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Design Considerations and Feasibility for a Clinical Trial to Examine Coronary Screening Before Kidney Transplantation (COST)

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Abstract

Background—It is unclear whether benefits outweigh harms for routine screening and prophylactic revascularization to prevent coronary artery disease (CAD) in asymptomatic kidney transplant candidates.

Study Design—Pilot feasibility study with prospective observational data collection and patient interviews.

Setting and Participants—Consecutive patients referred for kidney and/or pancreas transplant at 26 major transplant centers in the US.

Predictors—Older age, diabetes, prior cardiovascular disease and multiple traditional CAD risk factors.

Outcomes—Eligibility and willingness to participate in a randomized controlled trial (RCT) to study the effect of CAD screening on major adverse cardiac events.

Measurements—Patients who would be candidates for a hypothetical RCT of CAD screening were interviewed and asked if they would participate in such a trial. Sample size for the trial was estimated using data on Medicare patients in the United States Renal Data System with major adverse cardiac events as the primary endpoint.

Results—Among consecutive eligible patients, CAD evaluation was not indicated in 398 (24%), already completed before referral in 602 (36%), and pending (and hence eligible for a RCT) in 665 (40%). Of 241 interviewed, 73% indicated they would be willing to participate in a RCT. We

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estimated that approximately 4000 would need to be enrolled to detect a 20% reduction in major adverse cardiac events at greater than 80% power at $P < 0.05$.

Limitations—Willingness to participate in an actual clinical trial may be different than indicated in an interview.

Conclusion—A RCT to compare the effects of routine screening for CAD versus no screening on major adverse cardiac events is feasible.

Keywords

Cardiovascular disease; coronary artery disease; acute myocardial infarction; preoperative evaluation; chronic kidney disease; screening; clinical practice guidelines; randomized controlled trial; major adverse cardiac events

Cardiovascular disease is the leading cause of death after kidney transplant, and the incidence of myocardial infarction is highest in the period immediately after transplant.⁽¹⁾ Therefore, a compelling argument can be made to screen transplant candidates for occlusive coronary artery disease (CAD) in order to identify lesions for preemptive coronary revascularization and thereby reduce the risk of kidney transplant. Indeed, the standard practice in the US has been to screen high-risk asymptomatic patients for CAD with non-invasive testing and/or coronary angiography.^(2;3) Patients who are found to have critical lesions (generally $>70\%$ occlusion) undergo preemptive revascularization. Opinion-based, consensus guidelines have generally recommended this approach as part of the routine pre-transplant evaluation.⁽⁴⁻⁶⁾ However, recent evidence from the general population suggests that routine screening for CAD in asymptomatic patients prior to major non-cardiac surgery may not improve outcomes that are important to patients.⁽⁷⁻⁹⁾ The American College of Cardiology (ACC) / American Heart Association (AHA) does not recommend routinely screening asymptomatic patients facing intermediate-to-high risk surgery, if their functional status allows them to perform 4 or more metabolic equivalents.⁽¹⁰⁾ Thus, the ACC/AHA guidelines for the general population are in direct conflict with those for CKD patients facing kidney transplant.

There are a number of potential benefits and harms associated with CAD screening in asymptomatic patients referred for transplantation (Box 1). A RCT would be appropriate to determine whether routine CAD screening effectively reduces adverse outcomes important to patients, e.g. mortality, acute myocardial infarction, and acute coronary syndrome, and that the benefits of screening would outweigh the harms. This study was carried out to determine whether such a trial would be feasible.

Methods

Proposed Randomized Controlled Trial Design

Most transplant centers in the US screen asymptomatic patients who are considered high risk for CAD, as described in the American Society of Transplantation guidelines.⁽⁴⁾ Screening is usually carried out for patients who have one or more of the following 4 characteristics:

1. Prior cardiovascular disease (including CAD, strokes, transient ischemic attacks, amputations and peripheral revascularization procedures)
2. Diabetes (duration variously defined)
3. Two or more “traditional” CAD risk factors-(11)
4. Older age (variously defined)

Subsequent screening is usually repeated after a prescribed (but center-specific) interval.

