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Cardiac risk assessment for end-stage renal disease patients on the renal transplant waiting list

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ABSTRACT

Cardiovascular disease is a leading cause of morbidity and mortality and is becoming more prevalent as the population ages and risk factors increase. This is most apparent in the end-stage renal disease (ESRD) patient population. In part, this is due to cofactors such as diabetes and hypertension commonly predisposing to progressive renal disease, as well as being a direct consequence of having renal failure. Of all major organ failures, kidney failure is the most likely to be managed chronically using renal replacement therapy and, ultimately, transplant. However, lack of transplant organs and a large renal failure cohort means waiting lists are often quite long and may extend to 5–10 years. Due to the cardiac risk factors inherent in patients awaiting transplant, many succumb to cardiac issues while waiting and present an increased per-procedural cardiac risk that extends into the post-transplant period. We aim to review the epidemiology of coronary artery disease in this population and the etiology as it relates to ESRD and its associated co-factors. We also will review the current approaches, recommendations and evidence for management of these patients as it relates to transplant waiting lists before and after the surgery. Recommendations on how to best manage patients in this cohort revolve around the available evidence and are best customized to the institution and the structure of the program. It is not clear whether the revascularization of patients without symptoms and with a good functional status yields any improvement in outcomes. Therefore, each individual case should be considered based on the risk factors, symptoms and functional status, and approached as part of a multi-disciplinary assessment program.

Keywords: cardiovascular risk, coronary artery disease, end-stage renal disease, pre-operative evaluation, renal transplant

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among end-stage renal disease (ESRD) patients, both before and after transplantation. Estimates of the cumulative incidence of myocardial infarction (MI) based on Medicare billing claims have ranged from 8.7% to 16.7% by 3 years after kidney transplant listing and from 4.7% to 11.1% after kidney transplantation [1].

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According to the Organ Procurement and Transplant Network records, nearly 85 000 candidates were on the waiting list for kidney transplantation in 2010, whereas approximately 17 700 kidney transplants (including 828 kidney–pancreas transplantations) were performed [2]. In 2011, 62% of kidney transplantation candidates were >50 years of age compared with 28.7% of kidney transplantation candidates in 1991. The incidence of cardiac disease, already elevated in patients with ESRD, would be further amplified as the transplant candidate population ages.

Coronary artery disease in the diabetic population

Coronary artery diseases (CADs), identified on angiography or by hemodynamic assessment tests, in aggregate make up the most common cause of death in patients with functioning allografts at all times after kidney transplantation, accounting for 30% of mortality overall. The highest rates are in the peri-transplantation period [3].

The Framingham study [4] followed patients with diabetes mellitus (DM) for 20 years and found that these patients had a 2- to 3-fold increased risk for CAD compared with the general population. In addition, when researchers looked at the relationship between glycosylated hemoglobin (HbA1c) and the risk for CAD, they found a statistically significant association between HbA1c and CAD for women [5]. An increase of HbA1c by 1% increased the relative odds of CAD by 1.39-fold [95% confidence interval (CI) 1.06–1.83].

Renal insufficiency is very common in diabetics and ∼35% of Type 1 diabetics will have diabetic nephropathy. Also, about 25% of the patients entering ESRD programs in USA have DM. These numbers show how diabetic nephropathy and diabetic vasculopathy constitute a major medical problem in society today [6].

In patients beginning hemodialysis, the incidence of Type 2 DM has been found to be about 35%. Ramanathan *et al.* [3] evaluated 97 asymptomatic Types 1 and 2 DM kidney and kidney–pancreas transplant candidates. About 33% of Type 1 and 48% of Type 2 DM patients had significant stenosis (≥70%) in one or more coronary arteries. In addition, body mass index >25, smoking history and older age were associated with a higher incidence of CAD.

A series of studies in the 1970–90s [7–9] examined the prevalence of angiographic CAD in ESRD patients, particularly in diabetic patients. Benett *et al.* [7] examined 11 asymptomatic diabetic ESRD patients who voluntarily underwent coronary angiography and found multivessel CAD in all patients. Weinrauch *et al.* [8] evaluated 21 Type 1 diabetic ESRD patients with no clinical or electrocardiographic evidence of CAD and found that about 50% of these patients had CAD, and 38% had 'significant' CAD on coronary angiography. These studies highlight the fact that diabetic patients, particularly those with ESRD, can have significant CAD without any symptoms [10].

