Cardiovascular risk assessment in kidney transplantation

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Cardiovascular disease (CVD) remains the most common cause of death after kidney transplantation worldwide, with the highest event rate in the early postoperative period. In an attempt to address this issue, screening for CVD prior to transplant is common, but the clinical utility of screening asymptomatic transplant candidates remains unclear. A large degree of variation exists among both transplant center practice patterns and clinical practice guidelines regarding who should be screened, and opinions are based on mixed observational data with great potential for bias. In this review, we discuss the potential risks, benefits, and evidence for screening for CVD in kidney transplant candidates, and also the next steps to better evaluate and treat asymptomatic kidney transplant candidates.

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Cardiovascular disease (CVD) is a significant cause of morbidity and mortality for wait-listed kidney transplant candidates,[1] and it is the most common cause of death in transplant recipients.[2] The risk of a major adverse cardiac event (MACE) is relatively constant while on the waiting list, then rises markedly in the early posttransplant period and declines to a lower rate thereafter[3–7] (Figure 1). Understandably, clinicians are highly motivated to screen for CVD before transplant, hoping to prevent events early after transplant and to improve long-term outcomes.

Asymptomatic chronic kidney disease (CKD) patients often have significant coronary artery disease (CAD), with prevalence estimates of 37–53% for at least one coronary artery with 50% or greater stenosis.[8–12] This high prevalence of asymptomatic CAD presents a compelling argument to screen transplant candidates with prior CAD, older age, or those with diabetes to identify asymptomatic patients who may benefit from preemptive coronary revascularization, both to improve perioperative MACE and also to improve the long-term outcomes after transplantation. It has also been argued that screening can be used to exclude high-risk individuals from transplantation and thereby protect a scarce resource. Finally, screening low-risk patients may identify those who would benefit most from risk-factor intervention.

Although the potential benefits of screening are compelling, they must be cost-effective and outweigh the potential for harm. This is particularly challenging in the CKD population where a high proportion of patients have noncoronary CVD, and the sensitivity and specificity of testing for CAD may be less than that in the general population. Testing for CAD may include noninvasive measures such as myocardial perfusion studies (MPS), dobutamine stress echocardiograms (DSE), biomarkers, or cardiac computed tomography (CT) followed by evaluation with coronary angiography.

Any screening test should be cost-effective, with benefits outweighing harms. Specifically, testing must improve outcomes of importance to patients, not consume resources that would be better spent in other ways, and not produce harms that outweigh the benefits. In the absence of randomized controlled trials (RCTs), the optimal method, or even the benefit, of pretransplant screening and intervention remains unclear. The evidence in favor of CAD screening before

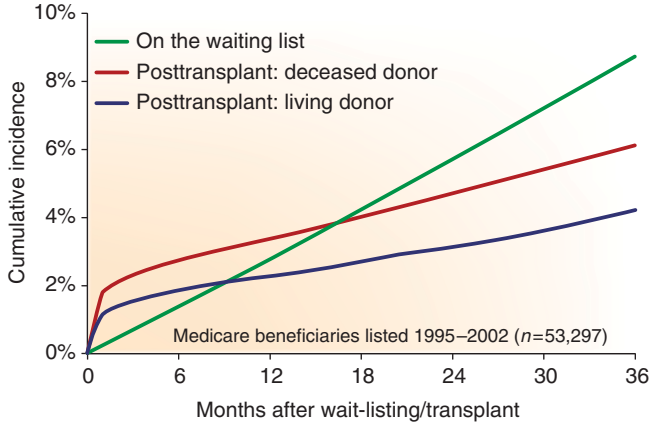

Figure 1 | Waiting list and posttransplant acute myocardial infarction (used with permission from Kasiske *et al.*[4]).

kidney transplantation, including the accuracy of noninvasive tests, the prognostic value for future clinical outcomes, and the evidence for both screening and intervention on CAD before transplantation is weak at best. We first review the evidence for screening and revascularization in asymptomatic high-risk patients unselected for CKD, followed by the evidence in patients with CKD unselected for transplant candidacy. Finally, we review the evidence for screening and revascularization in kidney transplant candidates who are likely healthier than those unselected for candidacy but also undergo the additional risk of surgery, and discuss the next steps to ensure the best management and outcomes in these high-risk patients.