We assumed that a RCT would include a “standard practice” control group that would call for screening asymptomatic high-risk patients with non-invasive stress testing, followed by coronary angiography in patients with an abnormal stress test, and prophylactic revascularization of critical coronary lesions found on angiography. The intervention group in the proposed RCT would call for patients to receive care as described in the ACC/AHA guidelines for perioperative management of patients undergoing non-cardiac surgery.(10) These guidelines indicate that asymptomatic patients undergoing kidney transplant would generally not be screened as described above, unless their functional status was restricted to the point that they could not perform 4 metabolic equivalents.

In the proposed RCT, all patients with signs and symptoms suggesting unstable coronary disease, e.g. an acute coronary syndrome or unstable angina, would be excluded. These symptomatic patients would receive all necessary testing and intervention that is required to relieve their symptoms. In the proposed RCT, all patients would receive maximal medical care per the transplant center's usual practice. The primary endpoint would be major adverse cardiac events (MACE), and would include: myocardial infarction, acute coronary revascularization (to relieve symptoms), and cardiac death. The analysis would be by intention-to-treat and time-to-event.

Pilot Feasibility Study Design

This pilot study was designed to determine whether it would be feasible to conduct a RCT of routine screening versus not screening for CAD prior to kidney transplant. The questions that we set out to answer in this pilot study included:

1. Would enough transplant programs be willing to participate in the proposed RCT?
2. Would participating centers have enough eligible patients in the proposed RCT?
3. Would enough eligible patients agree to participate in the proposed RCT?

We assumed that the proposed RCT would randomly allocate patients referred for kidney or simultaneous kidney and pancreas transplant to follow either the current standard of practice for CAD screening at the center, or to follow the 2007 ACC/AHA guidelines for perioperative management of non-cardiac surgery.(10).

Participating Centers

We contacted kidney transplant centers in the US that were in the top 50th percentile based on the numbers of adult living donor transplants in the previous 2 years (2006-07). The numbers of living donor transplants were determined from data reported to the Organ Procurement and Transplantation Network (OPTN) (12). We used living donor transplants as the criteria for selecting centers, because we initially anticipated that the trial would enroll only patients who were likely to receive a living donor transplant. The goal was to have 30 centers participate.

Pilot Feasibility Study Protocol

The pilot study was approved at the Institutional Review Board (IRB) at each study site. Study coordinators at each site were asked to fill out case report forms that included information on each patient referred for transplant during the pilot study, i.e. from the time the site first began looking for patients to interview until the time the 10th and final interview at their site was completed. We set out to recruit 30 sites, a number which was based on the anticipated number of sites that would be needed to recruit patients for the proposed RCT. There were 35 centers contacted before we were able to meet the goal of 30

participating centers. Although 5 centers declined to participate in this pilot study, 2 of the declining centers indicated they would likely participate in the proposed RCT if asked.

The coordinator at each site was asked assess *all* consecutive patients referred for transplant evaluation and to interview those who qualified for the hypothetical study (and agreed to be interviewed). Thus, interviewees were chosen in the same manner that study subjects would be chosen and asked to participate if the study were actually being conducted. We asked the coordinator at each site to continue screening for potential participants and conducting interviews until 10 interviews had been completed. Thus, the sample of patients at each site included all consecutive patients who were referred for evaluation from the start of the pilot study to the time that 10 interviews were completed. At some sites, many patients were screened to get 10 interviews, while in others very few were screened to complete the 10 interviews. For those who were screened, but not interviewed, the reasons they were not interviewed (unable to give consent, etc) were tabulated.

Data Collected in the Pilot Feasibility Study

The following information was collected for each patient referred for transplant evaluation:

1. able to give informed consent (and if not the reason why not),
2. age,
3. gender,
4. self-reported race/ethnicity by OPTN categories,
5. if a living donor transplant was thought to be possible,
6. history of prior cardiovascular disease (and specific events),
7. whether a cardiac evaluation had been completed in the prior 12 months,
8. reasons for cardiac screening (diabetes, prior cardiovascular disease, older age, multiple cardiac risk factors, other), and
9. whether an interview was completed (or whether declined, or if not interviewed because the patient would not be a candidate for the proposed RCT and the reason).

In addition, each participant who was interviewed was asked whether or not he/she could perform activities at a level of 4 metabolic equivalents, e.g. light housework, or climbing a flight of stairs. Interviewees were also asked whether they would participate in a RCT (after it was described) if the study were being held today: 1) definitely yes, 2) probably yes, 3) probably not, 4) definitely not, or 5) other, and indicate the reason.

