AJKD
Original Investigation

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

*Bertram L. Kasiske, MD,[1,2] Ajay K. Israni, MD, MS,[1] Jon J. Snyder, PhD, MS,[2] and Alexa Camarena, MS,[3] on behalf of the COST Investigators**

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 & Participants: Consecutive patients referred for kidney and/or pancreas transplant at 26 major transplant centers in the United States.

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 for Medicare patients in the US Renal Data System with major adverse cardiac events as the primary end point.

Results: Of consecutive eligible patients, CAD evaluation was not indicated in 398 (24%), already completed before referral in 602 (36%), and pending (and hence eligible for an RCT) in 665 (40%). Of 241 interviewed, 73% indicated they would be willing to participate in an RCT. We estimated that ~4,000 would need to be enrolled to detect a 20% decrease in major adverse cardiac events at >80% power at $P < 0.05$.

Limitations: Willingness to participate in an actual clinical trial may be different from indicated in an interview.

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

Am J Kidney Dis. 57(6):908-916.

INDEX WORDS: 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) to identify lesions for pre-emptive coronary revascularization and thereby decrease the risk of kidney transplant. The standard practice in the United States has been to screen high-risk asymptomatic patients for CAD using noninvasive testing and/or coronary angiography.[2,3] Patients who are found to have critical lesions (generally >70% occlusion) undergo pre-emptive revascularization. Opinion-based consensus guidelines generally have recommended this approach as part of the routine pretransplant evaluation.[4-6] However, recent evidence from the general population suggests that routine screening for CAD in asymptomatic patients before major noncardiac 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 equivalent tasks.[10] Thus, ACC/AHA guidelines for the general population are in direct conflict with those for patients with chronic kidney disease facing kidney transplant.

There are a number of potential benefits and harms associated with CAD screening in asymptomatic patients referred for transplant (Box 1). A randomized controlled trial (RCT) would be appropriate to deter-

From the [1]Department of Medicine, Hennepin County Medical Center, and the University of Minnesota;[2]Chronic Disease Research Group, Minneapolis Medical Research Foundation; and [3]The Berman Center for Outcomes and Clinical Research, Minneapolis Medical Research Foundation, Minneapolis, MN.

** A list of the COST Investigators is provided in the Acknowledgements.*

Received September 4, 2010. Accepted in revised form January 12, 2011. Originally published online March 16, 2011.

Address correspondence to Bertram L. Kasiske, MD, Department of Medicine, Hennepin County Medical Center, 701 Park Ave, Minneapolis, MN 55415. E-mail: kasis001@umn.edu

0272-6386/$36.00
doi:10.1053/j.ajkd.2011.01.020

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. Radiocontrast nephropathy from angiography.
3. Surgical bleeding risk from antiplatelet 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.

mine whether routine CAD screening effectively decreases adverse outcomes important to patients, for example, 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 RCT Design

Most transplant centers in the United States screen asymptomatic patients who are considered at high risk of CAD, as described in the American Society of Transplantation guidelines.[4] Screening usually is 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) 2 or more traditional CAD risk factors,[11] and (4) older age (variously defined). Subsequent screening usually is repeated after a prescribed (but center-specific) interval.

We assumed that an RCT would include a "standard practice" control group that would call for screening asymptomatic high-risk patients using noninvasive stress testing, followed by coronary angiography in patients with an abnormal stress test result 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 noncardiac surgery.[10] These guidelines indicate that asymptomatic patients undergoing kidney transplant generally would not be screened as described unless their functional status was restricted to the point that they could not perform 4 metabolic equivalent tasks.

In the proposed RCT, all patients with signs and symptoms suggesting unstable coronary disease, for example, acute coronary syndrome or unstable angina, would be excluded. These symptomatic patients would receive all necessary testing and intervention required to relieve their symptoms. In the proposed RCT, all patients would receive maximal medical care according to the transplant center's usual practice. The primary end point would be major adverse cardiac events (MACEs) and would include myocardial infarction, acute coronary revascularization (to relieve symptoms), and cardiac death. 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 an RCT of routine screening versus not screening for CAD before kidney transplant. The questions that we set out to answer in this pilot study included the following. (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 the 2007 ACC/AHA guidelines for perioperative management of noncardiac surgery.[10]

Participating Centers

We contacted kidney transplant centers in the United States that were in the top 50th percentile based on the numbers of adult living donor transplants in the previous 2 years (2006-2007). 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 at each study site. Study coordinators at each site were asked to fill out case report forms that included information for each patient referred for transplant during the pilot study, that is, 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 based on the anticipated number of sites that would be needed to recruit patients for the proposed RCT. We contacted 35 centers 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 likely would participate in the proposed RCT if asked.

The coordinator at each site was asked to assess all consecutive patients referred for transplant evaluation and interview those who qualified for the hypothetical study (and agreed to be interviewed). Thus, interviewees were chosen in the same manner that study participants would be chosen and asked to participate if the study were 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 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, whereas 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), (2) age, (3) sex, (4) self-reported race/ethnicity by OPTN categories, (5) if a living donor transplant was thought to be possible, (6) history of cardiovascular disease (and specific events), (7) whether a cardiac evaluation had been com-