As a result of this, these patients can have significant multivessel CAD prior to the occurrence of any symptoms, which can delay recognition and treatment of CAD and worsen outcomes during and after kidney transplantation. In addition, there are several risk factors that contribute to the increase risk of CAD in diabetics, including but not limited to hypertension, obesity, smoking and dyslipidemia. In addition to CAD, diabetic patients are also at a higher risk for myocardial dysfunction leading to heart failure (diabetic cardiomyopathy) [11]. Factors contributing to this include the presence of severe CAD, long-standing hypertension, microvascular disease and autonomic neuropathy [11].

The American College of Cardiology (ACC)/American Heart Association (AHA) have published recommendations for the evaluation of CVD in diabetic patients [12]. Prognostic information from stress testing can be derived in asymptomatic diabetic patients with at least one additional risk factor including: age >35 years, duration of diabetes (>10 years for Type 2 and >15 years for Type 1), microvascular disease (retinopathy and nephropathy including microalbuminuria), peripheral vascular disease and autonomic neuropathy.

Risk of CAD in chronic kidney disease and ESRD patients

Similar to DM, renal insufficiency is also an independent risk factor for CAD [1, 13]. The US Renal Data System collects registry data on renal transplant recipients. Medicare billing data and death records from 35 847 adult renal allograft recipients from 1995 to 2000 revealed high incidence of post-renal transplant MI with a cumulative incidence of 4.3, 5.6 and 11% at 6, 12 and 36 months, respectively, after kidney transplant. Older age, pre-transplant DM, peripheral vascular disease and prior MI in the recipients, older or deceased donors and delayed graft function were all determined to increase risk for MI. In addition to the higher risk for MI in the ESRD/chronic kidney disease (CKD) population, these patients also have worse outcomes following MI. A single-center study found that patients with even mild CKD experienced a >2-fold risk for death after an MI as compared with those with normal renal function [14, 15].

Kasiske *et al.* [16] analyzed Medicare data from 53 297 patients on the renal transplant list and found that the risk for acute myocardial infarction (AMI) was higher in patients on the waiting list as compared with after renal transplantation. Despite extensive pretransplant screening and revascularization, the risk for AMI is the highest in the immediate post-transplant period, likely due to the risks of recent surgery, immunosuppression and the prevalence of subclinical CAD.

Small angiographic studies on asymptomatic CKD patients have revealed significant CAD in several of these patients. Ohtake *et al.* [17] found angiographically significant CAD in 53% of 30 asymptomatic advanced CKD patients at the initiation of dialysis. They found that in this subgroup of patients, nuclear stress testing was ineffective in detecting hidden ischemia. They also found that DM was a significant independent predictor for CAD in these asymptomatic patients. Although it has been established that ESRD patients have a higher prevalence of CAD as compared with the general population, the correlation between these finding and actual clinical events is unclear. A majority of the studies have reported increased incidence of major adverse cardiac events (MACEs) and higher mortality in patients with angiographically significant CAD, although some have identified subgroups at a higher risk for MACE such as patients with more proximal CAD. However, as patients with significant CAD often undergo revascularization, it is difficult to accurately compare mortality and MACE in ESRD patients with and without significant CAD.

Proteinuria and risk for CAD

Proteinuria as a clinical predictor of CVD and its associated morbidity and mortality was studied early on in the diabetic population [18–20]. Its value was then expanded to nondiabetic

patients with hypertension and CKD. Studies showed that urinary albumin excretion rate (UAER) cut-off ranges >9.36–10.08 mg/24 h or the 90th percentile was associated with an elevated risk of CVD [21, 22]. Even in a healthy population, UAER >9.216 mg/24 h was associated with an increased risk of CVD [23, 24].

A higher urinary albumin concentration increased the risk of both cardiovascular and noncardiovascular death after adjustment for other well-recognized cardiovascular risk factors, with the increase being significantly higher for CVD mortality than for non-CVD mortality. A 2-fold increase in albuminuria from 5 to 10 mg/L or 20 to 40 mg/L was associated with a relative risk of 1.29 for cardiovascular mortality (95% CI 1.18–1.40) and 1.12 (95% CI 1.04—1.21) for noncardiovascular mortality [24].

Furthermore, Bello *et al.* [25] demonstrated that proteinuria at each stage of CKD conferred a higher risk of CVD complications measured by rates of peripheral vascular disease, coronary revascularization, heart failure or cerebrovascular events.

