Canadian-Australasian Randomised trial of screening kidney transplant candidates for coronary artery disease—A trial protocol for the CARSK study☆

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Transplantation is the preferred treatment for patients with kidney failure, but the need exceeds the supply of transplantable kidneys, and patients routinely wait >5 years on dialysis for a transplant. Coronary artery disease (CAD) is common in kidney failure and can exclude patients from transplantation or result in death before or after transplantation. Screening asymptomatic patients for CAD using noninvasive tests prior to wait-listing and at regular intervals (ie, annually) after wait-listing until transplantation is the established standard of care and is justified by the need to avoid adverse patient outcomes and loss of organs. Patients with abnormal screening tests undergo coronary angiography, and those with critical stenoses are revascularized. Screening is potentially harmful because patients may be excluded or delayed from transplantation, and complications after revascularization are more frequent in this population. CARSK will test the hypothesis that eliminating screening tests for occult CAD after wait-listing is not inferior to regular screening for the prevention of *major adverse cardiac events* defined as the composite of cardiovascular death, nonfatal myocardial infarction, urgent revascularization, and hospitalization for unstable angina. Secondary outcomes include the transplant rate, safety measures, and the cost-effectiveness of screening. Enrolment of 3,306 patients over 3 years is required, with patients followed for up to 5 years during wait-listing and for 1 year after transplantation. By validating or refuting the use of screening tests during wait-listing, CARSK will ensure judicious use of health resources and optimal patient outcomes. (Am Heart J 2019;214:175-83.)

Transplantation is associated with better survival, higher quality of life, and cost savings compared to dialysis and is the preferred treatment for kidney failure patients.[1-3] However, because of a shortage of organs, less than 15% of dialysis treated patients are wait-listed for a deceased donor kidney transplant,[4] and wait-listed patients routinely wait 2 to 10 years on dialysis for a transplant depending on ABO blood group and level of anti-HLA antibodies.[4,5]

Kidney disease is an established risk factor for coronary artery disease (CAD).[6] CAD can exclude patients from transplantation or result in death before or after a transplant.[7,8] The cumulative incidence of myocardial infarction (MI) ranges from 8.7% to 16.7% by 3 years after wait-listing and from 4.7% to 11.1% after transplantation.[7,9] The risk of CAD events is highest in the peritransplant period and then declines over the first posttransplant year.[10,11] CAD can be hard to diagnose in kidney failure patients who may not develop classic symptoms due to uremia and diabetes.[12]

The current standard of care (SOC) involves screening asymptomatic patients for CAD using noninvasive tests (ie, dobutamine stress echocardiography or myocardial perfusion scintigraphy) in 2 phases: (1) prior to acceptance onto the transplant waiting list and (2) at regular intervals (ie, annually or biennially) after wait-listing until transplantation.[13] Asymptomatic patients with abnormal screening tests are referred for coronary angiography, and patients with critical coronary stenoses are prophylactically revascularized. The goal of this strategy is to reduce peritransplant MI. Secondary objectives include maintenance of wait-list eligibilty for transplantation and increased long-term posttransplant patient and kidney allograft survival. Only 1 randomised trial

☆RCT# IDACTRN12616000736448 and NCT03674307
☆☆Funding:Auckland District Health Board Charitable Trust (A+ Trust) grant 6405, New ZealandHeart Foundation Project grant 1647, New ZealandNational Health and Medical Research Council Project grant 1084454, AustraliaThe authors have no declaration of interests.
Submitted December 24, 2018; accepted May 13, 2019.
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https://doi.org/10.1016/j.ahj.2019.05.008