EVIDENCE FOR SCREENING AND REVASCULARIZATION IN ASYMPTOMATIC HIGH-RISK PATIENTS FROM THE GENERAL POPULATION

Noninvasive screening

Two large RCTs examined the utility of noninvasive screening of asymptomatic individuals to improve outcomes. Although the subjects in these trials were not selected for the presence of kidney disease, they include either perioperative screening for high-risk surgery or screening high-risk patients. In 2006, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) II investigators reported on a trial in which 770 subjects with 1 or 2 risk factors were randomized to echocardiographic stress testing or no testing before major vascular surgery. All subjects were on beta blockers, with the dose adjusted to a target resting heart rate of 60–65 b.p.m. No difference was found between the two groups in either cardiac death or myocardial infarction (MI) (Refs 13, 14; The integrity of the data from the DECREASE trials has been called into question; however, having reviewed the available evidence, the journals have not retracted the articles. Nonetheless, we have cited the JACC Notice of Concern whenever any data using DECREASE trial data are cited.). In 2009, Young *et al.*[15] reported on the Detection of Ischemia in Asymptomatic Diabetes (DIAD) trial in which 1123 subjects with type 2 diabetes and no symptoms of CAD were randomized to MPS versus no screening and detected no difference in cardiac death or nonfatal MI at 4.8 years. In both of these trials, very few of those subjects who were screened were revascularized (3% in the DECREASE II trial and 5.5% in the DIAD trial), bringing into question both the cost benefit and clinical utility of screening asymptomatic patients.

Revascularization

Although demand-mediated ischemia from obstructive plaques contributes to perioperative cardiac events, rupture of nonobstructive plaques has long been understood to be a major contributor in both the nonoperative and perioperative settings.[16–18] Several RCTs have therefore investigated whether intervening on asymptomatic obstructive CAD affects clinical outcomes in an era of marked improvements in medical management for CVD and with the knowledge that nonobstructive plaques are often responsible for perioperative MACE. The Coronary Artery Revascularization Prophylaxis (CARP) trial was undertaken to address a lack of RCT evidence for preoperative revascularization in a high-risk group, a situation very similar to that currently faced by the kidney transplant community. Before this study, retrospective and prospective observational data suggested that patients who underwent screening and revascularization before high-risk vascular surgery had better outcomes. A total of 510 subjects at 18 Veterans Affairs medical centers who underwent coronary angiography on the basis of risk factors or positive noninvasive stress tests and were found to have $>70\%$ stenosis in one or more major coronary vessel were randomized to either revascularization or medical management. No difference was seen in mortality at a median of 2.7 years, or in 30-day postoperative MI,[19] although in the *post hoc* analysis some benefit may have been seen in the 4.6% of subjects with unprotected left main disease.[20]

In 2007, the DECREASE V investigators sought to further investigate this issue among the highest-risk patients by assigning all high-risk (three or more risk factors) patients to noninvasive stress testing, and then randomizing the 101 subjects with extensive stress-induced ischemia to revascularization or medical management before vascular surgery. In all, 20% of these subjects had a history of renal failure, although the degree was not further defined, and 75% had three-vessel or left main CAD. Even in these high-risk subjects, this study found no difference in all-cause mortality or MI at either 30 days or 1 year.[14,21] The long-term follow-up published in 2009 at a median of 2.8 years continued to show no benefit to revascularization.[14,22]

In a nonperioperative setting, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized 2287 patients with objective evidence of both myocardial ischemia and significant CAD on angiography to either optimal medical management or percutaneous intervention, and found no difference in

Table 1 | Summary of RCT evidence for screening or intervening on asymptomatic CAD

Study	N	Population	P-value
COURAGE[63]	2287	Known CAD	0.62
DIAD[55]	1123	Type 2 diabetes	0.73
CARP[59]	510	Treatable lesions before vascular surgery	0.92
DECREASE II[53,54]	386	High risk before vascular surgery	0.30
DECREASE V[61,54]	101	Treatable lesions before vascular surgery	0.61
Manske *et al.*[52]	26	Treatable lesions before transplantation	<0.01

Abbreviations: CAD, coronary artery disease; N, number; RCT, randomized control trial.

all-cause mortality or nonfatal MI at a median follow-up of 4.6 years.[23] These trials suggest that, even among the highest-risk patients, screening for and intervening on asymptomatic CAD before kidney transplantation may not benefit patients, nor justify the associated cost and risk involved (Table 1).

