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Cardiovascular Risk Assessment Among Potential Kidney Transplant Candidates: Approaches and Controversies

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Abstract

Cardiovascular disease is the most common cause of death after kidney transplant. However, uncertainties regarding the optimal assessment of cardiovascular risk in potential transplant candidates have produced controversy and inconsistency in pretransplant cardiac evaluation practices. In this review, we consider the evidence supporting cardiac evaluation in kidney transplant candidates, generally focused on coronary artery disease, according to the World Health Organization principles for screening. The importance of pretransplant cardiac evaluation is supported by the high prevalence of coronary artery disease and by the incidence and adverse consequences of acute coronary syndromes in this population. Testing for coronary artery disease may be performed non-invasively by modalities including nuclear myocardial perfusion studies and dobutamine stress echocardiography. These tests have prognostic value for mortality but imperfect sensitivity and specificity for detecting angiographically-defined coronary artery disease in end-stage renal disease patients. Associations of angiographically-defined coronary artery disease with subsequent survival are also inconsistent, likely because plaque instability is more critical for infarction risk than angiographic stenosis. The efficacy and best methods of myocardial revascularization have not been examined in large, contemporary clinical trials among end-stage renal disease patients. Biomarkers such as cardiac troponin have prognostic value in end-stage renal disease but require further study to determine clinical applications in directing more expensive and invasive cardiac evaluation.

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Keywords

Cardiovascular disease; Kidney transplant; Myocardial revascularization; Physician's practice patterns; Risk assessment

Many advances have been made in the field of kidney transplantation since the first demonstration of this procedure as a viable form of renal replacement more than fifty years ago. However, questions remain regarding the optimal assessment of cardiovascular risk in renal transplant candidates. In 1968, the World Health Organization (WHO) articulated characteristics of diseases amenable to effective screening programs that hold substantial relevance for clinical evaluation policies today [1]. In this review we consider the evidence supporting cardiac evaluation for coronary heart disease in kidney transplant candidates according to WHO principles (Box 1). Specifically, we summarize current knowledge from this population on: 1) the public health importance of coronary artery disease (CAD) and ischemic heart disease; 2) disease natural history in terms of the relationship of coronary artery stenoses to cardiac events and mortality; 3) the accuracy and use of testing for CAD; and 4) the efficacy and use of revascularization. We also briefly discuss cardiac biomarkers as emerging tools for cardiac evaluation and the importance of non-coronary heart disease in this population.

Public Health Importance of CAD in Kidney Transplant Candidates and Recipients

The main objectives of pretransplant cardiac evaluation are to identify existing cardiac conditions amenable to risk modification, and to exclude patients with such short expected near-term survival due to cardiac morbidity that transplantation would not yield adequate benefit from the allograft. It is known that patients on dialysis experience age-adjusted mortality substantially higher than that of the general population, and that the primary cause of death is heart disease. The challenge in conducting comprehensive, accurate and cost-effective pretransplant cardiac evaluation is exemplified by both the large size of the target population and the prevalent disease burden. The number of total listings for kidney and kidney-pancreas transplantation increased five-fold since 1991, such that per current Organ Procurement and Transplant Network (OPTN) records, more than 80,000 persons are awaiting these organs in 2009[2]. Significant shifts in the age composition of the waitlist towards older adults aged >50 years (with marked increases in patients aged ≥65 years) is also increasing the comorbidity burden and medical complexity of the waitlist3.

Current evaluation and selection procedures have not eliminated cardiovascular disease as a major public health problem in ESRD patients after candidate selection or transplantation. Estimates of three-year cumulative incidence of myocardial infarction based on billing claims algorithms have ranged from 8.7% to 16.7% after candidate listing, and from 4.7% to 11.1% after transplant[4,5]. Observational studies have shown particularly high frequencies of cardiovascular diagnoses in the first months after transplant[4,6,7]. Registry data identify cardiovascular diseases in aggregate as the most common cause of death with graft function at all time periods after transplant, accounting for 30% of graft loss from death overall, with the highest rates early after transplant (Figure 1)[8].

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Natural History – Relationship of CAD to Subsequent Clinical Events in ESRD Patients

Angiographic studies from the 1970s to early 1990s detected CAD in high proportions of patients on long-term dialysis[9–13]. More recently, angiographically significant CAD was found in 53% of a sample of 30 incident ESRD patients without known cardiac history who consented to screening angiography, including 83% of the 12 participants with diabetes, although notably angiographic significance was liberally defined as lesions >50%[14]. Recent reports of angiography in patients undergoing transplant evaluation have documented CAD in 42%–81% of participants, with prevalence being higher in samples selected as facing "high-risk" by clinical criteria and with use of more liberal angiographic definitions of CAD[15–22] (Table 1).

Studies describing associations of angiographic coronary stenoses with subsequent clinical events in ESRD patients including those undergoing transplant evaluations have reached inconsistent conclusions (Table 2). De Lima et al prospectively studied 126 renal transplant candidates clinically classified as moderate (age ≥50 years) or high (diabetes, extracardiac vascular disease or known CAD) coronary risk with myocardial perfusion studies (MPS), dobutamine stress echocardiography (DSE) and coronary angiography[16]. Significant CAD, defined as >70% stenosis in ≥1 major epicardial artery on angiography, was found 42% of the sample. After median follow-up of 46 months, clinical risk stratification and coronary angiography predicted major cardiac events, but MPS and DSE did not. The probability of reaching the composite endpoint at 1,2 and 4 years in patients with angiographic CAD was 13%, 39%, 46% versus 2%, 6%, 6% in those without CAD (P<0.001).