involving 26 patients and published in 1992 has ever informed the SOC that is now in conflict with current general cardiology guidelines for the management of elective nontransplant surgical candidates.[14,15] Although well intentioned, the SOC may paradoxically increase morbidity and mortality by exposing asymptomatic patients to angiography and revascularization procedures that are higher risk in the setting of kidney failure[16,17] and by delaying or excluding patients from life-saving transplantation.[18] Transplantation is the *only treatment* that significantly decreases the risk of death and MI in kidney failure.[2,19,20] Kidney failure patients with CAD are less likely to be treated with coronary revascularization than patients without kidney disease because they are considered too risky for cardiac surgery or because they have diffuse CAD without suitable targets for revascularization.[9] Therefore, asymptomatic patients with postive screening tests may simply be permanently removed from the waiting list. A positive screening test invariably delays transplantation because patients are placed on "wait-list hold" while a cardiology evaluation is completed. Finally, the current SOC is costly. The cost of a single screening test for the approximately 100,000 wait-listed patients in North America alone is greater than $200 million.[21] Given the widening gap between the need and the supply of kidneys for transplantation, and the projected rise in the burden and cost of kidney failure worldwide,[22] a randomised controlled trial evaluating the benefits and potential harms of existing CAD screening practices is urgently required to ensure optimal use of scarcely available health care resources including deceased donor kidneys.

Methods

Objectives and trial design

The Canadian-Australasian Randomised Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease (CARSK) study is a parallel-arm randomised controlled trial of 3,306 adult kidney transplant candidates. The objective of CARSK is to determine whether eliminating the use of noninvasive screening tests for CAD after wait-listing is noninferior to screening asymptomatic wait-listed kidney transplant candidates at regular intervals for CAD for the prevention of major adverse cardiac events (MACE). Secondary analyses will assess the impact of screening on the rate of transplantation, and the costs associated with regular CAD screening versus no screening from a health system perspective.

The rationale for focusing on the use of CAD screening tests *after* wait-listing is due to the unwillingness of physicians to forgo the use of CAD screening tests prior to wait-list activation.

In a survey of 15 Canadian kidney transplant centers performed to inform the trial design, 13 (87%) did not support randomization of patients prior to wait-list activation, as CAD screening prior to wait-list activation was deemed to be essential for establishing initial patient medical suitability for transplantation. In contrast, all transplant centers would support a randomised controlled trial of screening versus no screening for CAD after wait-list activation because there was greater clinical practice variation in the frequency of screening after wait-listing, screening after wait-listing is labor intensive, and screening patients multiple times after wait-listing has a greater cost than the 1-time screening done prior to wait-list activation.

Prior work and feasibility

The feasibility of the CARSK trial was tested in a Canadian Institute for Health Research–funded pilot study conducted in 6 Canadian centers (Clinicaltrials.gov #NCT020282483). The pilot study met the enrolment target of 144 patients in 6 months. Protocol violation and patient withdrawal were infrequent. Of 144 patients, 9 patients (6.3%) had an off-protocol test during the median follow-up of 529 days, and only 2 (1.4%) patients withdrew from the study. Eligible pilot study participants will continue follow-up within CARSK.

Ethics approval and trial registration

Ethical approval for the study was granted for each of Australia, Canada, and New Zealand (NZ) by the Human Research Ethics Committee for lead sites in each country (Australia: X15-0090, NZ: 15/NTB/149/AM02, and Canada, University of British Columbia H16-01335). The trial was prospectively registered on the Australian New Zealand Clinical Trials Registry (ANZCTR Trial: IDACTRN126160007364448) and on Clinicaltrials.gov (NCT03674307).

