cumulative incidence of the primary outcome between randomized treatment arms in patients listed for kidney transplant. The blue line represents those in the conservative arm; the red line represents those in the invasive arm. Number at risk at each time point is listed below the graph. **Abbreviations:** CON=conservative arm; INV=invasive arm.

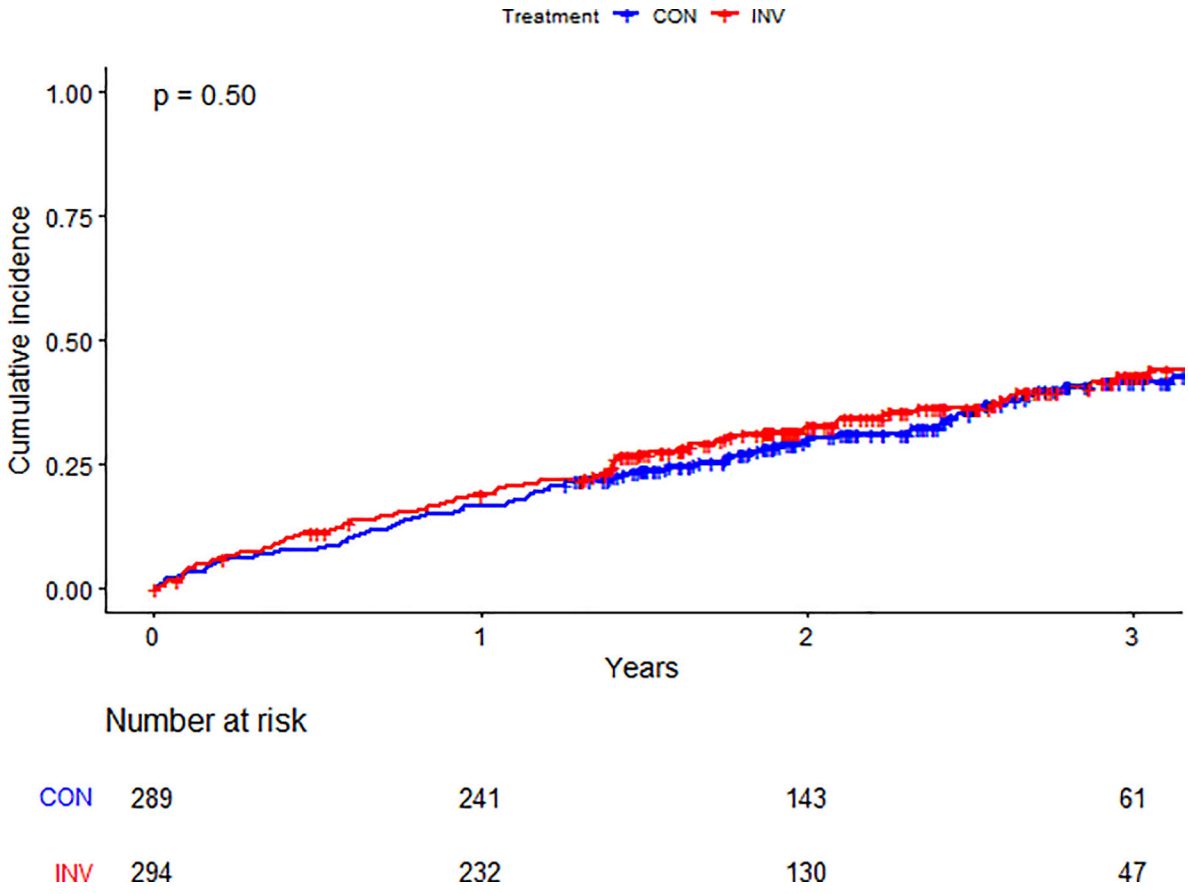


Figure 3c. Secondary outcome by treatment arm in patients not listed.