Statistical Analysis

The characteristics of patients and the results of the survey questionnaire were tested for differences between study sites using a chi-square test. As part of this pilot feasibility study, we also performed a sample size calculation that was not based on the results of the pilot study per se, but made assumptions on enrollment and event rates for a primary MACE endpoint using a superiority design. Rates were estimated from the United States Renal Data System incident End-Stage Renal Disease population 2000-06. We included high risk patients with a live donor kidney transplant or registered on the deceased donor kidney transplant waiting list and at least one of: 1) age 50 or older, 2) diabetes, or 3) prior cardiovascular disease. The rate of deceased donor transplant among patients wait-listed without a living donor (N=77,834) was 25.29 per 100 patient-years. The rate of living donor transplants among patients with a living donor (N=34,802) was 133.77 per 100 patient-

years. The percent with a living donor would be 31%. We also assumed that 30 transplant centers would participate.

Results

Participating Centers

Thirty centers agreed to participate, however 4 were not able to conduct interviews or to submit data, and these 4 centers were excluded from further analysis. Six centers completed fewer than 10 interviews (N=4, 5, 6, 7, 9, and 9 interviews, respectively), and 20 centers completed all 10 interviews. Thus, the total number of interviews completed was 241. Of the 241 interviews conducted, 10 were in patients who had a low functional capacity (i.e., could perform less than 4 metabolic equivalents) and may therefore not have been candidates to be randomized to cardiac screening, but were nevertheless interviewed.

Transplant Candidates and Cardiac Evaluations

During the period of study, there were 1752 patients referred to the 26 participating centers for transplant evaluation. Of these, 72 could not give informed consent due to: language barriers (N=60; 83%), cognitive limitations (N=13, 14%), or other reasons not specified (N=2, 3%). Of the remaining 1680 participants, 10 had severely limited functional capacity (could perform less than 4 metabolic equivalents) thereby making cardiac stress testing something to be considered under the ACC/AHA guidelines.⁽¹⁰⁾ This left 1670 who would have been able to participate in a RCT of cardiac evaluations.

There were 5 patients in whom it was not known whether cardiac evaluation was already completed, or if not completed whether it was indicated, and these 5 were excluded from further analysis. Of the remaining 1665 patients (Table 1), 602 (36%) had already had a cardiac evaluation performed before they were referred to the transplant center. This practice of prereferral cardiac evaluation varied substantially from center to center (Fig. 1). In 3 of the 26 participating centers, over half of the patients had already undergone a cardiac evaluation before referral. However, in 12 centers this occurred in 25% or less of the referred transplant candidates.

Of the 1665 transplant candidates that were referred to the 26 centers during the period of this study, 1267 (76%) would have been asked to undergo a cardiac evaluation (Fig. 2). However, this varied between 100% at 5 centers, to less than 75% at 5 centers, with the other 16 centers between 75-100% (Fig. 2).

Reasons that were given for requiring cardiac evaluations included diabetes, prior cardiovascular disease, older age (variably defined), multiple cardiovascular disease risk factors, and other or unknown (Table 2). The most common reason for “other” was a single cardiovascular risk factor, e.g. hypertension, obesity, or cigarette smoking.

In this pilot feasibility study, we asked centers to estimate the number of transplant candidates referred for evaluation who would likely have a suitable living donor. Of the 1665 candidates referred to the participating 26 centers, 1110 (67%) were thought to have a potential living donor-(Fig. 3). Six centers thought more than 95% of their candidate referrals had a potential living donor, while 3 centers thought less than 50% had potential living donors (Fig. 3).

Interview Results

There were 241 interviews conducted at 26 centers. Of these, 10 were obtained from patients who may not have been candidates for a RCT, because they could not perform 4 or more

metabolic equivalents, and may have required testing under the ACC/AHA guidelines.⁽¹⁰⁾ Of the remaining 231 who were interviewed, 18 had already had a cardiac evaluation performed and 1 was judged not to need a cardiac evaluation; In theory, these 19 patients may not have been eligible for a RCT (and should not have been interviewed). Although we tabulated the results for all 241 interviews, the results were similar for the subsets of interviews that excluded the patients that may not have been candidates for a RCT (Table 2). Among the 241 interviewed, 73.0% said they would participate. However, there was substantial center-to-center variability in responses (Fig. 4). In a regression analysis, there were 5 centers where the response rate was significantly different from the others (Fig. 4).