Additional observational studies have also reported increased unadjusted risk of all-cause mortality and major cardiovascular events in patients with angiographic CAD[15,18] while other investigations identified risk only certain patient sub-groups, such as those with proximal CAD[17] or with non-diabetic renal failure19. Several recent studies have found no associations of CAD with subsequent patient survival, although it is difficult to disentangle the impact of revascularization from that of CAD itself in these observational designs20–22. Notably, investigations in the general population have demonstrated that most myocardial infarctions result from plaques that rupture or erode, resulting in thrombus formation and either partial or total occlusion of arteries that did not previously contain significant stenoses[23]. Infarction may be most likely with "vulnerable" or "unstable" plaques that have thinner epithelial layering ("thin wall atheromoa") than surrounding plaque but are more vulnerable to rupture and subsequent thrombosis[24].

Accuracy of Non-invasive Testing for CAD in Potential Kidney Transplant Candidates

Non-invasive testing for CAD is available as myocardial perfusion studies (MPS), stress echocardiography and most recently cardiac computed tomographic angiography (Table 2). These tests have imperfect sensitivity and specificity in patients with renal failure, or in the case of tomographic angiography, have not been evaluated in this population. Abnormalities on MPS correlate well with the presence of CAD in the general population, with mean weighted sensitivity 88% and mean weighted specificity 74%[25]. The performance MPS in identifying CAD among ESRD patients is more variable, with reported sensitivities and specificities ranging from 37–90% and 40–90%, respectively26–29. Nonetheless, MPS results do have prognostic value for cardiac events and mortality in the ESRD population30,31. In a meta-analysis of twelve studies involving thallium-201 scintigraphy and dobutamine stress echocardiography (DSE), ESRD patients with inducible ischemia had approximately six-times the risk of myocardial infarction and four-times the risk of cardiac death as patients without

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inducible defects[32]. Moreover, patients with fixed defects also had nearly five-times the risk of cardiac death. The prognostic value of MPS has been demonstrated with other perfusion tracers. For example, in a study of 126 ESRD patients who underwent 99m-technetium MPS as part of their pretransplant assessment, presence of a reversible defect was associated with three-times the risk of post-transplant cardiac events (HR 3.1, 95% CI 1.1–18.2) and nearly twice the risk of death (HR 1.92, 95% CI 1.1–4.4) compared to normal test results33.

DSE is a commonly used, safe method of non-invasive CAD risk assessment. Among patients without advanced kidney disease, stress echocardiography has mean weighted sensitivity of 86% and specificity of 81% for detecting angiographically significant CAD (variably defined across studies as ≥50–75% stenosis)[34]. As with MPS and other non-invasive tests, the accuracy of DSE increases for higher degree stenoses (≥70%) and multivessel obstructive CAD. Similar to MPS, the accuracy of DSE for detecting CAD in ESRD patients including transplant candidates has been variable, with reported sensitivities of 37–95% and specificities of 71–95%15,35–39. However, abnormal test results have been associated with increased risk of adverse clinical outcomes15,35–41. Among 485 patients with advanced kidney disease (on dialysis or with serum creatinine >3 mg/dl) the percentage of ischemic segments by DSE was an independent predictor of mortality and offered prognostic information incremental to clinical data[42]. Nonetheless, inconsistent results in some studies have led some to question the routine use of DSE for pre-transplant cardiac evaluation. In an aforementioned investigation of 126 renal transplant candidates studied with MPS, the accuracy of non-invasive testing to detect CAD was limited: MPS sensitivity 64%, specificity 53%; DSE sensitivity 44%, specificity 87%16. Clinical risk stratification and coronary angiography predicted the freedom from cardiac events, but non-invasive test results did not.

The incorporation of clinical risk scores may better identify which patients will benefit from pretransplant testing with either DSE or MPS43, 44. In a study of 244 patients with chronic kidney disease (mean age 54 years; 169 dialysis-dependent), participants were classified dichotomously as either low or high-risk based on Framingham, Portland and Brisbane risk scores, then further stratified according to DSE results and followed 20±14 months for major cardiac events (defined as cardiovascular death, myocardial infarction, acute coronary syndrome)[41]. Based on the different clinical scoring systems, the prevalence of high-risk clinical classification varied from 34%–79% and the proportion of high-risk patients with an abnormal DSE ranged from 39%–50%. Depending on the clinical score chosen, 25%–44% of high-risk patients with an abnormal DSE had a cardiac event, compared with 8%–22% of high-risk patients with a normal DSE. Cardiac events occurred in 2.0%–9.7% of the low-risk patients and DSE results did not improve event prediction in the low-clinical risk subgroups. It is also notable that while low-risk clinical status was associated with better outcomes, it did not predict freedom from subsequent cardiac events.

Recently, the development of electron beam and multi-detector cardiac computed tomography for detection and quantification of coronary artery calcification (CAC) has been shown to improve cardiovascular risk prediction as compared to the Framingham score in asymptomatic patients without kidney disease[45]. Among 205 maintenance hemodialysis patients aged >18 years, Raggi et al detected evidence of CAC in >83% of the participants46. These results were concordant with prior studies documenting significantly greater intracoronary calcification in ESRD compared with non-ESRD patients, with particular disparities in young cohorts47–49. Although one study found CAC to be an independent predictor of death in maintenance hemodialysis patients[50], the role of CAC as a prognostic marker in the ESRD population is yet to be adequately defined[51]. Other studies demonstrate a poor correlation between CAC score and angiographic CAD in patients with advanced kidney disease[52–54]. This has been hypothesized to reflect a high burden of medial vascular calcification in ESRD compared to the intimal calcification seen in the non-ESRD population[55]. For these reasons, CAC

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quantification is not currently recommended for assessment of pretransplant cardiovascular risk.