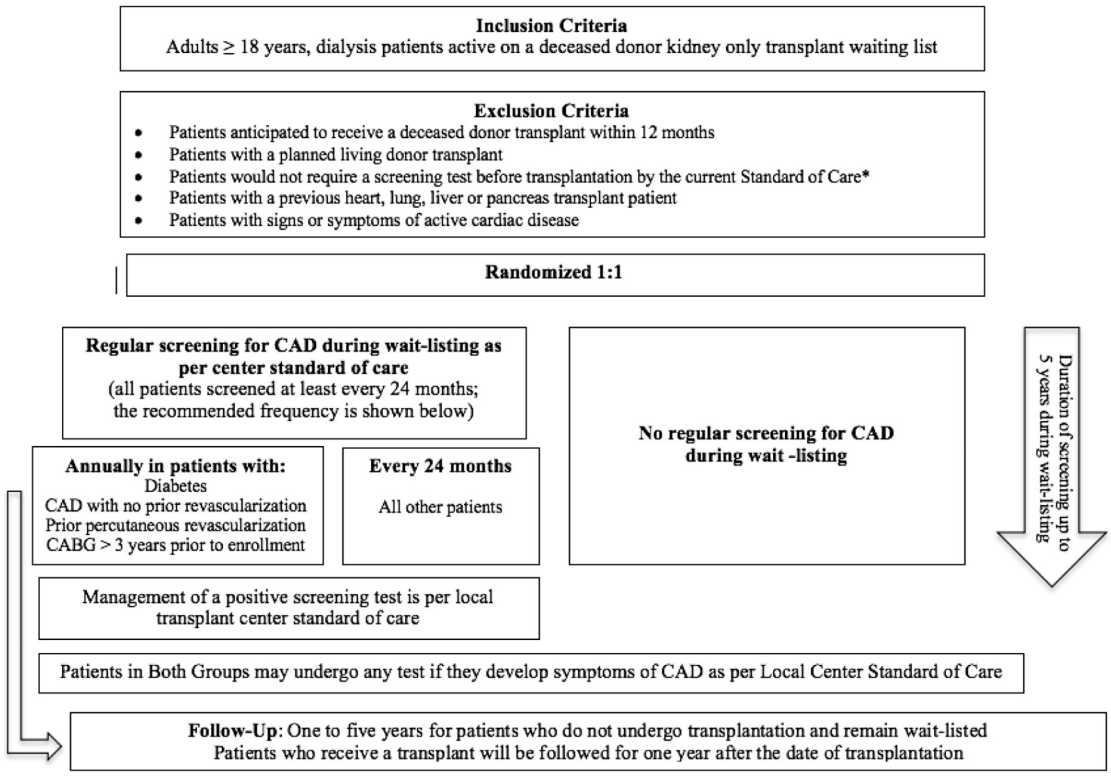
Funding

Funding for the trial is provided in Australia by a National Health and Medical Research Council project grant (1084454), in Canada by Canadian Institute for Health Research project grant (389992), and in NZ by the National Heart Foundation and the A+ Trust.

Study setting and population

The study is being conducted in Canada (2 sites active), Australia, and NZ (13 sites active). A total of 26 sites have been planned (Supplementary Table I). CARSK enrolls adult dialysis-treated patients from academic and nonacademic dialysis facilities that refer patients for consideration of deceased donor kidney transplantation to a kidney transplant center in Canada and Australasia.

Figure 1



Trial overview including inclusion and exclusion criteria.

The study inclusion and exclusion criteria are shown in Figure 1. All consenting adults (18 years or older) with dialysis-dependent kidney failure that are active on the kidney transplant wait-list are eligible for inclusion. Patients are expected to require further screening for CAD prior to transplantation by the SOC and are anticipated to undergo transplantation more than 12 months from the date of randomization. The timing of transplantation is expected to be variable between transplant centers because of regional differences in deceased organ donation rates. Patients with a history of prior nonkidney organ transplantation, candidates for a multiorgan transplant (eg, a combined kidney-pancreas transplant), and patients with a planned living kidney donor transplant are excluded. Any patient with signs or symptoms suggestive of unstable cardiac disease, such as unstable coronary syndromes, decompensated heart failure, uncontrolled arrhythmia, and severe valvular heart disease, are also excluded. (See Table I.)

Randomization

A Web-based randomization method is being used. Patients are stratified by transplant center and diabetic status. A statistician, independent of the trial team, will generate the randomization scheme. The randomization process consists of a computer-generated random listing of the treatment allocations stratified as above in variable permuted block sizes that will not be known to investigators. After confirming eligibility and obtaining informed consent, the study nurse will access the trial Web site and provide the subject's unique study identifier and a confirmation of consent and eligibility. The Web site provides the next available randomization number.