Sample Size Calculation for the Proposed RCT

Rates of MACE were determined from USRDS data (Table 3). We estimated that the number of transplant candidates that would need to be enrolled to detect a 20% reduction in MACE at greater than 80% power would be approximately 4000 (Table 4).

Discussion

The principle findings in this study were: 1) most transplant centers were willing to participate in the proposed RCT, 2) very few patients would not be able to give informed consent or would not have adequate functional status (4 metabolic equivalents), 3) a number of centers reported that the cardiac evaluations were already completed in a high proportion of patients even before they were referred for transplant evaluation, 4) 76% of patients referred would have needed a cardiac evaluation by criteria currently employed by the evaluating kidney transplant centers, if such an evaluation had not already been obtained, 5) many patients would be excluded if the study required transplant to occur soon after evaluation (restricting the RCT to patients with a living donor), and 6) about 75% of the patients interviewed indicated they would be willing to participate in the proposed RCT.

Virtually all of the centers that participated in this pilot feasibility study indicated they would also participate in the proposed RCT. Of 35 centers that were initially asked to participate in this pilot study, only 5/35 (14%) declined. Another 4 indicated that they wanted to participate, but ultimately they were not able to conduct the data collection and interviews. This high participation rate indicates a high level of interest and likelihood that there would be enough centers to conduct the proposed RCT.

Of the 1752 patients referred for transplant evaluation during the study period, only 72 (4.1%) could not give informed consent (Fig. 5). Most of these were due to language barriers that could be overcome if the RCT accommodated Spanish-speaking candidates. Similarly, only 10 (0.6%) had functional capacity reduced to 4 METS or less (Fig. 5), thus making them candidates for cardiac evaluation according to the ACC/AHA guidelines,⁽¹⁰⁾ and ineligible to participate in a RCT.

A major barrier to conducting the proposed RCT was encountered in centers that indicated that cardiac evaluations were often performed in patients before they were referred to the transplant center. However, this practice varied greatly from center-to-center, and it would be possible to exclude centers from a RCT where most of the patients referred already had cardiac evaluations. There were only 3 of the 26 participating centers where more than half had already had a cardiac evaluation before referral (Fig. 1). It is also possible that some centers could persuade their referring physicians to defer evaluations until patients were asked if they wished to participate in the RCT.

It was remarkable that 76% of patients required a cardiac evaluation as part of the transplant work up (Fig. 2). This was a consistent finding across all participating transplant centers.

The most common reasons given for needing a cardiac evaluation were older age, diabetes, and multiple cardiac risk factors (Table 2). Although study coordinators were allowed to record more than one reason for the cardiac evaluation, none of them did so, and the results therefore likely represent the “primary reason” for the evaluation.

A RCT that used MACE *after* transplant as the primary endpoint would likely need to limit enrollment to patients that would be transplanted soon after evaluation (and randomization). This requirement would mean that most participants would need to have a living donor. Unfortunately, in this pilot study only about two-thirds had a potential living donor at the time of evaluation (Fig. 3). Therefore, restricting enrollment to patients having a potential living donor would substantially restrict enrollment in a RCT (Fig. 5). In addition, the relevance of the study results could be questioned if enrollment were restricted to mostly candidates with living donors. Similarly, with a primary MACE endpoint restricted to events occurring after transplant, patients would be censored if MACE occurred while they were waiting for transplant. This would reduce the power of the study and increase the number of patients that would need to be recruited. Therefore, it is likely that a RCT would not require that patients be transplanted soon after enrollment, and would use as the primary endpoint MACE occurring after randomization, either before or after transplant.

It was encouraging that about 75% of potential RCT participants that were interviewed indicated “if the study were held today” they would be willing to participate (Table 3). Interestingly, there was remarkable variability in the responses between centers (Fig. 4). This variability could be due to the way in which the study was presented to patients. It is possible that if coordinators were adequately trained and coached in presenting the study to eligible participants, that more would participate.