Cardiac computed tomography angiography (64–320 slice and dual-source) is a highly sensitive tool for evaluating symptomatic patients with low-intermediate pre-test probability of obstructive CAD[56,57]. However, this modality has not been studied in patients with significant kidney disease, and its accuracy may be limited in this population due to a high burden of calcified coronary atherosclerosis. Further, safety may be limited by the attendant exposure to iodinated contrast.

Use and Efficacy of Angiography and Revascularization in ESRD Patients

Coronary angiography remains the gold standard modality for detecting CAD. Despite the imperfect performance of non-invasive testing described above, commonly suggested algorithms for cardiac evaluation of asymptomatic kidney transplant candidates reserve coronary angiography for patients with abnormal non-invasive testing[43,44,58]. The rationale for non-invasive testing prior to angiography relates to concerns for procedure-related risks and costs. Contrast-induced nephropathy has been reported to complicate angiography in 2%–50% of samples depending on case definition and patient mix, with increased risk associated with chronic kidney disease, congestive heart failure, diabetes, advanced age, and intravascular volume depletion[59–62].

Two recent randomized trials failed to support benefit of revascularization over contemporary medical management in stable general population samples, including patients awaiting major vascular surgery[63, 64], although the relevance of these findings to ESRD patients is not known. There are limited direct data on the efficacy of coronary revascularization in ESRD patients. In 1992, Manske et al randomly assigned 31 insulin-dependent diabetic transplant candidates with CAD (>75% stenosis) to revascularization or medical therapy with a calcium channel blocker and aspirin[65]. Ultimately, 10 of 13 medically managed and 2 of 13 revascularized patients reached the primary endpoint of unstable angina, myocardial infarction, or cardiac death. Contemporary relevance of these findings is limited by the small study sample size, high event rate among the medically managed group, and subsequent advances in “standard” medical management of CAD including angiotensin-converting enzyme inhibitors and statins.

Several recent observational studies have reported outcomes after revascularization in selected samples of potential transplant candidates. In a study of 300 patients who underwent multimodality non-invasive testing as part of the candidate evaluation at one center, crude survival was not different in patients who underwent revascularization compared to those who underwent angiography without revascularization or no angiography, although there was suggestion of a benefit of revascularization in the subset of 34 patients found to have obstructive CAD (15% versus 52% mortality)[21]. Hage et al described 3,698 patients evaluated for kidney transplant at a single center in 2001–2004. MPS was performed in 60% and 7% of the sample subsequently underwent coronary angiography. The presence and severity of CAD on angiography was not predictive of survival, and coronary revascularization was only associated with survival in patients with three-vessel CAD20. The relatively low use of coronary interventions after pre-transplant cardiac evaluation is also motivating scrutiny of the clinical and cost effectiveness of pre-transplant cardiac evaluation as currently applied. Several single center observational and a registry study have found that only 2.9%–9.5% of patients who receive pretransplant cardiac testing proceed to angioplasty or surgical bypass[21,31,43,66,67].

The best method of revascularization in patients with advanced kidney disease is controversial. A retrospective study of dialysis patients captured in the United States Renal Data System (USRDS) prior to the wide-spread use of drug-eluting stents (DES) suggested a slight long-

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term benefit of surgical bypass over percutaneous intervention. However, these data are limited by the retrospective design and the inherent risk for procedure referral bias based on coronary anatomy and patient characteristics68. An updated analysis of USRDS data from 2003–2005 by the same authors including patients treated with DES found superior 12-month, unadjusted post-procedure survival in dialysis patients who received DES (69.7%) compared to bypass (66.6%) or non-DES (63.6%)69. However, unadjusted 36-month survival favored bypass over DES (42.0% versus 38.1%), especially among patients who received an internal mammary artery bypass conduit. In multivariable regression, there was no significant difference in overall adjusted mortality with DES versus bypass, although non-DES was associated with higher adjusted mortality compared to surgery. These data highlight the relatively grave prognosis faced by hemodialysis patients who undergo cardiac bypass surgery compared to mean five-year survival estimates after bypass in the general population of 85%–90%70. Current guidelines do not consider the degree of kidney disease in recommendations for angioplasty and bypass except that the presence of significant kidney disease is a factor in risk prediction models for perioperative mortality with bypass surgery70.

Current Practice Variations and Consensus-Based Guidelines

Uncertainties regarding the clinical implications of test results and the impact of revascularization have lead to practice variation in pretransplant cardiac evaluation. In a 1993 survey of directors at OPTN-participating centers, noninvasive stress testing was reported as the most common first approach to cardiac evaluation of asymptomatic patients, prompted by diabetes at 86% of responding centers, age (mean threshold 52 years) at 67%, and risk factor burden at 68%71. Notable minorities of centers advocated first-line angiography for patients with diabetes (15%), older age (7%; mean threshold 57 yrs) or multiple risk factors (8%). A subsequent survey of OPTN centers found that 8% of programs reported use of cardiac testing for all deceased-donor transplant candidates whereas 18% did not routinely order cardiac evaluation for any asymptomatic patient group72. Cardiac re-evaluation policies among listed candidates appear equally variable. In a survey of 68 centers in 2005, 51% of program representatives indicated reliance on the initial cardiac evaluation and cardiac history, 7% used American College of Cardiology/American Heart Association (ACC/AHA) criteria for non-cardiac surgery in the general population to guide cardiac revaluation, and 32% applied a combination of ACC/AHA criteria, the initial cardiac evaluation and cardiac history73.

Complementary to survey-based studies, a retrospective study of the USRDS registry used billing claims as measures of cardiac evaluation services in Medicare beneficiaries transplanted in 1991–2004[67]. Forty-six percent of the sample received non-invasive stress testing or angiography at some time before transplant (65% of high risk - defined as diabetes, prior ischemic heart disease, or ≥2 other coronary risk factors, and 20% of “lower risk”). There was substantial heterogeneity in cardiac evaluation frequency according to patient-level factors even within risk groups. After adjustment for patient traits and consistent within risk profile-stratified samples, transplantation without cardiac evaluation was also more likely for African American persons, women, and patients in certain geographic regions.