Trial interventions

During wait-listing, participants randomised to the intervention arm will receive no further regular noninvasive CAD screening test. Participants randomised to the control arm will receive regular noninvasive CAD screening test every 1-2 years during wait-listing according to local standard practice (Figure 1) consistent with

Table I. Outcome definitions for each component of MACE

Outcome	Definition
Cardiovascular death[23]	Death by any of the following mechanisms: 1. Acute MI 2. Sudden cardiac death 3. Heart failure 4. Stroke 5. Cardiovascular procedure-related 6. Cardiovascular hemorrhage
Nonfatal MI[24]	A clinical syndrome where there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, where the event does not result in death. Nonfatal MI can be subclassified into the following: **Type 1: spontaneous MI:** event related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in 1 or more of the coronary arteries, leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. **Type 2: MI secondary to an ischemic imbalance**: a syndrome where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and demand, for example, coronary artery spasm, anemia, hypotension. **Type 4: percutaneous coronary intervention–related, stent thrombosis or stent restenosis** **Type 5: coronary artery bypass graft surgery related**
Urgent revascularization[23]	Defined as the need for coronary revascularization procedure performed by either percutaneous coronary intervention or coronary artery bypass grafting. *Urgent revascularization* is defined as a procedure which should be performed on an inpatient basis and prior to discharge because of significant concerns that there is a risk of myocardial ischemia, MI and/or death. Note: Revascularization as result of a screening test in an asymptomatic patient is **not considered** an urgent revascularization.
Hospitalization with unstable angina (UA)[23]	*Hospitalization for UA* is defined as: (1) Ischemic discomfort (angina or symptoms thought to be equivalent) occurring at rest or in an accelerating pattern AND (2) Prompting an unscheduled hospitalization within 24 h of the most recent symptom. *Hospitalization* is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-h stay. AND (3) At least one of the following: (*a*) new ST or T wave changes on resting ECG; (*b*) evidence of myocardial ischemia as demonstrated by a positive result in exercise stress test, stress echocardiography, myocardial perfusion study, or magnetic resonance imaging; (*c*) angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs. AND (4) Negative cardiac biomarkers and no evidence of acute MI

existing guidelines. The Kidney Disease Outcomes Quality Initiative guidelines recommend annual screening of diabetic patients, patients with known CAD that are not revascularized, patients with previous percutaneous coronary artery revascularization, patients with complete coronary revascularization that are more than 3 years post–coronary artery bypass grafting, and patients with incomplete coronary artery bypass grafting. Patients with a known history of CAD or peripheral vascular disease, patients with ≥2 traditional risk factors, and patients

>1 year of dialysis exposure are recommended to be evaluated every 2 years.[13]

The type of noninvasive CAD screening tests will be as per the SOC in each transplant center and may include the following: exercise stress test (treadmill), exercise or pharmacological stress echocardiography or myocardial perfusion scintigraphy, as well as coronary computed tomography angiography. The management of an abnormal screening test including use of angiography, medical therapies, and coronary revascularization procedures will be as per the usual SOC in individual transplant centers. Patients in both groups who develop symptoms of CAD will be investigated and managed according to the local SOC in the hospital to which they present for acute care including the use of any clinically necessary test including noninvasive or invasive cardiac testing.