Although the pathophysiology behind albuminuria and its relation to CVD is not well known, it is hypothesized that microalbuminuria may reflect an inflammatory process with endothelial dysfunction leading to an increase in vascular permeability and an altered coagulable state [26–29]. The transcapillary escape of macromolecules that accelerate atherosclerosis such as albumin and lipoproteins in conjunction with changes in levels of Von Willebrand factor, fibrinogen, thrombomodulin and plasminogen activator inhibitor are thought to increase CVD [30, 31]. These studies suggest a role for proteinuria to risk-stratify patients with an elevated risk for CVD. For CKD patients who are on the renal transplant waitlist and are of intermediate CVD risk, proteinuria can be used to re-stratify them as low or high risk. In the general, this may help identify patients who are at an increased susceptibility to future CVD.

Peri-operative cardiac risk with renal transplant surgery

Several studies have identified indices to aid in cardiac risk stratification [32–35]. In respect to the intra-operative period, there are surgical and anesthetic factors that affect morbidity and mortality. The stress response to surgery has been well established and is characterized by an activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system. This hormonal response is typically negligible in the absence of exacerbating factors such as volume depletion, hypothermia or hypoxia. However, in major surgical procedures, this response produces a catabolic state with adaptive responses of tachycardia, hypertension, fluid retention and hypercoagulability to maintain cardiovascular homeostasis [36, 37]. Although this is an adaptive response to the stress of surgery, in excess it may be maladaptive in ESRD patients who have increased risk for cardiovascular complications at baseline and increased peri-operative mortality and morbidity [38–41].

In addition, the peri-operative management of fluid status can be complicated in ESRD patients. Intra-operatively, aggressive volume expansion is recommended at rates up to 30 mL/kg/h with a central venous pressure goal of 15 mmHg to optimize graft recovery. However, this may be poorly tolerated in transplant candidates who are already at risk of volume overload, acute respiratory failure and prolonged ventilation [42]. A study by De Gasperi *et al.* [43] found that a more conservative approach may be adequate in a select patient group with >50 years of age being the only significant risk factor.

These factors have led to the classification of renal transplant surgery as an intermediate to intermediate–high-risk surgery based on a peri-operative cardiac mortality of ~1.1% compared with aortic surgery with the highest cardiovascular mortality at 1.8%, and breast, dental, eye and gynecology surgery the lowest at 0.1% [44].

With the use of anesthetics, the stress response is blunted intra-operatively. In fact, it is well known that the major peri-operative hormonal response stressor is not the surgical procedure, but the anesthesia reversal and recovery [44]. This, along with improved anesthetic technique, is likely attributable to the low rate of intra-operative events compared with the high rate of post-operative cardiac morbidity and mortality [45, 46]. In renal transplantation, anesthetic use must take into account renal clearance, electrolyte imbalance and if applicable, cardiomyopathy. Select anesthetics have been shown to depress myocardial contractility and cardiac output leading to an increased risk of heart failure [47]. Although general anesthesia is generally performed, there have been several reports of regional anesthesia through epidural, spinal or a combination being employed to decrease hemodynamic fluctuation imposed by inhalation anesthetics [48, 49].

Furthermore, hyperkalemia, a common problem in ESRD patients, is combined with calcium deposition in the cardiac conduction system and can induce progressive arrhythmia including high grade heart blocks [50–52] during this stress response.

In conclusion, the surgical technique for renal transplantation has been well established with minimal surgical complications intra-operatively [53–57]. This can be attributed to the refined surgical and anesthetic techniques in a highly controlled environment with continuous hemodynamic monitoring. The peri-operative cardiac complications are mainly associated with the early post-operative period. Post-operatively, it is of utmost importance to maintain close hemodynamic monitoring with appropriate control of the stress response after reversal of the anesthetic through the proper opioid pain management.

Other cardiac disease in ESRD patients

In addition to the increased risk for CAD, patients with CKD are also at risk for other cardiovascular disorders, particularly left ventricular (LV) dysfunction. LV systolic dysfunction has been described in 16–18% of pre-renal transplant candidates in single-center studies using stress single-photon emission computed tomography [58, 59]. Of these patients, around 60% did not demonstrate any ischemia on stress perfusion testing, indicating that the etiology of the LV dysfunction was likely nonischemic. The incidence of new-onset heart failure was estimated at 7, 12 and 32% at 6, 12 and 36 months, respectively, after patients were listed for renal transplant from Medicare billing claims [60]. Reversal of cardiac dysfunction after transplant has been documented in small prospective echocardiographic studies [61–63]. Furthermore, patients with moderate ischemic LV dysfunction have similar post-transplant outcomes to those with preserved LV function.