Several national organizations have sponsored consensus-based guidelines in efforts to standardize cardiac evaluation practices in the pretransplant and general surgical patient (Table 3)74–76. However, differences in recommendations can lead to disparate conclusions on the appropriateness of cardiac evaluation for the individual patient. A recent study considered the recommended frequencies of cardiac evaluation that would result from application of these guidelines to 328 patients referred for transplant evaluation at one center in 2004–2007[77]. Recommended cardiac evaluation based on the clinical characteristics of the sample ranged from 19% with application of ACC/AHA guidelines for noncardiac surgery in the general

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population to 94% with use of American Society of Transplantation (AST) guidelines for the evaluation of kidney transplant candidates.

An argument that "periodic cardiac surveillance testing after waitlist may be unnecessary" is offered by a prospective, observational study of 604 patients on the kidney transplant waitlist in British Columbia in 1998–2001. The reference cardiac surveillance guideline was specified as: a) among patients with normal cardiac evaluation at listing – annual testing in those with diabetes, every two years in those with ischemic heart disease or peripheral vascular disease, or every three years in others; b) among patient revascularized as part of listing process – annual testing after percutaneous revascularization and every three years after coronary artery bypass grafting. Surveillance based on ongoing clinical assessment resulted in fewer investigations (n=171) than suggested by guidelines (n=503) over a mean period of mean follow-up of 3.7 ± 1.8 years[78]. There was no difference in total cardiovascular event rates after listing among subsets who did receive the recommended frequency of investigations (99 per 1000-person years) and those who did not (67 per 1000-person years).

Biomarkers for Cardiac Risk Assessment in Transplant Candidates

Several biomarkers, namely the cardiac troponins (cTn), have been proposed as tools in the cardiac evaluation of ESRD patients. The kidneys participate in clearance of cTnT but the source of elevations, even in dialysis patients, appears to be cardiac. While a dynamic rise and fall in cTn with appropriate clinical signs or symptoms is suggestive of acute coronary syndromes, persistent elevations in cTn may reflect other forms of cardiac injury such as strain from hypertension, volume overload or left ventricular hypertrophy that portend worse prognosis[79]. Risk stratification of asymptomatic patients with biomarkers is distinct from, but complementary to, the task of diagnosing acute coronary syndromes. A number of studies have shown consistent associations of elevated levels of cTnT isoforms with all-cause and cardiac death risk in asymptomatic ESRD patients. In a recent meta-analysis of 28 studies in this patient population, cTnT >0.10 ng/ml was associated with more than doubling of the mortality experienced by patients with lower cTnT levels (pooled RR 2.62, 95% CI 2.17–3.20)80. Risk in relation to cTnI has been more heterogeneous, and may reflect lack of assay standardization and/or use of a broader range of cut-points.

The Food and Drug Administration approved the measurement of cTnT for mortality prediction in persons with chronic renal failure in 2004, but use of this biomarker is not yet adopted in the clinical practice guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI). Putative applications of cardiac biomarkers in potential kidney transplant candidates include risk stratification within protocols for initial disease screening and surveillance after listing. Two recent studies examined cTnT among patients referred for kidney transplant candidates in relation to subsequent death (Table 4). In a cohort study of 144 patients evaluated for transplant candidacy and followed for vital status over an average of 2.3 years, Sharma et al found that concomitant elevation in cTnT >0.06 ng/ml and ischemia-modified albumin >95 KU/L was associated with seven times the odds of death after adjustment for multiple factors including severe CAD and positive DSE, although the individual markers were not independently associated with mortality[81]. Hickson et al. studied cTnT at evaluation in relation to transplant-censored mortality among 644 potential candidates, and observed a 64% increase in the adjusted relative risk of death with each increment in cTnT level according to the cutpoints: <0.01, 0.01–0.03, 0.04–0.09, and ≥0.10 ng/ml[22]. A recent prospective cohort study found correlations of cTnT with death among stable transplant recipients, estimating 2.7-times the mortality over an average of 3.8 years follow-up with cTnT ≥0.03 versus <0.01[82]. Although intriguing, it is currently not known how cTn may be rationally applied to direct use of more expensive or invasive diagnostic testing such as MPS, DSE or angiography in practice.

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Other Forms of Heart Disease in ESRD Patients

In addition to CAD, other forms of cardiovascular disease are common among kidney transplant candidates and bear important relationships with mortality. Perhaps the best studied of these is cardiomyopathy with or without clinical heart failure. Two reports from one large center using stress single photon emission computed tomography (SPECT) in potential candidates meeting AST criteria for pretransplant ischemia evaluation found left ventricular systolic dysfunction (LVSD), defined as left ventricular ejection fraction (LVEF) ≤40%–45%, in 16%–18%83,84. The majority (61–63%) of these patients did not have evidence of ischemia by perfusion imaging, suggesting nonischemic etiologies. Of note, these studies were retrospective and included patients with incidentally detected LVSD. Since an unspecified number of patients with prior diagnoses of heart failure were excluded and SPECT was performed in a selected 50–60% of patients meeting AST criteria, the prevalence of LVSD in the full cohort of potential candidates is not known. Based on Medicare billing claims as measures of clinical diagnoses in a recent USRDS cohort, the adjusted incidence of new-onsetheart failure was estimated as 7%, 12%, and 32% at 6, 12, and 36 months after listing, respectively6.