Outcomes

The primary outcome is a composite outcome of MACE, which consist of cardiovascular death, nonfatal MI, urgent coronary revascularization for symptoms, and hospitalization with unstable angina. All primary outcomes events will be adjudicated by a clinical end points committee, which will be blinded to the intervention allocation, using prespecified definitions that have been previously published (Table I).[23,24]

Secondary outcomes will capture the potential safety issues associated with each group and will include the following adjudicated outcomes: individual components of MACE, all-cause death, procedure-related death, major bleed (requiring hospitalization or blood transfusion), and stroke.[23] Nonadjudicated secondary outcomes will include the incidence of deceased donor transplantation, cancellation of transplant surgery due to CAD, permanent removal from the wait-list for cardiac reasons, and duration of time patients are placed on wait-list hold for CAD (including the number of events and total days of temporary suspensions). Tertiary outcomes will include permanent removal from the wait-list for noncardiac reasons, and death after permanent removal from the waiting list for any cause. CARSK will also measure health-related quality of life with the EuroQoL EQ-5D-5L[25] and Kidney Disease Quality of Life (KDQOL)-36[26] instruments to measure the impact of regular CAD screening versus no screening and subsequent events on patients' well-being while on the wait-list. Screening-related health resource use will also be captured as a secondary outcome, which in combination with the health-related quality of life measures will enable a cost-utility analysis (health-economic evaluation).

Recruitment and study duration

Recruitment of 3,306 patients (900 from Australia, 200 from NZ, and 2,206 from Canada) will occur over 3 years, with a total study duration of 5 years.

Recruitment in Australia and NZ commenced at selected sites in July 2016, and to date, 503 patients (15%) have been randomised. The majority of the randomised patients (485/503) are from Australia and NZ. Whereas NZ has met their enrollment target of 200, recruitment in Australia has been slower than anticipated. Transplantation rates at 2 high-volume kidney transplant centers in Australia have increased dramatically, thus excluding the majority of their wait-listed candidates for the trial. Two additional Australian sites are planned for 2019.

Because of differences among countries in the timing of funding commencement, recruitment began in 2 sites in Canada in December 2018, with the remaining sites expected to begin recruitment by May 2019. We anticipate that once all sites are initiated, recruitment will be completed in 2021 and follow-up completed in 2023. If enrolment targets are not met, an extension of the enrolment period and recruitment of additional sites (including international sites) will occur.