Cumulative incidence of secondary outcome between randomized treatment arms in patients not listed for kidney transplant. The blue line represents those in the conservative arm; the red line represents those in the invasive arm. Number at risk at each time point is listed below the graph. **Abbreviations:** CON=conservative arm; INV=invasive arm.

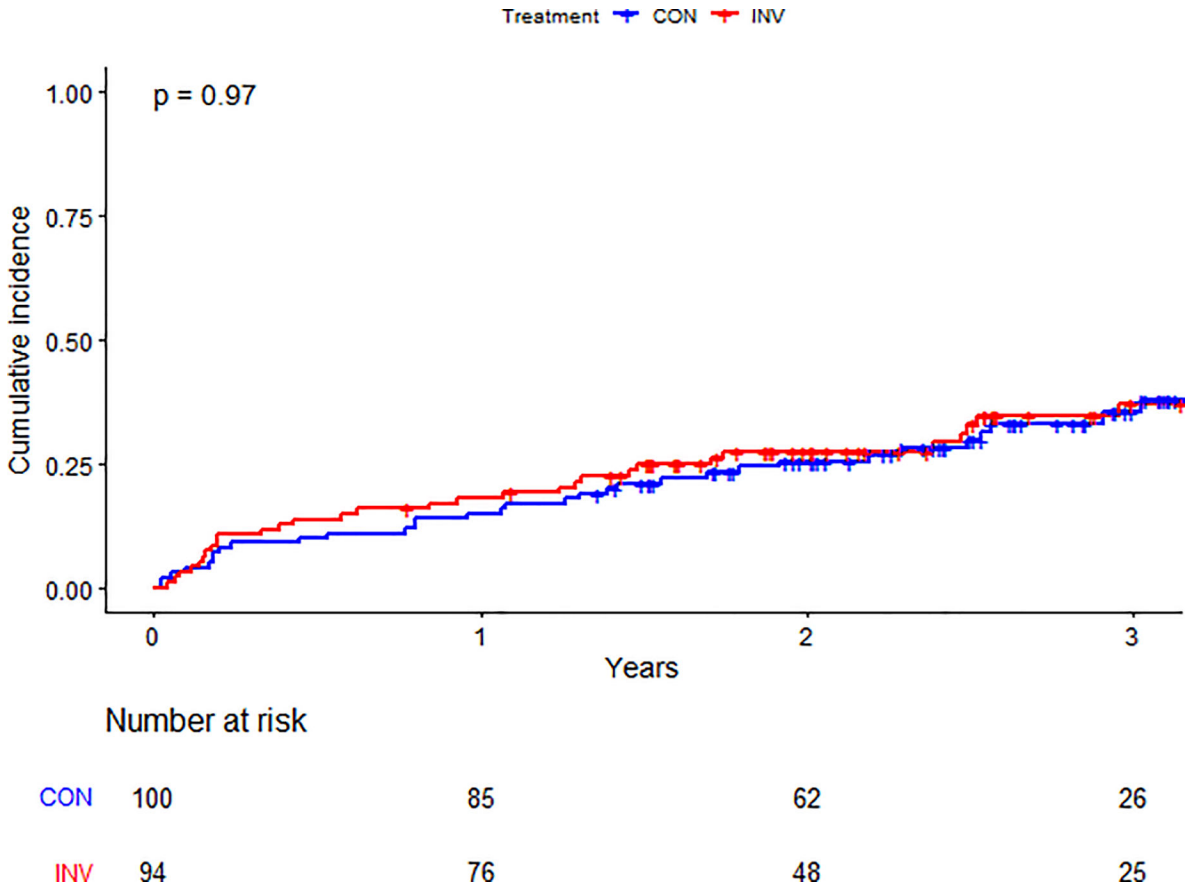
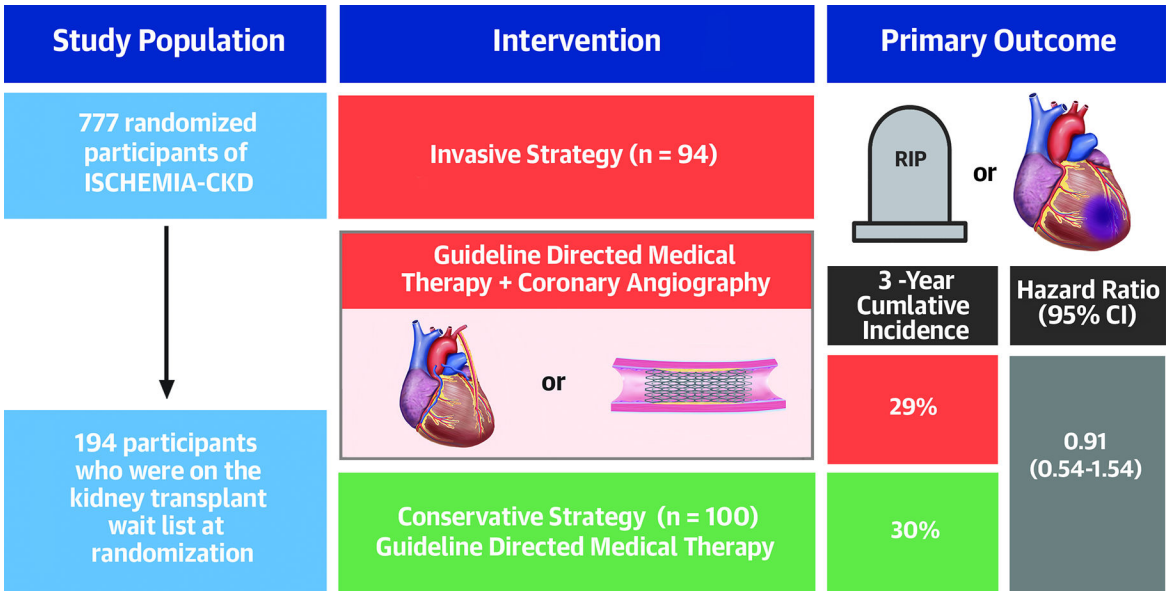