EVIDENCE FOR SCREENING AND REVASCULARIZATION IN PATIENTS WITH CKD

Prognostic value of noninvasive tests in advanced CKD

In subjects with CKD or end-stage renal disease (ESRD), several observational studies have shown an association between MPS and DSE results and either future MACE or mortality;[24–26] however, the sensitivity and specificity of these tests for CAD diagnosed by coronary angiography is marginal.[27–35] In addition to stress tests, biomarkers such as cardiac troponins in asymptomatic patients with advanced CKD may have prognostic value for risk stratification beyond the traditional use of rising troponins to detect acute coronary syndrome. Persistent elevations in troponin may reflect cardiac stress beyond CAD, such as left ventricular hypertrophy, diastolic dysfunction, and volume overload. A meta-analysis of 28 studies of asymptomatic patients with ESRD found that elevated troponin T was associated with more than twice the risk of all-cause mortality. The association between troponin I was not significant, possibly owing to a lack of assay standardization.[36]

Coronary artery calcification detected by cardiac CT is another noninvasive screening test that is increasingly used in the general population, as it has been shown to improve cardiac risk prognostication in asymptomatic patients without CKD;[37] however, its association with CAD in patients with advanced CKD is much less clear. The utility in this population may be limited owing to the high degree of medial vascular calcification in advanced CKD patients compared with the intimal vascular calcification seen in the general population.[38] As many as 83% of patients on hemodialysis have been found to have elevated CT calcium scores.[8] Matsuoka *et al.*[39] did report an association between CT calcium scores and death in hemodialysis patients, but most of the studies have found poor correlations between CT calcification and angiographic CAD in patients with advanced CKD.[40–42] Cardiac CT angiography is a sensitive tool in patients without CKD, but it has not been studied in patients with significant CKD, and its safety is limited by the need for iodinated contrast.

Coronary angiography and revascularization in advanced CKD

Fewer studies have evaluated the association between CAD diagnosed on angiography and future cardiac events or death. In 2007, Charytan *et al.*[11] reported on a series of hemodialysis patients who underwent coronary angiogram, and found that those with 50% or greater stenosis in at least one vessel had greater than three times the risk of death at a median follow-up of 2.7 years.

The only RCT data to assess the benefit of revascularization in asymptomatic CKD patients to date is a *post hoc* analysis of the COURAGE trial. As outlined above, the COURAGE trial found no benefit to PCI over optimal medical management in asymptomatic patients unselected for CKD with objective evidence of ischemia and CAD. To investigate whether the lack of benefit persisted among those with CKD, Sedlis *et al.*[43] evaluated the 320 participants with an estimated glomerular filtration rate < 60 ml/min per 1.73 m^2 compared with those with an estimated glomerular filtration rate ≥ 60 ml/min per 1.73 m^2. Although CKD remained an independent predictor of death or nonfatal MI, again no difference was seen in all-cause mortality or nonfatal MI in those who received PCI versus optimal medical management.[43]

EVIDENCE FOR SCREENING AND REVASCULARIZATION IN KIDNEY TRANSPLANT CANDIDATES

Sensitivity and specificity of noninvasive stress tests in kidney transplant candidates

Many studies have investigated the sensitivity and specificity of both DSE and MPS for the detection of angiographic CAD in kidney transplant candidates, reporting a wide range of values that are generally lower than those in the general population. For DSE, estimates for the sensitivity and specificity ranged from 37 to 95% and 71 to 95%, respectively.[27–31] Reported sensitivity and specificity for MPS ranged from 37 to 80% and 37 to 73%, respectively.[29,32,33] In 2011, Wang *et al.*[34] published a systematic review and meta-analysis with pooled estimates for DSE and MPS from 18 studies. DSE had a pooled sensitivity of 0.80 (95% CI (confidence interval), 0.64–0.90) and pooled specificity of 0.89 (95% CI, 0.79–0.94). MPS had pooled sensitivity of 0.69 (95% CI, 0.48-0.85) and specificity of 0.77 (95% CI, 0.59–0.89). Only two studies had head-to-head comparisons, which seemed to show superior specificity of DSE over MPS and equivalent sensitivity. In pooled indirect comparisons, DSE again appeared to be more accurate; however, this difference was no longer significant when studies of lower quality were excluded.[34,35] In addition, many studies included symptomatic patients and several others did not specify whether symptomatic patients were included, making it more difficult to apply the results to an asymptomatic kidney transplant candidate.

