Update on Cardiac Risk Stratification of Renal Transplant Candidates

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Numerous modifiable and unmodifiable risk factors have been identified that contribute to increased cardiovascular risk in renal transplant recipients. We reviewed several clinical studies and journal articles to identify these risk factors in an attempt to risk stratify chronic kidney disease patients who are candidates for renal transplantation. Cardiovascular disease has been identified as the leading cause of death with graft function among renal transplant recipients. No single test or diagnostic modality has been found to provide complete diagnostic and prognostic information. Hence, a combination of clinical, biochemical, and radiographic data is essential to risk stratify renal transplantation candidates.

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Key words: Risk stratify • Renal transplant candidates • Cardiovascular disease • Chronic kidney disease

Recent studies have demonstrated considerable improvement in patient and graft survival after renal transplantation. The 5- and 10-year post-transplant survival rates currently are approximately 85% and 66%, respectively, and allograft half-lives stood at 10.9 years in the mid-1990s.[1] Numerous modifiable and unmodifiable risk factors contribute to increased cardiovascular risk in renal transplant recipients. Various studies have attempted to risk stratify patients with chronic kidney disease (CKD) based on clinical, biochemical, and imaging criteria.

The leading cause of death after renal transplantation is cardiovascular disease (CVD). A population-based survival analysis of US patients with end-stage renal disease (ESRD) who underwent renal transplant between 1988 and 1997 was performed by Ojo and colleagues,[2] which showed CVD as the leading cause of death with graft function (DWGF) (36.1%). Interestingly, 50% of post-transplant DWGF occurring within 30 days was due to CVD, primarily acute myocardial infarction (MI). Figure 1 shows causes of DWGF after renal transplantation.

The leading cause of death after renal transplantation is cardiovascular disease.

This study underlines the significance of identifying patients with or at high risk for coronary artery disease (CAD) before renal transplantation to prevent perioperative mortality. CAD is a major risk factor for increased morbidity and mortality in renal transplant recipients. In a small randomized study done by Manske and associates,[3] coronary artery bypass graft prior to renal transplantation was associated with a decrease in cardiac events and mortality. This reiterates the significance of identification of CAD prior to renal transplantation in patients with CKD.

Importance of C-Reactive Protein Level

Serum levels of C-reactive protein (CRP) have been shown to correlate with future development of coronary heart disease events in the general population.[4] Parekh and coworkers[5] performed a prospective study of a cohort of 1041 ESRD patients for a median of 2.5 years. Higher levels of CRP were associated with a 2-fold increased adjusted risk of sudden cardiac death. Participants in the highest tertile of high-sensitivity RP (hsCRP) (median hsCRP, 1.49 mg/100 mL) were twice as likely to experience sudden cardiac death as their counterparts in the lowest tertile (median hsCRP, 0.12 mg/100 mL; $P < .001$). This risk remained significant after adjusting for comorbidities, calcium-phosphorus product, potassium, and other inflammatory markers.[5]

Calcium-Phosphorus Product

CKD patients have altered calcium and phosphorus homeostasis. Hyperphosphatemia in renal dysfunction stimulates mobilization of calcium from bones through parathyroid hormone, leading to bone disorder and vascular and soft tissue calcification.[6] In addition to the vascular intimal calcification seen in CKD patients, calcification of the vascular media, known as Monckeberg's sclerosis, is also seen in CKD and is a sign of accelerated atherosclerosis.[7] Block and colleagues[8] analyzed data from 2 large cohorts of more than 6000 ESRD patients and found that phosphorus level above 6.5 mg/dL was associated with increased mortality risk and as the calcium-phosphorus product increased above 72 mg^2/dL^2, the risk of death increased by 34% when compared with the reference range of 42 to 52 mg^2/dL^2.

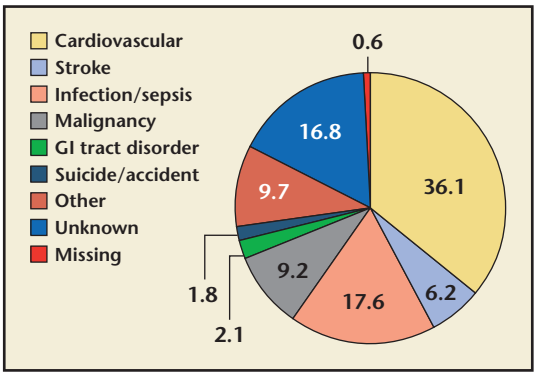

Figure 1. *Causes of death among renal transplant patients with graft function, from 1988-1997. GI, gastrointestinal. Data from Ojo AO et al.*[2]