Figure 3d. Secondary outcome by treatment arm in patients listed for transplant.

Cumulative incidence of secondary outcome between randomized treatment arms in patients not listed for kidney transplant. The blue line represents those in the conservative arm; the red line represents those in the invasive arm. Number at risk at each time point is listed below the graph. **Abbreviations:** CON=conservative arm; INV=invasive arm.



Central Illustration: Kidney Transplant List Status and Outcomes in ISCHEMIA-CKD

Estimated cumulative incidence for primary and secondary outcomes by treatment strategy for participants listed for kidney transplant. Abbreviations: MI = Myocardial Infarction; UA = Unstable Angina; HF = Heart Failure; RCA = Resuscitated Cardiac Arrest; HR = Hazard Ratio; CI = Confidence Interval

Table 1.

Participant Baseline Characteristics by Transplant Listing Status

	Not listed	Listed	P-value*
	(n=583)	(n=194)	
Age at randomization, years			0.000
N	583	194	
Median (Q1, Q3)	65 (57, 72)	60 (54, 64)	
Female			0.051
	193/583 (33%)	49/194 (25%)	
Race			0.002
American Indian or Alaskan Native	2/567 (0%)	3/180 (2%)	
Asian	164/567 (29%)	27/180 (15%)	
Native Hawaiian or Other Pacific Islander	3/567 (1%)	3/180 (2%)	
Black or African American	45/567 (8%)	18/180 (10%)	
White	352/567 (62%)	129/180 (72%)	
Multiple Races Reported	1/567 (0%)	0/180 (0%)	
Degree of ischemia on stress test			0.008
Moderate	340/575 (59%)	136/194 (70%)	
Severe	235/575 (41%)	58/194 (30%)	
Hypertension			0.520
	537/581 (92%)	174/192 (91%)	
Diabetes			0.658
	330/583 (57%)	114/194 (59%)	
Smoking status			0.030
Never smoked	280/583 (48%)	91/194 (47%)	
Former smoker	231/583 (40%)	91/194 (47%)	
Current Smoker	72/583 (12%)	12/194 (6%)	
Previous myocardial infarction			0.095
	108/583 (19%)	25/193 (13%)	
Previous heart failure			0.255
	107/583 (18%)	28/194 (14%)	
Previous stroke			0.467
	54/583 (9%)	14/194 (7%)	
History of cerebrovascular disease or PAD†			0.016
	112/583 (19%)	22/194 (11%)	
Previous PCI‡			0.992
	109/583 (19%)	37/194 (19%)	
Previous CABG§			0.119
	17/583 (3%)	11/194 (6%)	