The presence of LVSD has prognostic implications after renal transplantation, independent of CAD and ischemia. In a single center study, median survival in patients with LVEF <40% was 49 months compared with 72 months in patients with higher LVEF; after adjustment for ischemia and other risk factors, the relative risk of mortality increased by 2.5% for each percent decline in LVEF84. Cumulative mortality for patients with LVSD awaiting transplantation was almost 6-fold higher than the reported mortality for patients with similar degrees of LVSD in the general population85. In a study of transplant recipients from the same center, LVSD was associated with 4.8-times the risk of cardiac death, 2-times the risk of all-cause mortality, and 1.8-times the risk of cardiac complications compared to patients with normal cardiac function[83]. A registry-based study also found that new-onset heart failure after transplant is a potent predictor of subsequent death (adjusted HR 2.6, 95% CI 2.4–2.9)[6].

Because of the serious prognostic implications of heart failure, many patients with LVSD are not considered candidates for renal transplantation. However, reversal of some cases of cardiac dysfunction after transplant has been documented in case reports and a small but growing body of prospective, serial echocardiographic studies86–89. In the largest study, which included 103 recipients at a single center, mean LVEF improved from 32% pretransplant to 52% one year after transplant[89]. While these data are impressive, it is important to note that 50% of these patients were also found to have CAD prior to transplantation and 90% of these patients underwent subsequent revascularization. In addition, most of the patients in this study were taking cardioprotective medications (beta-blockers, angiotensin-converting enzyme inhibitors, Angiotensin-2 receptor blockers), whereas other studies have reported less use of these medications in transplant candidates with LVSD. Use of devices such as implantable cardioverter-defibrillators have not been studied in this population, which is important since LVSD may contribute to the high rate of sudden cardiac death afflicting ESRD populations[90].

Conclusions

Defining best practices for pretransplant cardiac evaluation based on current evidence is challenging.. DSE, a non-invasive, relatively inexpensive tool with minimal risk for nephrotoxicity, is an attractive method for cardiac evaluation in renal transplant candidates. Although the accuracy of DSE for detection of angiographic CAD is imperfect in this population, with specificity (71–95%) appearing better than sensitivity (37–95%), both DSE and MPS offer some prognostic value for the risk of future cardiac events and mortality.

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Incorporation of clinical risk profiles and possibly biomarkers may guide more selective testing and hence may improve clinical and cost effectiveness, but further study is required for broad implementation. As many plaque ruptures producing myocardial infarction are not localized to sites of angiographic stenosis and angiography poses risks such as contrast nephropathy, the role and best methods of pretransplant revascularization of CAD in ESRD patients are also controversial. Further, the extent of revascularization and the subsequent impact of revascularization on short and long term cardiovascular risk are not well-defined, leading to uncertainty about the timing and frequency of diagnostic testing and interventions. Nevertheless, given the prevalence of CAD and its contribution to morbidity and mortality before and after kidney transplantation, focused screening among patients at highest risk (e.g. known multi-vessel disease, multiple risk factors, or findings suggestive of prior infarction) should be pursued. Other forms of heart disease such as cardiomyopathy with and without heart failure also have important prognostic implications in this population and warrant consideration as potential targets of evaluation protocols. In all cases, risk factor reduction for primary and secondary prevention of ischemic heart disease, is indicated. Broader prospective data, ideally from clinical trials, is urgently needed to strengthen the evidence base for pretransplant cardiac evaluation practices.

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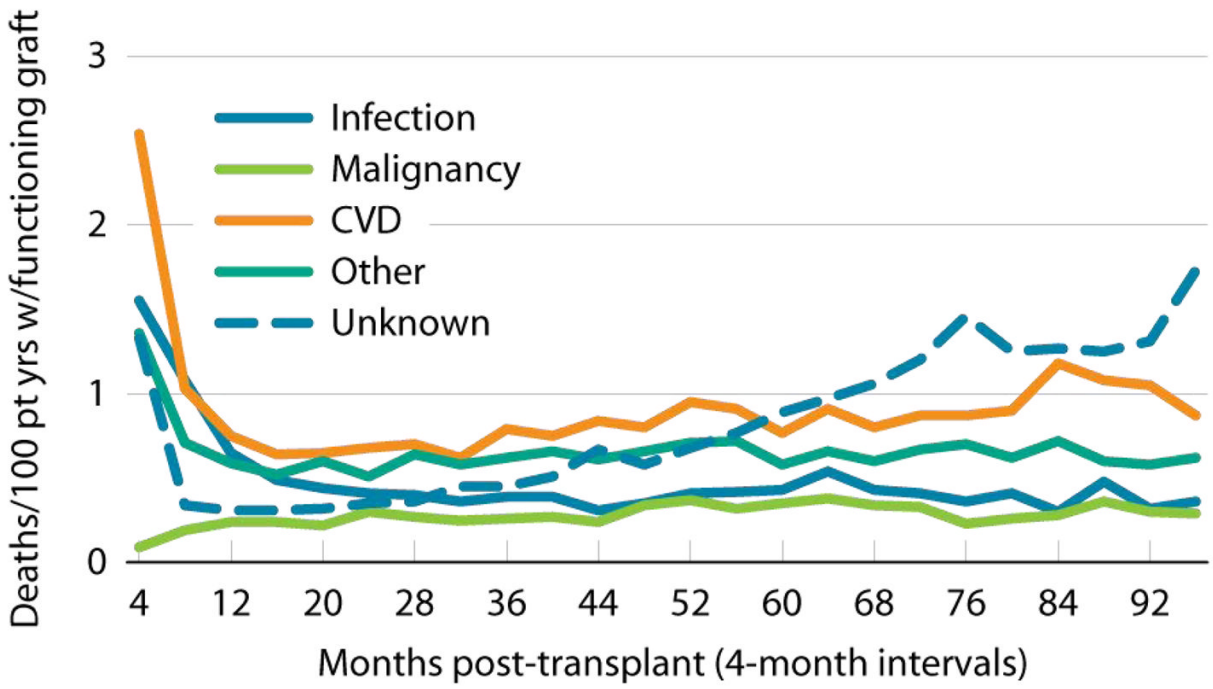

Figure 1. Cardiovascular disease is the leading cause of death with graft function after kidney transplantation

First-time, kidney-only transplant recipients, age 18 & older & transplanted 1997–2006, who died with a functioning graft (N=14,169). Cause of death obtained from OPTN when available, otherwise taken from ESRD Death Notification form. From the United States Renal Data System 2008 Annual Data Report[8].