Prognostic value of noninvasive tests in kidney transplant candidates

In kidney transplant candidates, the association between DSE or MPS results and future cardiac events is more mixed than the data in CKD patients unselected for transplant candidacy. Earlier observational studies reported significant associations between positive noninvasive stress tests and future cardiac events,[28,44–46] and a meta-analysis by Rabbat *et al.*[47] in 2003 using data from 12 studies reported a positive association between noninvasive tests and future MACE in kidney transplant candidates. Since that meta-analysis, several studies have found no association. In 2003, De Lima *et al.*[29] found that neither MPS nor DSE results were independently associated with future MACE in moderate-to high-risk kidney transplant candidates, a finding duplicated by Gill *et al.*[1] in 2005 and by Welsh *et al.*[48] in 2011. Gill *et al.*[1] also found no difference in the rates of MACE or survival in those transplant candidates who subsequently underwent scheduled periodic DSE or MPS while on the waiting list compared with those who did not. In contrast to these studies, Patel *et al.*[49] and Wong *et al.*[50] did find an association between MPS results at the time of transplant evaluation and future MACE. The observational data available are therefore inconclusive as to whether noninvasive cardiac stress testing is an accurate prognosticator for future clinical outcomes.

As with patients with CKD unselected for transplant candidacy, biomarkers may provide additional prognostic information in transplant candidates. In one cohort, troponin T was associated with higher transplantation-censored mortality,[51] and multiple studies have noted an association between either troponin T[52–54] or TnI[55–57] measured at the time of transplantation and either post-op MACE or mortality. Although this prognostic information may be interesting, the clinical utility and impact on patient care remains uncertain. Similarly, although it has not been well-studied in kidney transplant candidates, no clear clinical application for cardiac CT exists in this group given the data in CKD patients unselected for transplant candidacy.

Prognostic value of coronary angiography in kidney transplant candidates

As with the prognostic value of noninvasive tests in kidney transplant candidates, the data for the value of coronary angiography in high-risk transplant candidates are mixed. De Lima *et al.*[29] reported that the finding of CAD on coronary angiography, but not noninvasive screening, was associated with an increased risk of future MACE, as did Welsh *et al.*[48] in 2011. Conversely, Hage *et al.*[58] found that neither the presence nor severity of coronary disease on angiography was associated with survival in kidney transplant candidates.

Revascularization and outcomes in kidney transplant candidates

The prognostic information gained from screening kidney transplant candidates for CAD may be useful for identifying and counseling those who would benefit most from risk-factor intervention, and some argue that it may be used to exclude high-risk individuals from transplantation. However, even those candidates at highest risk for MACE show improved survival and quality-of-life benefit from transplantation when compared with those who remain on dialysis,[3,59,60] making it difficult to argue that exclusion based on CAD alone is in the best interest of the patient. Therefore, the main justification for screening is to have the opportunity to intervene before transplant when patients are stable, both to prevent perioperative MACE and to improve long-term outcomes after transplantation.

Several observational studies have attempted to investigate the effect of intervention on outcomes in kidney transplant candidates. In 2007, Hage *et al.*[58] published data on a retrospective cohort of 260 subjects who underwent coronary angiography for a history of CAD or a positive noninvasive stress test. Ninety-four of the 260 subjects subsequently underwent revascularization but did not have improved survival compared with those who did not undergo revascularization, except in those found to have 3-vessel disease. However, given the observational nature of the study, we cannot know whether those subjects with the intervention would have worse outcomes had they not undergone revascularization. Furthermore, the overall rate of perioperative MI was very low in this cohort.[58] Similarly, in 2008, Patel *et al.*[49] published a report of a prospective cohort of 300 kidney transplant candidates, 99 of whom were deemed high-risk and underwent coronary angiography (age > 50 years, ESRD due to diabetes, symptomatic ischemic heart disease, or positive noninvasive stress test). They found no survival difference between those subjects who subsequently received an intervention and either those who had coronary angiography with no subsequent intervention or those who did not undergo angiography.[61] However, this study included symptomatic subjects, and again, given the observational design, it is unknown whether the subjects who underwent intervention would have had worse outcomes with medical management alone.