	Not listed	Listed	P-value*
	(n=583)	(n=194)	
Ejection fraction (%)			0.398
N	463	156	
Median (Q1, Q3)	58 (50, 64)	59 (51, 64)	
On dialysis			0.000
	254/583 (44%)	161/194 (83%)	
Duration of dialysis (years)			0.004
N	224	145	
Median (Q1, Q3)	3 (1, 6)	2 (1, 4)	
Dialysis type			0.039
Peritoneal dialysis	29/247 (12%)	31/157 (20%)	
eGFR among those not receiving dialysis (ml/min/1.73m^2)			0.000
N	329	33	
Median (Q1, Q3)	23 (18, 27)	16 (14, 20)	
SAQ# Summary score			0.000
N	536	188	
Median (Q1, Q3)	74 (58, 88)	92 (77, 100)	
SAQ# Angina Frequency score			0.000
N	536	188	
Median (Q1, Q3)	90 (80, 100)	100 (90, 100)	
SAQ# Physical Limitation score			0.000
N	416	159	
Median (Q1, Q3)	75 (50, 100)	92 (71, 100)	
SAQ# Quality of Life score			0.000
N	535	188	
Median (Q1, Q3)	63 (38, 88)	88 (63, 100)	
Canadian Cardiovascular Society angina class			0.000
None	171/583 (29%)	121/193 (63%)	
I	118/583 (20%)	37/193 (19%)	
II	264/583 (45%)	34/193 (18%)	
III	30/583 (5%)	1/193 (1%)	
New York Heart Association class			0.009
I	99/337 (29%)	37/78 (47%)	
II	237/337 (70%)	41/78 (53%)	
III	1/337 (0%)	0/78 (0%)	
Type of stress testing			0.002
Nuclear	358/581 (62%)	121/194 (62%)	
ECHO	100/581 (17%)	52/194 (27%)	

	Not listed	Listed	P-value*
	(n=583)	(n=194)	
CMR††	1/581 (0%)	0/194 (0%)	
ETT‡‡	122/581 (21%)	21/194 (11%)	
Treatment strategy			0.694
Initial Invasive	294/583 (50%)	94/194 (48%)	

When the denominator is smaller than the column title population size, it represents the non-missing statistics

*P-values were obtained using the Wilcoxon Rank Sum test for continuous variables. For categorical variables, Pearson's chi-squared test was used

†PAD: peripheral arterial disease

‡PCI: percutaneous coronary intervention

§CABG: coronary artery bypass graft

‖eGFR: estimated glomerular filtration rate

#SAQ: Seattle Angina Questionnaire

**ECHO: echocardiography

††CMR: Cardiac Magnetic Resonance Imaging

‡‡ETT: exercise treadmill test

Table 2.

Participant Baseline Characteristics by Listing Status and Treatment Strategy.