Oxidative stress plays a key role in the pathophysiological process of CVD and LV dysfunction. The level of oxidative stress markers is known to increase as CKD progresses. A recent review article by Tabriziani *et al.* showed that successful kidney transplantation results in near normalization of the antioxidant status and lipid metabolism by

eliminating free radicals. This success is associated with both improved renal function, reduced cardiovascular complications and overall improved morbidity and mortality [64].

Recommendations

There are discrepancies between various national organizations regarding appropriate pre-transplant work-up as patients with ESRD have unique challenges associated with evaluation and management of CAD. Guidelines put forth by major societies include

- The ACC and AHA issued guidelines on peri-operative cardiovascular evaluation for noncardiac surgery and recommended no further testing in asymptomatic patients, with a functional capacity of >4 Metabolic Equivalent Tasks, regardless of the risk factors for CAD [65]. These guidelines, while appropriate for the general non-ESRD population, might not adequately estimate cardiac risk in the ESRD population as these patients can have significant CAD in the absence of symptoms. Moreover, these guidelines specifically focus on assessing short-term cardiac risk prior to elective surgery, whereas in ESRD patients on the transplant list long-term cardiac risks must also be considered as donor organ availability and the actual time of transplant can take anywhere from months to years.
- The European Renal Best Practices guidelines suggest that an initial resting ElectroCardioGram (ECG), a chest X-ray and a detailed physician exam are sufficient to enroll a candidate for transplant evaluation. Patient with increased risk due to older age, diabetes or a history of CVD would then be referred for standard exercise tolerance testing. Further cardiac investigation for CAD such as with noninvasive stress imaging can be done in patients with inconclusive exercise tolerance testing.
- The National Kidney Foundation (NKF) published the 'Clinical Practice Guidelines for CVD in Dialysis Patients' within the Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) which recommends more aggressive screening and treatment of CAD in the ESRD population [66] including screening echocardiogram, stress test and invasive studies as indicated.
- Similarly, the American Society of Transplantation (AST) also recommends a more aggressive approach to screening pre-renal transplant patients based on the presence of clinical risk factors [67].
- The Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient [68] recommends a more intermediate approach to cardiac testing based on the presence of clinical risk factors.

Friedman *et al.* [69] retrospectively studied a cohort of 204 pre-renal transplant candidates, of whom 87% underwent noninvasive cardiac testing and 3% underwent coronary angiography. Ischemic cardiac disease was identified in 10% ($n = 178$) of the total population. They retrospectively applied each of the major guidelines to this population and determined that while the ACC/AHA guidelines would recommend testing in only 20% of the cohort and would have identified 4 of the 10 (40%) patients who required revascularization, the KDOQI and AST guidelines would have identified all of the patients who subsequent to stress testing underwent revascularization. The Lisbon report resulted in an intermediate approach recommending testing in 68% of the population. What confounds the application of either of these guidelines further is the fact that it is unclear if revascularization in these patients results in any discernible survival benefit over medical therapy.

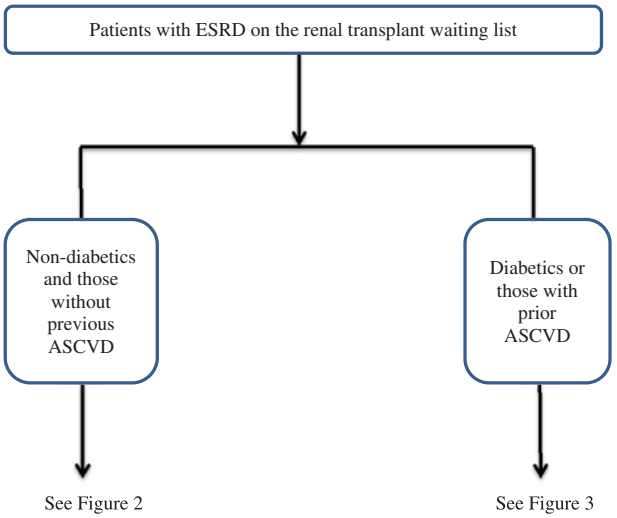

FIGURE 1: Recommendations for pre-renal transplant cardiac testing for patients on the renal transplant waiting list based on KDOQI, AST and Lisbon Report guidelines. ASCVD, atherosclerotic CVD (nonfatal myocardial infarction, CAD or stroke).