In contrast to these studies, two observational studies have found better survival in candidates who underwent an intervention. In 2011, Kahn *et al.*[62] described a retrospective review of 357 kidney transplant recipients who had undergone coronary angiography as part of their pretransplant screening owing to an abnormal noninvasive stress test. A total of 212 (59%) candidates were found to have obstructive disease (>70% stenosis), and at 5 years posttransplant those with obstructive disease who were medically managed had worse survival compared with those who had undergone PCI or coronary artery bypass grafting. No difference was seen between those with nonobstructive disease and those who had undergone revascularization.[62] The same year, Kumar *et al.*[63] reported on 657 kidney transplant candidates who underwent coronary angiography due to risk factors (age > 50, diabetes, known CAD, abnormal electrocardiography, or symptoms). In this cohort, 184 candidates (28%) were offered revascularization and 16 declined; those who

declined had significantly worse 1- and 3-year survival compared with those who were revascularized.[63] However, all of those who declined revascularization were excluded from transplantation, likely confounding the association between lack of revascularization and survival.

As with the studies cited that found no benefit to revascularization, the observational design of these studies makes it impossible to discern whether any survival benefit is attributable to the intervention. Only one RCT has attempted to evaluate the benefit of screening and intervening on CAD before transplant in 26 diabetic kidney transplant candidates. This study, published in 1992, randomized 26 asymptomatic subjects with >75% stenosis in at least one vessel to medical treatment versus revascularization. In all, 2 of 13 revascularized subjects compared with 10 of 13 medically managed subjects had a cardiovascular event with a median follow-up of 8 months, and four medically managed subjects died of MI.[64] In this small trial, the cardiovascular event rate was markedly high, and medical management consisted only of a calcium channel blocker and aspirin, making the results difficult to interpret in the setting of much improved medical management of CVD. Given the lack of modern large trials among kidney transplant candidates, we will review RCTs evaluating the benefit of perioperative screening and intervention on CVD among other high-risk populations.

A NEED FOR RANDOMIZED TRIALS TO EVALUATE CARDIOVASCULAR SCREENING IN KIDNEY TRANSPLANT CANDIDATES

Current guidelines for pretransplant cardiovascular evaluation in asymptomatic kidney transplant candidates are based on expert opinion in the setting of observational data, which itself has mixed results. Those guidelines specific to transplant candidates generally recommend noninvasive stress testing in high-risk patients (usually defined as patients with diabetes, prior CAD, and those with two or more cardiac risk factors), followed by coronary angiogram and revascularization before transplant in those with evidence of ischemia[65–68] (Figure 2). These recommendations, when rated, are presented with the weakest strength and the lowest level of evidence ratings, reflecting a paucity of data and reliance on observational studies. Recent data in the general population suggest that preoperative screening and intervention on asymptomatic patients do not improve mortality or decrease the rates of MACE,[53,54,59,61] and in contrast to the recommendations specific to kidney transplant candidates the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for preoperative screening for noncardiac surgery do not recommend screening asymptomatic patients unless they have a functional status of less than four metabolic equivalent tasks.[69] However, one might argue that general population guidelines should not be applied to the kidney transplant candidate given the higher prevalence of asymptomatic disease. Not surprisingly, application of the different guidelines would result in very different screening rates. In 2011, Friedman *et al.*[70] reported that if four different screening guidelines were applied to the same patient population the range of proportion screened would be between 20–100%.[70,71] Practice patterns in screening these asymptomatic kidney transplant candidates for CAD also vary widely among transplant centers.[72–74]

Noninvasive stress testing appears to have at best moderate sensitivity and specificity in kidney transplant candidates for the detection of angiographic CAD, and the benefit of intervening on obstructive angiographic CAD in kidney transplant candidates has only been evaluated among kidney transplant candidates in one trial of 26 diabetic subjects conducted before major improvements in the medical management of CVD with beta blockers, statins, and angiotensin blockade. Large RCTs in nontransplant (but high-risk) populations have not shown benefit to screening or revascularization for asymptomatic CAD, although these trials may not be applicable to a population with advanced CKD and a high prevalence of asymptomatic CAD.