The Role of Anemia

Cardiorenal anemia is a term that has emerged recently and implies a cause-and-effect relationship among anemia, CKD, and heart failure. Anemia can cause or worsen heart failure or CKD and also can be a result of both conditions.[9] Severe anemia is a risk factor for worse prognosis in patients with congestive heart failure (CHF) and renal failure. However, various studies have shown conflicting results regarding the role of anemia correction in patients with CHF and CKD. A multicenter, randomized, double-blind, placebo-controlled trial by Ponikowski and colleagies[10] involving 41 patients with anemia and CHF did not show any improvement in New York Heart Association functional class after correction of anemia.[10] Toblli and coworkers[11] performed a trial of 40 patients with CHF (ejection fraction < 35%) and found that correction of anemia by administration of intravenous iron resulted in improvement in NYHA

functional class, renal function, and left ventricular (LV) ejection fraction.[11]

Dyslipidemia

CKD results in profound dysregulation of lipoprotein metabolism. Most patients have decreased high-density lipoprotein cholesterol and increased triglyceride-rich lipoproteins along with elevated low-density lipoprotein (LDL) cholesterol.[12-14] The Heart Protection Study[15] evaluated the benefit of lowering cholesterol with simvastatin, 40 mg/d, with primary outcomes of total mortality and fatal and nonfatal vascular events. The study enrolled 20,000 British men and women, of which a subgroup of 1329 patients was identified with CKD (creatinine 1.3-2.3 mg/dL). Results yielded a relative risk (RR) reduction of 28% (95% confidence interval [CI], 0.72-0.85; $P = .05$).[15] Similarly, the Cholesterol and Recurrent Events (CARE) study[16] enrolled over 4000 patients with previous MI and plasma total cholesterol < 240 mg/dL, who were then randomized to pravastatin, 40 mg/d, or placebo and followed for 5 years. Patients with mild CKD (creatinine clearance < 75 mL/min) were found to have a 28% RR reduction (95% CI, 0.55 to 0.95; $P = .02$) and a 4% absolute risk reduction in the primary endpoint when treated with pravastatin, 40 mg/d.[16]

The Assessment of Lescol in Renal Transplant Trial (ALERT) enrolled 2012 renal transplant recipients. ALERT was a randomized, double-blind, placebo-controlled study in which participants had a mean serum creatinine of 1.6 mg/dL and mean baseline LDL cholesterol of 160 mg/dL. Randomization to fluvastatin, 40-80 mg/d, resulted in a nonsignificant 17% risk reduction ($P = .139$) in the combined primary endpoint of nonfatal MI, cardiac death, or coronary procedures. Subsequently, however, analysis of the ALERT data using cardiac death and nonfatal MI as primary endpoint showed a significant 35% risk reduction ($P = .005$).[17,18]

There have been safety concerns regarding use of statins in patients with CKD. Adverse effects are often dose related and related to drug concentration in the blood. Statins excreted mainly through the kidneys will require dose reduction. Another factor to consider is that statins metabolized by the cytochrome P450-3A4 system are more likely to cause adverse effects due to drug–drug interactions. Another concern in some patients has been transient mild tubular proteinuria.[19-21] The Pravastatin Pooling Project[22] analyzed data from 3 randomized controlled trials comparing pravastatin, 40 mg/d, to placebo in over 18,000 patients with previous MI. There was an 8% reduction in the adjusted rate of kidney function loss (0.08 mL/min/1.73 m^2/y; 95% CI, 0.01-0.15) and 60% reduction of RR of acute renal failure (95% CI, 0.4-0.86; $P = .005$).[22] To summarize, statins may cause initial increased proteinuria, but they reduce inflammation, slow fibrosis, and result in less proteinuria in the long term.[23] The National Kidney Foundation and the National Lipid Association have issued recommendations for cautious use of fibrates in patients with CKD because they may cause a moderate reversible increase in serum creatinine and in serum concentrations of statins.[19,24]

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Obesity

Obese patients (body mass index [BMI] > 30 kg/m^2) have been found to have higher complication rates following renal transplantation, including wound infections, delayed graft function, and prolonged post-transplant hospitalization, and therefore increased cost when compared with nonobese patients.[25-30] Meier-Kriesche and colleagues[31] evaluated 405 patients who underwent transplantation at St. Barnabas Medical Center (Livingston, NJ) between 1990 and 1997. Patients were divided into 2 groups, BMI < 25 and BMI > 25. Endpoint was graft loss due to graft failure or patient loss. The Kaplan-Meier method was used to evaluate graft survival and patient survival. Chronic rejection was found to be the major cause for graft failure, accounting for 6.1% in the BMI > 25 group as compared with 2.5% in the BMI < 25 group, which barely missed statistical significance ($P = .06$). Significantly greater 7-year survival was observed in patients with BMI ≤ 25 than with BMI > 25 (Figure 2).[31]

Age

The RR of infection and chronic renal allograft failure has been found to increase with increasing age, as suggested by analysis of data from the US Renal Data System.[32,33] Ismail and associates[34] and Berthou and coworkers[35] have reported increased risk of death from CVD in older renal transplant recipients.