Guidelines proposed by renal societies, in general, advocate for more aggressive screening measures in the pre-renal population. Evaluation for CAD should be based on the individual patient's clinical status (Figures 1–3). Follow-up as suggested by the KDOQI guidelines includes evaluation for CAD every 12 months if the patients is a diabetic and their initial evaluation for CAD was negative, or if they have known CAD and were not revascularized, or if they underwent coronary stent placement. If the patient is not diabetic but considered 'high risk' based on clinical features, the evaluation of CAD risk assessment can be extended to every 24 months. Nondiabetic individuals with no high-risk features should be re-evaluated every 36 months while on the transplant waiting list (Figure 4). In addition, in patients who have significant CAD and undergo complete revascularization by means of coronary artery bypass grafting (CABG) should have their cardiac risk assessment for ischemia 3 years after the CABG, and annually thereafter.

It is important, however, to recognize that sudden cardiac death is still an important factor in patient moralist while on the transplant waiting list and may be attributable to factors other than CAD.

Utility of noninvasive cardiac testing in renal transplant candidates

There is no clear consensus among the major guideline societies regarding an exact protocol for cardiac testing in ESRD patients on the transplant list. The clinical and prognostic implications of pre-operative cardiac testing, especially in asymptomatic ESRD patients, are unclear. Moreover, the benefit of coronary revascularization is not well studied in the ESRD population due to their exclusion from many of the major trials.

A survey performed by the Clinical Practice Guidelines Committee of AST [68] of renal transplantation programs across