	Not Listed			Listed		
	CON	**INV**	**P-value***	**CON**	**INV**	**P-value***
	(n=289)	**(n=294)**		**(n=100)**	**(n=94)**	
Age at randomization, years			0.040			0.907
N	289	294		100	94	
Median (Q1, Q3)	66 (58, 73)	64 (56, 71)		61 (53, 65)	59 (54, 64)	
Female			0.748			0.802
Female	98/289 (34%)	95/294 (32%)		24/100 (24%)	25/94 (27%)	
Race			0.433			0.922
American Indian or Alaskan Native	2/281 (1%)	0/286 (0%)		1/93 (1%)	2/87 (2%)	
Asian	87/281 (31%)	77/286 (27%)		13/93 (14%)	14/87 (16%)	
Native Hawaiian or Other Pacific Islander	2/281 (1%)	1/286 (0%)		2/93 (2%)	1/87 (1%)	
Black or African American	20/281 (7%)	25/286 (9%)		10/93 (11%)	8/87 (9%)	
White	170/281 (60%)	182/286 (64%)		67/93 (72%)	62/87 (71%)	
Multiple Races Reported	0/281 (0%)	1/286 (0%)		0/93 (0%)	0/87 (0%)	
Degree of ischemia on stress test			0.540			0.850
Moderate	165/286 (58%)	175/289 (61%)		69/100 (69%)	67/94 (71%)	
Severe	121/286 (42%)	114/289 (39%)		31/100 (31%)	27/94 (29%)	
Hypertension			0.184			0.665
	270/287 (94%)	267/294 (91%)		92/100 (92%)	82/92 (89%)	
Diabetes			0.989			0.341
	163/289 (56%)	167/294 (57%)		55/100 (55%)	59/94 (63%)	
Smoke status			0.616			0.951
Never smoked	139/289 (48%)	141/294 (48%)		46/100 (46%)	45/94 (48%)	
Former smoker	118/289 (41%)	113/294 (38%)		48/100 (48%)	43/94 (46%)	
Current Smoker	32/289 (11%)	40/294 (14%)		6/100 (6%)	6/94 (6%)	
Previous myocardial infarction			0.528			0.815
	57/289 (20%)	51/294 (17%)		14/100 (14%)	11/93 (12%)	
Previous heart failure			0.599			1.000
	56/289 (19%)	51/294 (17%)		14/100 (14%)	14/94 (15%)	
Previous stroke			0.350			0.476
	23/289 (8%)	31/294 (11%)		9/100 (9%)	5/94 (5%)	
History of cerebrovascular disease or PAD†			0.291			0.599
	50/289 (17%)	62/294 (21%)		13/100 (13%)	9/94 (10%)	
Previous PCI‡			0.910			1.000
	53/289 (18%)	56/294 (19%)		19/100 (19%)	18/94 (19%)	
Previous CABG§			1.000			1.000