Fidelity

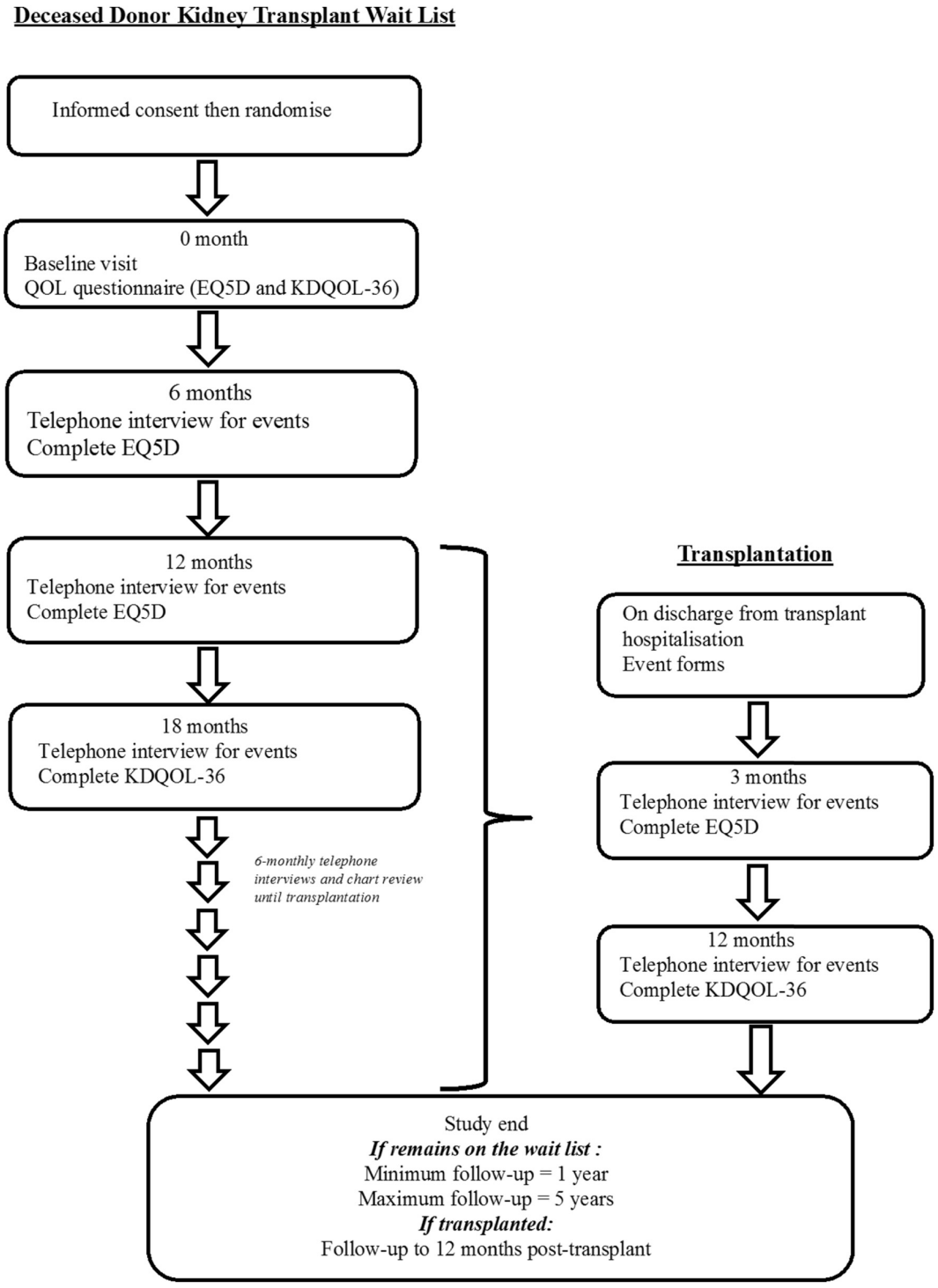
To enhance the fidelity of the study, procedures to minimize the use of off-protocol tests will include informing the participant's usual specialists and primary health care physician of their patient's participation in the study and the need to avoid CAD screening tests outside the study protocol; participants will also be asked to present a study wallet card to identify themselves as a CARSK trial participant whenever a cardiac test is scheduled by a treating physician. To date, protocol violations have occurred in 2/313 (0.95%) after 261 patient-years of follow-up, which are lower than anticipated.

Follow-up

Study follow-up procedures are summarized in Figure 2. Patients will remain in their study assigned treatment group while they remain on the transplant waiting list or a maximum of 5 years if they do not undergo transplantation. The minimum follow-up will be 1 year from the time the first scheduled screening test would have been scheduled. Patients who undergo transplantation from any donor source will be followed for 12 months after the date of transplantation. Follow-up to 12 months posttransplantation was chosen as the incidence of cardiovascular events is highest within the first year after transplantation.[10,27] Patients will exit the study at time of permanent removal from the waiting-list, death, withdrawal of study consent, or end of follow-up.

Patients who consent to the trial will complete 2 quality-of-life questionnaires, EQ-5D-5L (mandatory) and KDQOL-36 (optional at selected sites), at baseline, and relevant demographic and medical history will be recorded. Assignment to either regular CAD screening

Figure 2



Study follow-up procedure.

or no regular screening will be communicated to the transplant team and to the patient's treating nephrologist, cardiologist, and family physician.

Follow-up to ascertain study-related events will be embedded within current center clinical practice. It is standard practice for transplant centers to require nephrologists to regularly report events that may impact a patient's transplant eligibility during wait-listing. To supplement this information, a follow-up telephone interview and medical record review will be performed every 6 months after enrolment. An in-person interview and medical record review will occur at the time of discharge from hospital after transplantation, and a telephone interview and medical record review will occur at 3 and 12 months after transplantation. Patients will be sent follow-up quality-of-life questionnaires at the following time points after randomization: for EQ-5D-5L, at 6 and 12 months then yearly thereafter, and for KDQOL-36, at 18 months then yearly thereafter until study end. For patients undergoing transplantation, an EQ-5D-5L will be completed at 3 months after transplantation, and KDQOL-36 will be completed at 12 months after transplantation.