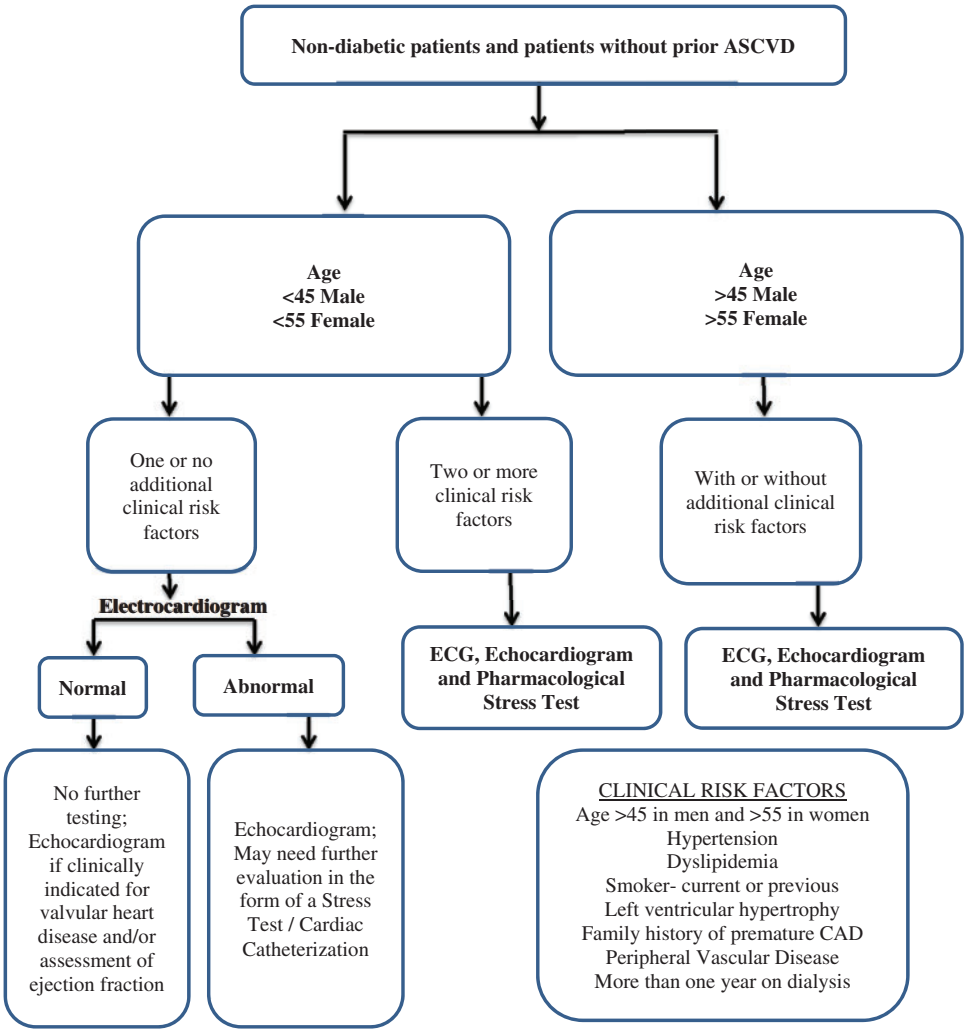

FIGURE 2: Recommendations for pre-renal transplant cardiac testing for 'nondiabetic' patients and patients without prior atherosclerotic CVD (ASCVD) on the renal transplant waiting list.

the USA found that most programs performed pre-operative cardiac evaluation on patients with risk factors for CAD such as DM, known history of CAD, obesity, hypertension and older age. Nuclear myocardial perfusion imaging was the initial test of choice in 40% of the programs surveyed, followed by thallium scanning in 33%, dobutamine stress echo (DSE) in 31% and coronary angiography in 15%.

A study of pre-operative cardiac testing by Lentine *et al.* [70] in Medicare beneficiaries who underwent renal transplantation from 1991 to 2000 revealed that 46% of this population underwent noninvasive stress testing or coronary angiography with 65% of the 'high risk' population and 20% of the 'low risk' population undergoing testing. Patients with DM, prior ischemic heart disease or two CAD risk factors were designated as high-risk patients.

There are differences in the choice of the initial noninvasive test most appropriate for the ESRD population due to various factors. Small studies have demonstrated different sensitivities and specificities for each of these tests (Table 1). Given the high incidence of LV hypertrophy, resting ST-T abnormalities on ECG, poor exercise tolerance, high resting heart rate, blunted heart rate and blood pressure response to exercise due to autonomic dysfunction in diabetics, exercise electrocardiography is not recommended in this population [71].

Other noninvasive modalities available include DSE, and nuclear imaging. Herzog *et al.* [72] found that the sensitivity and the specificity of DSE was 52 and 74%, respectively, in detecting CAD with >50% stenosis on angiography ($n = 50$ patients). Bates *et al.* [73] utilized DSE to classify 53 Type 1 diabetics on the renal and/or pancreatic transplant waiting list into high- and moderate-risk groups for adverse cardiac events. The rate of cardiac events in the DSE positive group was 45%, compared with 6% for those with a negative DSE- ($P = 0.0002$). Similarly, Reis *et al.* [74] found that DSE had a negative pre-dictive value of 97% in ESRD patients undergoing pre-operative cardiac testing ($n = 97$). Also, the percentage of ischemic segments on DSE can independently predict mortality and offer additional prognostic information [75]. In the general population, the sensitivity and specificity of myocardial perfusion imaging is 88 and 74%, respectively. In the ESRD population, based on small studies, a wide variety of values have been reported ranging from sensitivities of 37–86% to specificities of 73–79% [76].

These noninvasive tests are also useful for prognostication of patients. In a meta-analysis of 12 studies involving thallium-201 scintigraphy and DSE, ESRD patients with abnormal studies had a 6-fold higher rate of MIs and a 4-fold higher rate of cardiac death compared with those with negative results. Wong *et al.*