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Table 1

Recent descriptions of the outcome implications of angiographic coronary artery disease in ESRD patients including transplant candidates

Reference	Participants and Design	Selection Criteria for Angiography	Angiographic Definition of CAD	Estimated CAD Prevalence	Associations of CAD with Clinical Events
De Lima et al, 2003[16]	• 106 patients presenting for transplant evaluation at one center, deemed at moderate or high coronary risk (1998–2002). • Prospective	• Moderate-risk: Age ≥50 years • High-risk: History of diabetes, MI, angina, stroke, LV dysfunction, peripheral vascular disease. • Willing to consent	• ≥70% Stenosis in one or more epicardial arteries by visual estimation. • Evaluation by 2 observers	• CAD present in 42% (44/106) • 1, 2, 3 vessel disease in 19%, 16%, and 7% of the sample, respectively	• MACE, defined as: sudden death, MI, arrhythmia, heart failure, unstable angina, revascularization • Unadjusted probability of reaching endpoint at 1,2 and 4 years was higher with angiographic CAD (P<0.001): 13%, 39%, 46% versus 2%, 6%, 6% in absence of CAD
Sharma, et al, 2005[15]	• 125 consecutive patients referred for renal transplant evaluation.	• Age >18 years • Free of severe aortic stenosis, unstable angina • Willing to consent	• Severity by degree of luminal narrowing: Mild, <50%; Moderate, 50–70%; Severe, >70% • Evaluation by 2 observers	• CAD present in 64% (80/125) • Severe, moderate and mild in 29%, 14% and 21% of the sample	• Unadjusted survival at two-years was significantly lower among those with compared to without CAD (85% versus 100%, P=0.005)
Charytan et al, 2007[17]	• 67 prevalent hemodialysis patients (1998), subset of a larger study (n=224) • Prospective	• Free of ischemic symptoms at enrollment • Free of coronary events within 4 weeks • No coronary angiography within prior 2 yrs • Willing to consent	• >50% Narrowing compared to adjacent normal segment by digital calipers • Evaluation by 2 observers	• CAD in 42% (28/67), including involvement of proximal third of an epicardial vessel in 28.5% • Of 28 subjects with CAD, 75% had multivessel and 68% had proximal lesions	• Over median 2.7 years observation, the presence of any CAD was associated with increased risk of death • Only proximal CAD was associated with mortality in adjusted analyses (aHR 3.14, 95% CI 1.34–7.33)
Gowdak, et al, 2007[18]	• 301 patients referred for transplant evaluation and deemed at high coronary risk	• Inclusion criteria: History of diabetes, prior cardiovascular disease (MI, unstable angina, stroke, left ventricular dysfunction, or	• ≥70% luminal reduction in one or more epicardial arteries • Evaluation by 2 observers	• Significant CAD in 45% (136/301)	• MACE, defined as: MI, unstable angina, sudden death, unplanned coronary or peripheral arterial revascularization, stroke, or heart failure • Over median 1.8 years observation, crude

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Reference	Participants and Design	Selection Criteria for Angiography	Angiographic Definition of CAD	Estimated CAD Prevalence	Associations of CAD with Clinical Events
		extracardiac atherosclerosis), or age >50 years • Willing to consent			incidence of MACE was higher in those with CAD (45% *vs* 18%, P<0.001)
Gowdak, et al, 2007[19]	• 288 patients referred for transplant evaluation. Portion of the cohort in[18]	• High clinical risk, as defined in[18]	• ≥70% luminal reduction in one or more epicardial arteries • Evaluation by 2 observers	• Significant CAD in 43% (124/288)	• MACE as defined in [18] • CAD was associated with significantly higher crude relative risk of MACE among non-diabetic patients (HR 4.3, 95% CI 2.4–7.9, P<0.001) • No significant association of CAD with MACE in diabetic patients
Hage et al, 2007[20]	• 260 patients studied by angiography from a cohort of 3698 referred for transplant evaluation at one center (2001–2004). • Retrospective	• Positive stress myocardial perfusion imaging, known CAD, or discretion of Cardiologist	• >50% lumen diameter narrowing in any of 3 major coronary arteries or major branches. Left-main considered equivalent to 2-vessel disease • Results obtained from clinical reports	• CAD in 62% (162/260) • 1, 2, 3 vessel disease in 16%, 13%, and 33% of the sample submitted to angiography, respectively • 36% (94/260) of the angiography group underwent revascularization	• Presence and severity of CAD was not associated with crude survival among those who underwent angiography: 2-year survival 80%, 88%, 86% and 78% for 0, 1, 2, 3-vessel disease (P=0.6)
Patel et al, 2008[21]	• 99 patients studied by angiography from a cohort of 300 referred for KT evaluation at one center (2002–2005). • Retrospective	• Angiography suggested if: Age >50 yrs, ESRD due to diabetes, symptomatic ischemic heart disease, or positive non-invasive testing • Final selection based on clinical judgment and patient preference	• Obstructive, >75% • Non-obstructive, Stenosis present but ≤75%	• CAD in 57.6% (57/99) • Obstructive in 34.3% (34/99), including 1-, 2-, and 3-vessel disease in 13%, 15%, and 6% of the sample, respectively • Non-obstructive in 23.2% (23/99) • 17% (17/99) of the angiography group underwent revascularization	• No difference in crude four-year survival in patients found to have CAD and revascularized, compared to those who underwent angiography without revascularization, or those not studied by angiography (P=0.7).