Sample size

We estimate a baseline MACE rate of 6.0% in the trial. MACE rates in the United States are 13.2% per year on the waiting list and 8.7% in the first posttransplant year.[28] These rates are lower in Australia and Canada (ie, 8.0% and 3.0%, respectively). Using these latter estimates, the lowest MACE rate in our trial would be observed if all patients underwent transplantation rapidly after enrolment (ie, 1 year of wait-listing followed by 1 year of posttransplant follow-up). In this scenario, the MACE rate would be 5.5% (ie, an average of 8.0% and 3.0%). We estimate that 50% of participants will receive a transplant in the study and most of the person-time follow-up will be accrued on the waiting-list (when MACE rates are highest), thus justifying our estimated MACE rate of 6.0%.

We surveyed all Canadian transplant centers to define the largest clinically acceptable difference in MACE between the study groups. Given a MACE rate of 6% in the regular screening group, a rate of ≤7.5% (ie, absolute difference of 1.5%, 25% increase) in the no regular screening group would be clinically acceptable. In comparison, the incidence of cardiac death or nonfatal MI in the DIAD study was 2.7% among diabetic patients without kidney disease assigned to regular screening and 3.0% among nonscreened patients (absolute increase 0.3%, 11% increase).[29] The willingness of transplant physicians to accept a 25% increase in MACE between groups is justified given that the outcomes of urgent revascularization for symptoms and hospitalization for unstable angina are included as MACE.

The following parameters were considered in estimating the trial sample size: (1) a baseline MACE rate of 6.0% per year; (2) *noninferiority* defined as an absolute increase in the MACE rate of 1.4%, hazard ratio of MACE <1.25; (3) power of 80%; (4) 2-sided significance level of 5%; (5) dropout rate of 10%. Based on these parameters, a total of 3,306 patients must be randomised to claim noninferiority between the no screening and regular screening groups if the MACE rate in the no screening group is less than 1.4% higher than the rate of 6.0% expected in the regular screening group.

Statistical analyses

We will use the intention-to-treat principle for all outcomes in the primary analyses. Patients will be assessed according to their treatment allocation; however, we will also report per-protocol results. The per-protocol analysis will consist of the ITT population minus patients who inappropriately received a screening test (in the no screening arm) and those who did not receive a scheduled screening test (in the regular screening arm). Patients lost to follow-up will also be excluded in the per-protocol analyses. We will present the time-to-first MACE event (primary outcome) using the Kaplan-Meier estimator and compare no screening versus regular screening using log-rank tests. We will use a Cox proportional-hazards model to estimate the effect of no screening on the hazard ratio for the primary outcome and calculate the 95% CI. In addition, a competing risks model will be used to estimate the effect of no screening versus regular screening for all primary and secondary outcomes. Subgroup analyses will be conducted to test for a statistical interaction between the treatment arm and subgroup effects (study site, diabetes, preexisting revascularization, country, and transplantation) with the use of interaction terms. A 2-sided significance level of 5% will be used for all analyses.

Health economic evaluation

A cost-effectiveness and cost-utility analysis of no further screening compared to regular screening will be conducted from Australian and Canadian health system perspectives. Data on CAD-related resource use will be obtained using trial case report forms, supplemented by patient diaries completed at selected centers. In addition, resource use (hospitalization, outpatient visits, medicines) in each country will be determined by linkage to provincial or national data sets where available. Analyses will report the cost per MACE avoided, cost per life-year gained, and the cost per quality-adjusted life-year (QALY) gained of no further screening compared with regular screening. One-way sensitivity analyses will be conducted around key variables, including the most expensive item of resource use, frequency of cardiac screening (yearly vs every 2

years) and other variables that may differ with different practice patterns. Using the mean discounted costs in each trial arm and the mean discounted benefits in each arm, the incremental cost per life-year gained and cost per QALY gained of the no screening group versus regular screening group will be calculated, with results plotted on cost-effectiveness plane. Bootstrapping will be used to estimate the distribution around costs and health outcomes and to calculate CIs around the incremental cost-effectiveness ratios.