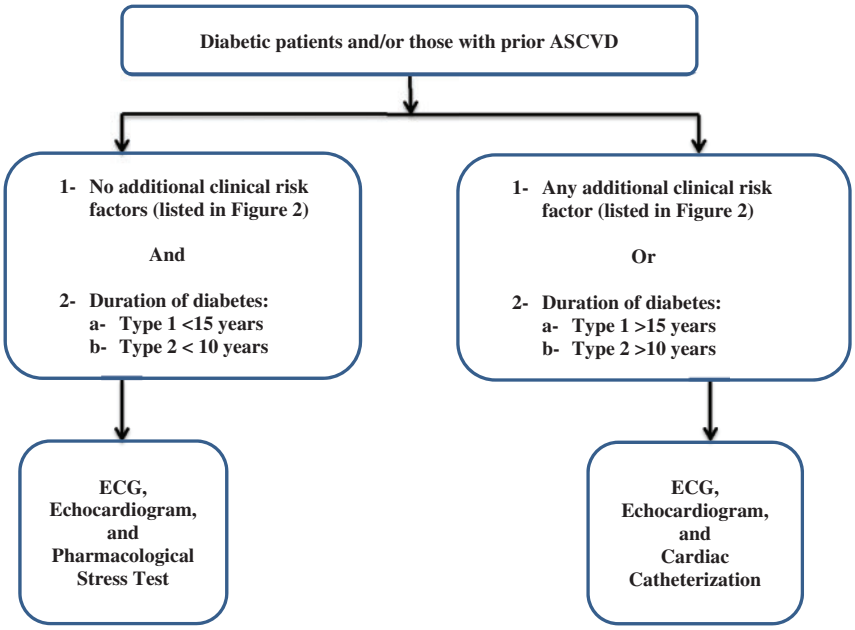

FIGURE 3: Recommendations for pre-renal transplant cardiac testing for 'diabetic' patients and/or patients with prior atherosclerotic CVD (ASCVD) on the renal transplant waiting list.

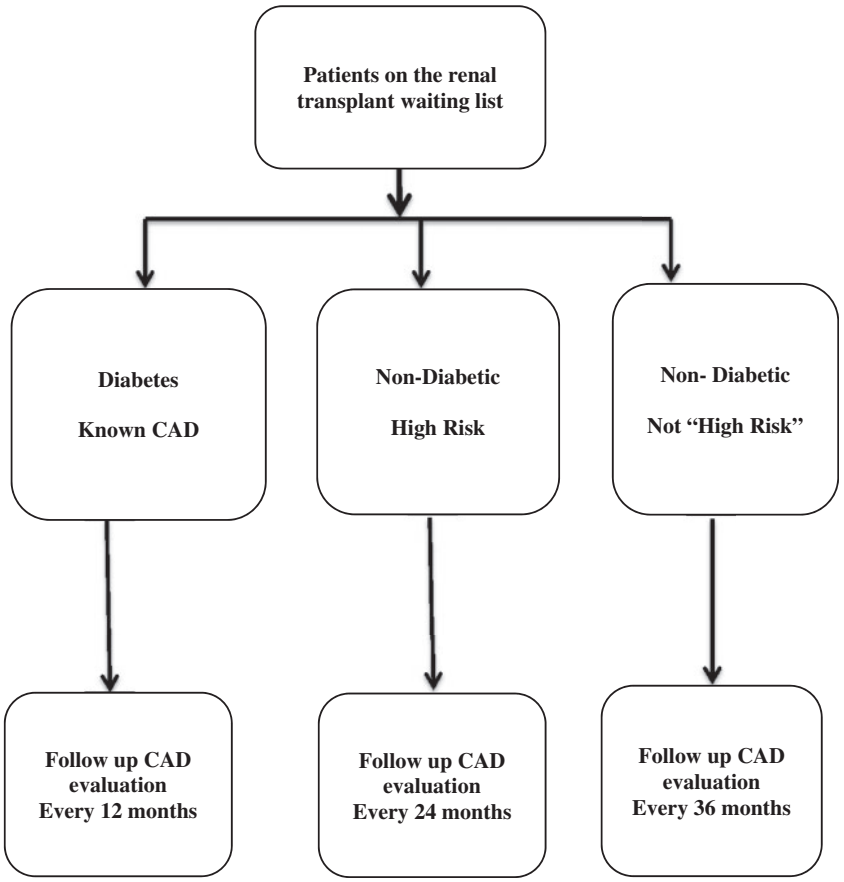

FIGURE 4: Follow-up evaluation of patients on the renal transplant waiting list.

[77] studied 126 ESRD patients who underwent a technetium-99m myocardial perfusion imaging and found that the presence of reversible ischemia was associated with a 3-fold higher risk for post-transplant cardiac events (hazard ratio 3.1; 95% CI 1.1–18.2) and nearly a 2-fold higher risk for death (hazard ratio 1.92; 95% CI 1.1–4.4) compared with those with a normal test.