The sample size calculation indicated that approximately 4000 participants would be needed to achieve enough statistical power (>80%) to detect a 20% difference in MACE between 2 study groups. Of course, this calculation is based on a number of assumptions. However, this number is same as the sample size calculated for the Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) trial. The FAVORIT trial randomly allocated stable kidney transplant recipients with elevated homocysteine levels to placebo or vitamin therapy to lower homocysteine in an effort to reduce MACE.⁽¹³⁾ Similarly, the Assessment of LEscol in Renal Transplantation (ALERT) study randomly allocated 2012 stable kidney transplant recipients to placebo versus treatment with fluvastatin to reduce MACE.⁽¹⁴⁾ Certainly, both the FAVORIT and the ALERT trials differ in many ways from the RCT of cardiac evaluations proposed here. However, it is encouraging that the sample size for our proposed RCT is similar to those of 2 trials that enrolled transplant patients and used a similar MACE endpoint.

There are many reasons that the results of the present study should be interpreted with caution. The patients studied may differ from patients who might be asked to participate in the proposed RCT. Whether patients indicating that they would participate “if the study were held today” would indeed participate in an actual RCT can only be determined by actually conducting a trial. Nevertheless, the information provided in this pilot feasibility study will be valuable for designing the RCT, and indicates that indeed such a trial is feasible. The sample size calculation that we conducted also indicates that a trial using the combined MACE endpoint would have enough statistical power to detect a clinically significant difference between 2 groups ($P<0.05$). We assumed that the only compelling reason to perform a cardiac evaluation prior to transplant is to improve patient outcomes. If centers use the results of screening to exclude patients from transplant, then the results of the proposed RCT may not influence their decisions for doing cardiac evaluations. However, it seems unlikely that many centers exclude patients on the basis of tests that are not proven to

accurately predict patient outcomes. Finally, we restricted our study to stress tests and coronary angiography used to detect CAD. We did not examine tests used to screen for left ventricular dysfunction. We are not aware of evidence that screening for left ventricular dysfunction improves patient outcomes, but there are data that LV dysfunction often improves as a result of transplant per se.(15)

In summary, trials in the general population have failed to provide evidence that screening asymptomatic uremic patients for CAD before major non-cardiac vascular surgery is indicated. However, screening candidates for kidney transplantation is the standard of care in the US. The results of the current study suggest that it would be feasible to randomly allocate patients referred for kidney and/or pancreas transplant to either 1) following the ACC/AHA guidelines (no routine screening if asymptomatic) or 2) screening high-risk individuals according to standard practice. If the primary endpoint were MACE, we estimate that approximately 4000 patients would be needed to have at least 80% power to detect a 20% difference in MACE ($P<0.05$).

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Box 1**Potential benefits and harms of coronary artery disease screening****Potential Benefits**

1. Reduction in coronary artery disease events by identifying patients who will benefit from revascularization
2. Reduction in coronary artery disease events by identifying patients who will benefit from optimal medical management.
3. Prevention of kidney transplant in patients with short life expectancy due to severe coronary artery disease

Potential Harms

1. Delay in transplant
2. Radio contrast nephropathy from angiography
3. Surgical bleeding risk from anti-platelet agents
4. Psychological burden of detecting asymptomatic disease
5. Other morbidity and mortality of angiography and revascularization procedures
6. Use of health care resources that could be applied more effectively elsewhere.

Figure 1.

The percent of patients referred for transplant evaluation that already had a cardiac evaluation completed at the time of referral, by transplant center. Dashed horizontal line indicates the mean for all patients combined. The total number of patients evaluated in each center is indicated in the row at the bottom marked “N”.

Figure 2.

The percent of patients referred for transplant that still needed a cardiac evaluation as part of the work up, by transplant center. Dashed horizontal line indicates the mean for all patients combined. The total number of patients evaluated in each center is indicated in the row at the bottom marked “N”.

Figure 3.

The percent of patients referred for transplant that had a potential living donor and would likely be transplanted within the next year, by transplant center. Dashed horizontal line indicates the mean for all patients combined. The total number of patients evaluated in each center is indicated in the row at the bottom marked “N”.

Figure 4.

The percent of patients interviewed that indicated they would likely participate in a randomized trial of cardiac evaluation, if the study were held today, by transplant center. Dashed horizontal line indicates the mean for all patients combined. The total number of patients evaluated in each center is indicated in the row at the bottom marked “N”.

Figure 5.

Recruitment and enrollment in the pilot feasibility study. The numbers within the dashed-line box assume that the study design would only enroll patients with a potential living donor (and therefore likely be transplanted within one year) resulting in total enrollment of 17.5%. Without this requirement the total enrollment would be 38.0%. The percentages (in parentheses) are of the total number referred for transplant evaluation (N=1752). Abbreviations: METS, metabolic equivalents; Eval., evaluation; Miss., missing.