The burden of CVD both on the waiting list and after transplantation is substantial, and CVD remains the most common cause of death with a functioning graft among kidney transplant recipients even in the face of improvements

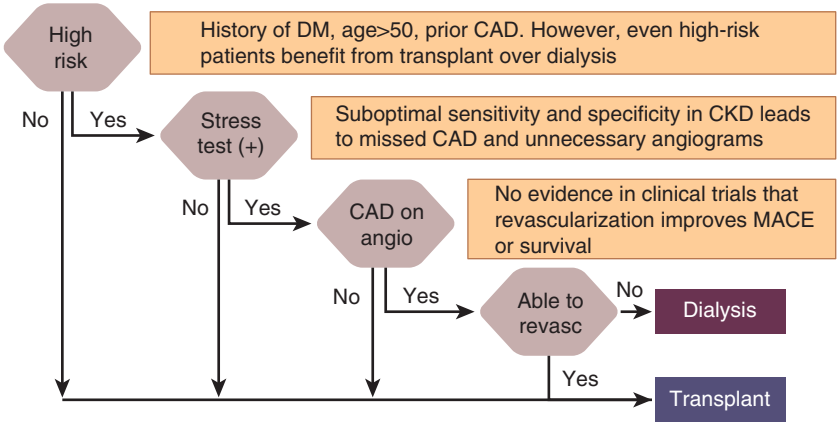

Figure 2 | Usual pretransplant screening and its uncertainties. MACE, major adverse cardiac event.

in medical management of CVD, prompting a drive to intervene, whenever possible, to improve outcomes. However, the potential harm of screening and intervention in asymptomatic transplant candidates is also substantial. The procedural risks of angiography, including radiocontrast nephropathy, are clear, and they are higher in patients with CKD.[75–80] Even radiation, instinctively disliked by many patients, may pose a risk. Indeed, Nguyen *et al.*[81] found in a cohort of transplanted patients, already at higher risk for malignancy, that 29% were exposed to high or very high levels of radiation in their pretransplant evaluations, and that nuclear medicine studies accounted for 83% of that exposure. The lower specificity of noninvasive testing in patients with ESRD and CKD often results in coronary angiograms without evidence of CAD. In addition, fear of precipitating ESRD and precluding advantageous preemptive transplantation makes clinicians reluctant to perform coronary angiography until after the initiation of dialysis. If revascularization is undertaken, there is both a procedural risk and subsequent increased risk of bleeding owing to the need for antiplatelet agents. Furthermore, in light of a recent systematic review of 13 RCTs and five meta-analyses proposing that patients with multi-vessel disease, left main disease, and diabetes should undergo CABG rather than PCI when possible,[82] a larger proportion of asymptomatic kidney transplant candidates may be faced with this more invasive and costly intervention without clear perioperative or long-term benefit. Recent changes in lipid management recommendations following the Study of Heart and Renal Protection (SHARP) trial, as well as new treatment guidelines from both the ACC/AHA and Kidney Disease: Improving Global Outcomes (KDIGO), may improve medical risk-factor management, potentially further reducing the benefit of invasive procedures.[83–85] Finally, the resource utilization of widespread screening is substantial while the yield is low; observational studies show that fewer than 10% of those screened go on to coronary intervention,[27,30,34,49,86–88] consuming healthcare resources, which could potentially be applied elsewhere.

The clinical utility of screening for CAD in asymptomatic kidney transplant candidates to improve outcomes cannot be evaluated in observational studies; in fact, the CARP trial, which found no benefit to coronary revascularization before major vascular surgery, followed a series of large observational studies that suggested significant benefit to revascularization with regard to mortality and incidence of MACE. Such a RCT in kidney transplant candidates is feasible; in 2011, Kasiske *et al.*[4] reported on the results of a feasibility study for a multicenter RCT of pretransplant cardiovascular screening. The proposed RCT would randomly allocate patients referred for kidney transplant 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. A total of 26 transplant centers participated, and 73% of eligible patients indicated that they would be willing to participate in the described RCT.[89] Given the high prevalence of the asymptomatic CAD, the substantial morbidity and mortality that it confers in kidney transplant recipients, the current widespread use of pretransplant screening and intervention, as well as the uncertainty regarding its management in kidney transplant candidates, such a trial would both benefit patients and ensure the best use of limited healthcare resources.

CONCLUSION

Screening for and intervening on asymptomatic CAD in kidney transplant candidates is extremely common, but the benefits of this practice are not clear and may not outweigh the risks. Current recommendations are based on observational data with mixed results and unavoidable bias. Trials in the general population, including in high-risk patients, have failed to provide evidence that screening prevents MACE or improves mortality. A large RCT is needed to assess whether the current practice is beneficial or whether we are harming patients and misdirecting clinical resources.

DISCLOSURE

All the authors declared no competing interests.

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