	Not Listed			Listed		
	CON	**INV**	**P-value***	**CON**	**INV**	**P-value***
	(n=289)	**(n=294)**		**(n=100)**	**(n=94)**	
	8/289 (3%)	9/294 (3%)		6/100 (6%)	5/94 (5%)	
Ejection fraction (%)			0.484			0.184
N	221	242		79	77	
Median (Q1, Q3)	58 (50, 64)	57 (50, 63)		60 (52, 65)	58 (50, 61)	
On dialysis			0.549			0.180
	130/289 (45%)	124/294 (42%)		87/100 (87%)	74/94 (79%)	
Duration of dialysis (years)			0.333			0.414
N	114	110		78	67	
Median (Q1, Q3)	2 (1, 5)	3 (1, 6)		2 (1, 3)	2 (1, 5)	
Dialysis type			0.676			0.551
Peritoneal dialysis	13/124	16/123		15/86	16/71	
	(10%)	(13%)		(17%)	(23%)	
eGFR// among those not receiving dialysis (ml/min/1.73m^2)			0.848			0.567
N	159	170		13	20	
Median (Q1, Q3)	23 (18, 27)	23 (17, 27)		16 (13, 19)	16 (15, 20)	
#SAQ Summary score			0.611			0.961
N	269	267		97	91	
Median (Q1, Q3)	75 (60, 88)	72 (54, 92)		90 (75, 100)	92 (78, 98)	
#SAQ Angina Frequency score			0.424			0.202
N	269	267		97	91	
Median (Q1, Q3)	90 (80, 100)	90 (70, 100)		100 (90, 100)	100 (100, 100)	
#SAQ Physical Limitation score			0.739			0.360
N	200	216		83	76	
Median (Q1, Q3)	75 (56, 92)	75 (50, 100)		92 (67, 100)	100 (75, 100)	
#SAQ Quality of Life score			0.685			0.738
N	268	267		97	91	
Median (Q1, Q3)	63 (38, 88)	63 (38, 88)		88 (50, 100)	88 (63, 100)	
Canadian Cardiovascular Society angina class			0.964			0.240
None	82/289 (28%)	89/294 (30%)		56/99 (57%)	65/94 (69%)	
I	60/289 (21%)	58/294 (20%)		23/99 (23%)	14/94 (15%)	
II	132/289 (46%)	132/294 (45%)		19/99 (19%)	15/94 (16%)	
III	15/289 (5%)	15/294 (5%)		1/99 (1%)	0/94 (0%)	
New York Heart Association class			0.579			0.338
I	48/168 (29%)	51/169 (30%)		23/43 (53%)	14/35 (40%)	
II	119/168 (71%)	118/169 (70%)		20/43 (47%)	21/35 (60%)	

	Not Listed			Listed		
	CON	**INV**	**P-value***	**CON**	**INV**	**P-value***
	(n=289)	**(n=294)**		**(n=100)**	**(n=94)**	
III	1/168 (1%)	0/169 (0%)		0/43 (0%)	0/35 (0%)	
Type of stress testing			0.377			0.755
Nuclear	185/288 (64%)	173/293 (59%)		60/100 (60%)	61/94 (65%)	
ECHO**	44/288 (15%)	56/293 (19%)		29/100 (29%)	23/94 (24%)	
CMR††	1/288 (0%)	0/293 (0%)		0/100 (0%)	0/94 (0%)	
ETT‡‡	58/288 (20%)	64/293 (22%)		11/100 (11%)	10/94 (11%)	

* P-values were obtained using the Wilcoxon Rank Sum test for continuous variables. For categorical variables, Pearson's chi-squared test was used. Initial Invasive (INV) and Initial Conservative (CON) strategy arms.

† PAD: peripheral arterial disease

‡ PCI: percutaneous coronary intervention

§ CABG: coronary artery bypass graft

‖ eGFR: estimated glomerular filtration rate

SAQ: Seattle Angina Questionnaire

** ECHO: echocardiography

†† CMR: Cardiac Magnetic Resonance Imaging

‡‡ ETT: exercise treadmill test;

Table 3.

Adjusted hazard ratios for invasive versus conservative strategy by renal transplant candidacy status

	No. (%) of Patients with an Event		Adj. HR[a] (95% CI)	P-value for Interaction
	CON (n=389)	INV(n=388)		
Primary Outcome				
Death or non-fatal MI				0.68
Not Listed	99/289 (34%)	96/294 (33%)	1.03 (0.78, 1.37)	
Listed	30/100 (30%)	27/94 (29%)	0.91 (0.54, 1.54)	
Secondary Outcomes				
Death, non-fatal MI, Unstable angina, Heart failure, RCA or Stroke				0.35
Not Listed	106/289 (37%)	110/294 (37%)	1.17 (0.89, 1.53)	
Listed	34/100 (34%)	31/94 (33%)	0.89 (0.55, 1.46)	

[a]Estimated from Cox proportional hazards models of the primary and secondary composite outcomes. All models are adjusted for age, sex, kidney function, left ventricular ejection fraction, and diabetes. The hazard ratio is for the invasive-strategy group as compared with the conservative-strategy group