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Reference	Participants and Design	Selection Criteria for Angiography	Angiographic Definition of CAD	Estimated CAD Prevalence	Associations of CAD with Clinical Events
Hickson, et al, 2008[22]	• 134 patients studied by angiography from a cohort of 644 referred for KT evaluation at one center (2004–2006) • Retrospective	• Angiography performed if dobutamine stress echo was positive Cardiologist recommended	• Severity by highest degree of stenosis of single major epidcaridal arteries: Mild, <50%; Moderate, 50–70%; Severe, >70% %	• CAD present in 81% (119/131) of those studied by angiography • Severe, moderate and mild in 56%, 20% and 25% of the angiography sample • 6.2% (40/644) of the full cohort underwent revascularization before listing	• Over median 6 months observation, the severity of CAD by angiography was not significantly associated with mortality in the full cohort (P=0.2)

aHR, adjusted hazards ratio; CAD, coronary artery disease; CI, confidence interval; KT, kidney transplant; MACE, major adverse cardiovascular events; MI, myocardial infarction

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Table 2

Advantages and disadvantages of available methods for detecting coronary artery disease.

Method	Advantages	Disadvantages
Myocardial Perfusion Study (MPS) • Exercise (E) *OR* • Pharmacologic (P) stress (adenosine, persantine or dobutamine)	• Non-invasive • Assesses ischemic burden and left ventricular function • Has prognostic value • Adenosine/persantine MPS preferred in patients with left bundle branch block • Assesses of functional status (E)	• Confers exposure to ionizing radiation • Attenuation artifacts (breast, bowel, motion) may limit accuracy • Requires delayed imaging to assess for myocardial viability • (P) form does not assess functional capacity • Expensive
Stress Echocardiography • Exercise (E) *OR* • Dobutamine (D) stress	• Non-invasive • Higher specificity compared to MPS • No exposure to ionizing radiation • Assesses ischemic burden, left ventricular function, and valvular function • Prognostic value demonstrated in some studies among patients with advanced kidney failure • Assessment of myocardial viability may be obtained with low dose dobutamine at time of scan • Assesses functional status (E)	• Poor image quality with some comorbidities (e.g., obesity, chronic obstructive pulmonary disease) • Peak exercise images may be technically challenging to obtain • Dobutamine side-effects may be intolerable (D) (e.g., arrhythmias, hypotension, hypertension, stress cardiomyopathy)
Cardiac Computed Tomography (CT) • With Coronary Artery Calcium (CAC) scoring • With CT Angiography	• Rapid, non-invasive means of defining cardiac and extracardiac anatomy • Retrospective gating protocols allow assessment of left ventricular function • Prospective gating protocols and other dose sparing techniques reduce radiation exposure	• Confers exposure to ionizing radiation • Confers exposure to iodinated contrast for angiography • Prognostic value of CAC scoring is controversial and CT angiography is untested in patients with advanced kidney failure • Image quality may be limited in patients with cardiac arrhythmias, poor heart rate control, advanced coronary calcification, and obesity • Does not assess functional status or ischemia
Invasive Coronary Angiography	• Gold standard for identifying obstructive coronary artery disease • Percutaneous coronary intervention may be performed at the time of angiography if needed • Measures of cardiac and valvular hemodynamics (e.g., left ventricular filling pressures) may be obtained	• Invasive and confers risks of major complications (e.g., vascular damage with major bleeding, arterial dissection, stroke, arrhythmia, myocardial infarction, death) • Confers exposure to radiation and iodinated contrast • Does not assess functional status, ischemia or viability • Expensive

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Table 3

Summary of current consensus-based guidelines for preoperative cardiac evaluation.

Organization and Target Population	Recommendations
American Society of Transplantation, Kidney Transplant Candidates[74]	**Clinical Practice Guidelines for the Evaluation of Renal Transplantation Candidates** • Assess CAD risk factors: age ≥45 years in men or ≥55 years in women, cigarette smoking, diabetes, hypertension, dyslipidemia, left ventricular hypertrophy • Aggressive risk factor modification for all candidates • "High-risk patients", defined as those with renal disease from diabetes, prior ischemia or ≥2 risk factors should have a cardiac stress test • Patients with positive stress tests should be studied by angiography for possible revascularization. • Patients with critical coronary lesions should undergo revascularization prior to transplant.
Kidney Disease Outcomes Quality Initiative (K/DOQI), Dialysis Patients on the Transplant Waitlist[75]	**Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients** • Annual performance of non-invasive stress tests for dialysis patients on the kidney transplant waiting list who have diabetes, known coronary artery disease or ≥2 traditional risk factors
American College of Cardiology/American Heart Association (ACC/AHA), General Patients Preparing for Noncardiac Surgery[76]	**Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery** • The decision to perform CE is based on surgery-specific risk, the patient's functional capacity and the patient's risk factors. • Patients with intermediate clinical predictors (angina pectoris, prior myocardial infarction, compensated or prior congestive heart failure, diabetes, and renal insufficiency), and moderate or excellent functional capacity >4 metabolic equivalents, should only undergo noninvasive testing if the surgical procedure is high risk

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Table 4

Summary of recent studies associations of cardiac biomarkers with clinical outcomes in kidney transplant candidates and recipients.