Other noninvasive tests include coronary artery calcification (CAC). In a study by Raggi *et al.* [78] on more than 200 ESRD

Table 1. Recommendations for dual antiplatelet therapy following percutaneous coronary intervention

Bare metal stent	Drug-eluting stent
Continue aspirin and a P2Y12 inhibitor for 6 weeks after which the P2Y12 inhibitor may be discontinued. Aspirin therapy indefinitely	Continue aspirin and P2Y12 inhibitor for a minimum of 12 months
Transplant surgery after the first 6 weeks after placemen of bare metal stent	Transplant surgery may be considered after 3 months after stent implantation with surgery being performed on dual antiplatelet therapy. Patients should be informed about increased risk of bleeding during and after surgery while on DAPT. In addition, they should also be informed about the risks of stent thrombosis if either antiplatelet agent were to be discontinued prematurely

DAPT, dual anti-platelet therapy; P2Y12 inhibitors: clopidogrel, prasugrel, ticagrelor.

patients, CAC was detected in >83% of the patients. Although CAC was found to be an independent predictor of death in hemodialysis patients in one study [79], the exact role of CAC as a prognostic indicator in the ESRD population is yet to be determined. Multiple studies [80–82] have shown poor correlation between the coronary calcium score obtained through CAC and CAD on angiography in the ESRD population. Severe medial vascular calcification in ESRD patients shows up as significant CAC on CT scans as compared with intimal calcification seen in the non-ESRD population [83]. Hence, currently CAC quantification is not recommended for pre-renal transplant cardiovascular risk assessment.

Coronary angiography is the gold standard for the detection of significant CAD; however, it is an invasive procedure and has associated vascular and bleeding complications. In a study of 300 patients, there was no significant survival benefit in patients who underwent revascularization compared with those who did not, although there was a slight trend towards better survival in those with obstructive CAD (subset of 34 patients). Hage *et al.* [84] studied 3698 patients, 60% of whom underwent myocardial perfusion imaging as a part of pre-renal transplant work-up at a single center and subsequently 7% underwent coronary angiography. Coronary revascularization was associated with survival in patients with triple vessel disease. Manske *et al.* [85] demonstrated a decrease in cardiac events in asymptomatic diabetic ESRD patients who had significant CAD defined as at least one coronary artery stenosis >75% compared with medical therapy. Data published by De Lima *et al.* [86] was more compelling in showing a relationship between event-free survival and CAD <70% in patients undergoing renal transplant in comparison with noninvasive stress testing.

The timing of these tests is unclear and significant heterogeneity exists among centers active in renal transplantation. While most centers perform a yearly assessment, based on population data, testing every 2 years may be reasonable if the baseline test was normal [87].

Biomarkers for cardiac risk assessment

Smaller studies have demonstrated an increased risk for all-cause, and cardiac mortality with increased levels of cardiac Troponin T (cTnT). In a meta-analysis of 28 studies a cTnT level >0.10 ng/mL was associated with twice the risk for death compared with those with lower levels (pooled relative risk: 2.62; 95% CI 2.17–3.20). Sharma *et al.* [88] found that a cTnT level >0.06 ng/mL and ischemia modified albumin level >95 kU/L was associated with a 7-fold increase in the risk for death.

Although biomarkers provide prognostic information in the ESRD population, they are not used in the pre-operative setting for cardiac risk assessment.

CONCLUSIONS

Cardiac disease presents a significant health issue for many patients before and after renal transplant. Management of these patients is not uniform, varying widely among institutions. A review of all current evidence and societal recommendations show that, whereas there is not a consistent approach, CAD does present a substantial risk to ESRD patients and the best approach is multi-disciplinary. There is no clear evidence to show that asymptomatic patients with good functional status would have survival benefit with coronary revascularization. This is in line with cardiac literature data showing the limited benefit of percutaneous coronary intervention in that cohort. Therefore, it is reasonable to primarily consider noninvasive testing as the principal methodology for evaluating patients prior to transplant. However, additional risk factors such as peripheral vascular disease, DM and uncontrolled hypertension obligate closer follow-up by both the transplant team and primary physician or cardiologist. A lower ejection fraction prior to transplant, provided it is not directly related to valvular disease or high coronary ischemic burden, does not seem to prohibit the patient from being a good transplant candidate. Each center has varying experience using assessment tests. This is reflected in the differences in sensitivity and specificity among institutions when applying echocardiography as opposed to nuclear stress testing, or magnetic resonance imaging. Recognition of the cardiovascular impact on this population is now well recognized resulting in more thoughtful, if not uniform, approach to patient transplantation and assessment. Data from Australia and New Zealand show improvement in patient outcomes based on the cardiovascular risk management [89]. This should be considered when designing a program's transplant assessment protocol. Finally, in order to continually improve the patient outcomes, internal data should be looked at in relation to the available evidence and program pathways adjusted accordingly.

CONFLICT OF INTEREST STATEMENT

None declared.

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