Table 1

Patient characteristics at time of referral for transplant evaluation.

Patient Characteristic	Status of Cardiac Evaluation ¹			P-Value ²
	Not Needed (n=398)	Done (n=602)	Pending (n=665)	
Age (years)	41.2±12.7	54.7±11.8	54.6±11.6	<0.001
Male	223 (56.0)	368 (61.1)	385 (67.9)	0.2
Race				0.1
Native American	1 (0.3)	6 (1.0)	4 (0.6)	
Asian/Indian	18 (4.5)	15 (2.5)	20 (3.0)	
African American	135 (33.9)	221 (36.7)	254 (38.2)	
Caucasian	240 (60.3)	343 (57.0)	378 (56.8)	
Other/Missing	4 (1.0)	17 (2.8)	9 (1.4)	
Ethnicity				
Hispanic	25 (6.3)	47 (7.8)	45 (6.8)	0.6
Reason(s) to screen ³				
Diabetes	6 (1.5)	224 (37.2)	270 (40.6)	<0.001
Prior CVD	3 (.8)	162 (26.9)	116 (17.4)	<0.001
Older age	10 (2.5)	311 (51.7)	331 (49.8)	<0.001
Multiple risk factors	9 (2.3)	212 (35.2)	220 (33.1)	<0.001
Other reason	4 (1.0)	116 (19.3)	119 (17.9)	<0.001
Multiple reasons	0 (0.0)	285 (47.3)	289 (43.5)	<0.001
No reasons given	0 (0.0)	61 (10.1)	39 (5.9)	<0.001
No potential live donor	72 (19.0)	125 (20.8)	358 (53.8)	<0.001
Interviewed (N=231) ⁴	1 (0.3)	18 (3.0)	212 (31.9)	<0.001

¹Except for age (mean ± standard deviation), values are counts (and percent of column total in parentheses).²Age was analyzed by analysis of variance and all others by chi-square.³Reason that a cardiac evaluation was indicated.⁴Ten patients not able to perform 4 Metabolic Equivalents (and not included in this table) were also interviewed; 2 of these 10 had already had a cardiac evaluation and 8 had cardiac evaluation pending.

Abbreviation: CVD, cardiovascular disease.

Table 2

Interview results.

Would be willing to participate in a RCT of cardiac evaluation, if the study were held today.	All tho were interviewed (n=241)	Excluding 10 not able to perform 4 METS ¹ (n=231)	Excluding 19 not requiring an evaluation ² (n=212)
Definitely yes	111 (46%)	107 (46%)	99 (47%)
Probably yes	65 (27%)	64 (28%)	59 (28%)
Probably not	21 (9%)	19 (8%)	16 (8%)
Definitely not	36 (15%)	33 (14%)	31 (15%)
Other/unknown	8 (3%)	8 (3%)	7 (3%)

Values given are number responding (percentage)

¹Ten were interviewed despite having a low functional capacity and therefore possibly ineligible for a randomized trial.²Nineteen were interviewed despite having already undergone screening (N=18) or thought not to need screening (N=1).

Abbreviations: RCT, randomized controlled trial for cardiac evaluations; METS, metabolic equivalents.

Table 3

Estimated event rates for sample size calculations.

Period	MACE Rates ^I	
	Preemptive LDT	Waiting List for DDT
Waiting for transplant	8.57	13.32
Months 0-3 post-transplant	13.63	28.72
Months 3-12 post-transplant	2.28	1.99
Months 12-36 post-transplant	3.47	2.00

^IRates were calculated using United States Renal Data System data (see text for details). Numbers are events per 100 patient years estimated from 50,379 who had Medicare as their primary insurance provider.

Abbreviations: MACE, major adverse cardiac events; LDT, live donor transplant; DDT, deceased donor transplant.

Table 4

Sample size estimation.

No. Needed Enrolled	Statistical Power		
	↑MACE by 30%	↑MMACE by 25%	↑MMACE by 20%
1500	75%		
1600	77%		
1700	81%		
1800	82%		
1900	85%		
2000	85%	72%	
2100		75%	
2200		75%	
2300		78%	
2400		78%	
2500		81%	
3800			79%
3900			81%
4000			82%

Abbreviation: MACE, major adverse cardiac events.