Authors, Year	Design & Data Source	Participants and Selection	Study Measures & Distributions	Clinical Outcomes	Associations/Effect Sizes
Sharma et al., 2006[81]	Prospective cohort, Medical records and phone calls for follow-up	• 114 evaluated for KT candidacy at one center in United Kingdom (January 2002–December 2003) • Free of unstable angina or severe aortic stenosis	• Single cTnT levels. Distribution ≥0.06 ng/ml, 45% • Single ischemia-modified albumin (IMA) levels. Distribution >95 KU/L, 40% • cTnT and IMA were both elevated in 33%	• Death over observation (multivariate modeling by logistic regression, and thus not time-dependent.) • After mean 2.3 yr follow-up, 15.8% died (55.6% of deaths were cardiovascular)	• Combined cTnT and IMA elevations significantly associated with 7-times the odds of death (aOR 7.12, 95% CI 4.14–10.12, P=0.005) compared to normal levels of both markers, after adjustment including severe CAD and positive DSE • cTnT and IMA individually associated with mortality in bivariate but not multivariate models
Connolly et al. 2008[82]	Prospective cohort, Registry mortality data and phone calls for follow-up	Convenience sample of 379 with functioning KT at two Irish hospitals, ≥3 mo post-KT and "well" at enrollment (June 2000–December 2002)	• Single cTnT level • Distribution, (ng/ml): <0.01, 91.7%; 0.02, 2.7%; ≥0.03, 5.6%	• Death over observation • After median 3.8 yr follow-up, 16.4% died (39% of deaths were cardiovascular)	• cTnT ≥0.03 versus <0.01 significantly associated with 2.7-times the risk of death (aHR 2.70, 95% CI 1.20–6.06, P=0.02) after adjustment including eGFR and C-reactive protein levels
Hickson et al, 2008[22]	Retrospective cohort, Clinical records of one center	644 evaluated for KT candidacy at one Midwestern center (September 2004–December 2006)	• Single cTnT level analyzed – most recent from initial evaluation or annual follow-up if listed • Distribution within 4 levels (ng/ml): <0.01, 39%; 0.01–0.03, 29%; 0.04–0.09, 20%; ≥0.10, 13%	• Death, censored at KT or December 2007. • After median 6.2 mo follow-up, 5.4% died (33% of known causes were cardiovascular), 58.5% received KT	• Each increment in cTnT level (as defined) significantly associated with 64% increase in death risk (aHR 1.64, 95% CI 1.07–2.51, P=0.02)

aHR, adjusted hazards ratio; aOR, adjusted odds ratio; CAD, coronary artery disease; CI, confidence interval; cTnT, cardiac troponin T; DSE, dobutamine stress echocardiography; KT, kidney transplant

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Box 1

Evidence regarding pretransplant evaluation for coronary heart disease considered according to the World Health Organization principles for screening (1968).

Public Health Impact

- The condition should be an important health problem[1]
  - Cardiovascular disease is the most common cause of death with graft function at all times after transplant[8].
  - Reports of angiography in patients undergoing transplant evaluation document CAD in 42%–81%[15–22].

Natural History of Disease includes a Latent Stage for Detection and Intervention

- There should be a latent stage of the disease[1]
- The natural history of the disease should be adequately understood[1]
  - Some observational studies report higher unadjusted risk of all-cause mortality and major cardiovascular events in potential transplant candidates with angiographic CAD[15,16,18].
  - Other investigations identified risk only certain patient sub-groups, such as those with proximal CAD[17] or with non-diabetic renal failure[19].
  - Still other recent studies have found no associations of CAD with subsequent survival in this population[20–22].
  - General population studies have shown that a coronary artery does not have to contain an angiographic stenosis to suddenly occlude and produce myocardial infarction[23].

Availability of Testing

- There should be a test or examination for the condition[1]
- The test should be acceptable to the population[1]
- Case-finding should be a continuous process, not just a “once and for all” project[1] – i.e., there is a role for surveillance
  - “Gold-standard” angiography poses risks including contrast nephropathy[59–62] and is more expensive than non-invasive testing.
  - Non-invasive testing for CAD includes MPS, stress echocardiography and cardiac computed tomographic angiography.
  - Non-invasive tests for CAD have imperfect sensitivity and specificity in patients with renal failure, or in the case of tomographic angiography, have not been evaluated in this population.
  - Reported sensitivities and specificities of non-invasive modalities for the detection of angiographic CAD in ESRD patients are 37–90% and 40–90%, respectively for MPS[26–29] and 37–95% and 71–95%, respectively, for DSE[15,35–39].
  - One single-center observational study found that cardiac surveillance on the waitlist based on ongoing clinical assessment resulted in fewer investigations than suggested by guidelines and no difference in total cardiovascular event rates[78].

Availability of Treatment

- There should be a treatment for the condition[1]
- There should be an agreed policy on who to treat[1]
- Facilities for diagnosis and treatment should be available[1]
  - There are limited direct data on the efficacy of coronary revascularization in ESRD patients. A 1992 trial in 31 insulin-dependent diabetic transplant candidates found benefit with

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	revascularization compared to medical therapy with a calcium channel blocker and aspirin[65], but contemporary relevance of these findings is limited by the small study sample size, high event rate among the medically-managed group, and subsequent advances in "standard" medical management of CAD.
Cost-effectiveness	
• The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole[1]	
– Insufficient data currently available.	
– However, the relatively low use of coronary interventions after pretransplant cardiac evaluation questions the cost effectiveness of pretransplant cardiac evaluation as currently applied. Several single center observational and a registry study have found that only 2.9%–9.5% of patients who receive pre-transplant cardiac testing proceed to angioplasty or surgical bypass[21,31,43,66,67]	

Abbreviations: CAD, coronary artery disease; DSE, dobutamine stress echocardiography; ESRD, end-stage renal disease; MPS, myocardial perfusion studies