Data management

Clinical electronic case record forms have been designed using an online database management tool called *REDCap*.[30] Participating sites enter data via a password-protected Web site. Ancillary data such as deidentified test reports and discharge letters are uploaded into the database. All data are stored electronically on servers at the Sydney Local Heath District Royal Prince Alfred data center in Australia. REDCap allows data to be inputted at multiple sites with Web authentication, data logging, and Secure Sockets Layer encryption. Data integrity and timeliness are monitored by lead sites in Canada and Australasia.

Study management

Study oversight will be provided by an executive steering committee involving international members from Canada and Australasia together with a broader, multidisciplinary, multinational Scientific Steering Committee. An independent data safety and monitoring board will monitor trial progress and ensure safety and adherence to study time line. Recommendations for stopping the trial will be an iterative process and will rely on clinical and statistical judgment to the rate of serious adverse events in the nonscreening (intervention) arm, which would be considered "excessive" compared with standard of care. The data safety and monitoring board will review adjudicated outcome data submitted by a Clinical Events Committee, comprised of members with expertise in the fields of cardiology, neurology, and nephrology from centers not participating in the trial. Patient group assignment or center identification will be blinded to the Clinical Events Committee at the time of the adjudication.

Discussion

Deceased donor kidney transplantation is unique among surgical procedures because it an elective surgical procedure performed under emergent conditions. Waiting times for deceased donor transplantation are long and variable, typically ranging from 1 to up to 10 years or more depending on the individual patient's ABO blood group and presence of antibodies to human leukocyte antigens as well as the rate of deceased organ donation in the patient's place of residence. Given the unpredictability of deceased donation, the timing surgery cannot be precisely determined in individual patients. Accordingly, the objectives of screening deceased donor candidates for CAD differ from those in other elective surgical procedures, including selection of appropriate wait-list candidates, maintenance of patient eligibility for transplantation during wait-listing and removal of patient who develop new or progressive disease that pose an unacceptable risk for transplantation, avoidance of CAD events in the peritransplant period, and optimization of posttransplant patient and transplant survival. These considerations have led to adoption of uniquely rigorous screening paradigm for CAD in asymptomatic kidney transplant candidates that is divergent from current general cardiology recommendations for patients undergoing elective nontransplant surgical procedures. This current standard of care is not evidence based, may be harmful, and is costly. With its innovative, pragmatic trial design and transcontinental collaboration, results from the CARSK trial will provide the data required to either justify current practice or alternately change clinical practices by removing the need for unnecessary screening test in asymptomatic patients.

The CARSK trial will inform policy makers of the costs of CAD screening to the health care system and of the cost-effectiveness of the alternative intervention (ie, no screening) for each QALY gained. This information will be invaluable to policy makers in their pursuit of more prudent use of health care resources in an era of burgeoning health care costs. From the clinicians' perspective, CARSK will inform transplant physicians on the best CAD screening practice and address an area of difficulty in decision making, for which there is clinical equipoise. Although not directly designed to test whether revascularization of CAD in an asymptomatic transplant candidate is beneficial, the relevance will be reduced if screening is shown to be unnecessary from this study. Finally, CARSK will evaluate patient-centered outcomes, including access to transplantation and quality of life. Irrespective of the outcome of CARSK, the results will have a significant impact on CAD screening practices for kidney transplant candidates around the world. The trial will either validate current practice and ensure optimal use of donor kidneys or save valuable resources by demonstrating that screening for CAD after wait-listing is unnecessary.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.05.008.

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