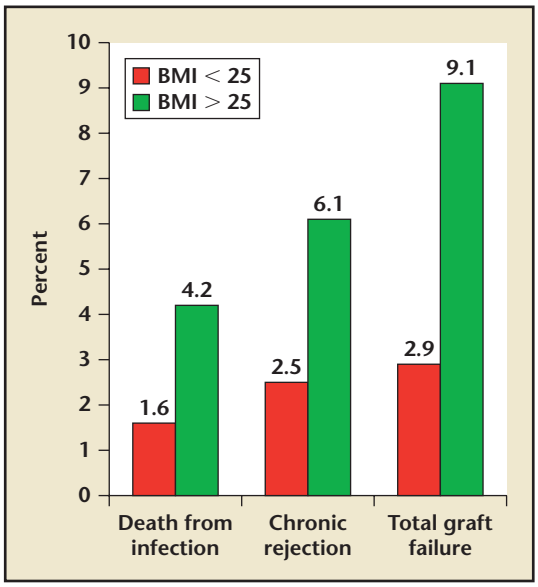


Figure 2. *Effect of body mass index (BMI) on graft survival and recipient death (%). Data from Meier-Kriesche HU et al.*[31]

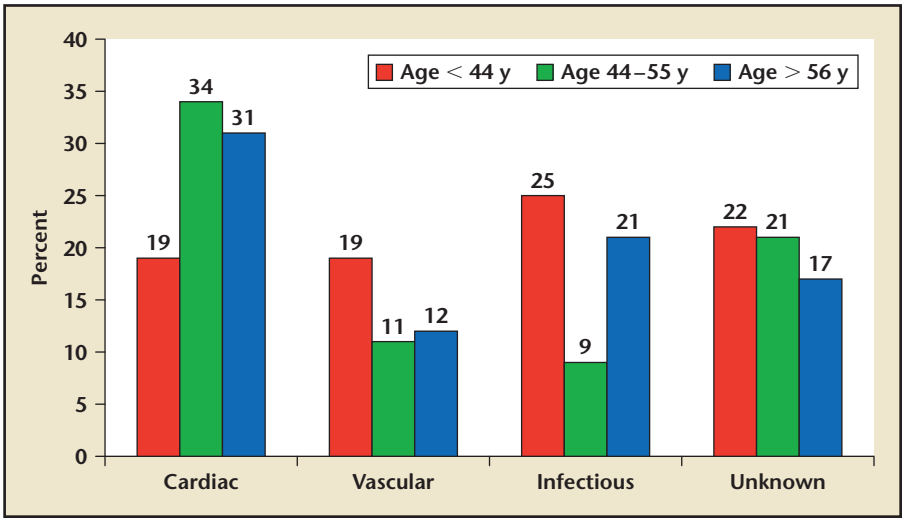
Roodnat and coauthors[36] studied 509 cyclosporine-treated recipients of a primary cadaveric kidney graft between July 1983 and July 1997. The population was divided into 3 comparable-sized groups according to their age at time of transplantation: 17 to 43 years, 44 to 55 years, and 56 to 75 years. Graft survival was defined as alive with a functioning graft and endpoint was defined as graft failure or death. No significant difference was observed among the 3 age groups for recipient sex, donor age, and blood group, and the number of mismatches on the human leukocyte antigen (HLA)-A, HLA-B, and HLA-DR loci. Patient survival was found to be significantly worse in the group of oldest recipients ($P < .0001$) and interestingly, graft survival censored for death was significantly better with increasing age. These opposing effects resulted in no significant difference in overall graft survival among the 3 age groups. Incidence of infections was found to be statistically increased in the age ≥ 56-year-old group when compared with the younger age groups ($P = .05$). The conclusion from this study was that, although donor and recipient age had a negative impact on transplant outcome, the age effects are now considered of minor importance due to drastically improved outcomes over time (Figure 3 and Figure 4).[36]

Diabetes Mellitus

Diabetes mellitus has been identified as the leading cause for ESRD in most industrialized countries.[37] According to the US Renal Data System, 48.4% of 72,000 new cases of ESRD were attributed to diabetes mellitus in 1998.[38] Diabetic patients undergoing transplantation have an increased mortality rate when compared with transplant recipients who are not diabetic.[39]

Juul and coworkers[40] performed a retrospective study involving 179 diabetic patients who underwent major noncardiac surgery (major surgery defined as surgery lasting > 1 h) at Herlev Hospital (Herlev, Denmark) during a 12-month period. These patients were followed for a maximum period of 18 months. Postoperative mortality was the main outcome measure. Poor metabolic control (defined as 1 or more blood glucose measurements > 13.9 mmol/L during postoperative days 1-5) was associated with a cumulative mortality of 39% (95% CI, 24-54) compared with 20% cumulative mortality (95% CI, 6%-34%) in patients with good metabolic control. This difference was statistically significant by Log-rank test ($P < .03$) and in the Cox univariate analysis ($P < .05$). However, when results were corrected for scheduled or urgent surgery, presence or absence of

Figure 3. *Causes of death (%) with regard to age of renal transplant recipient. Adapted from Roodnat J et al.*[36]



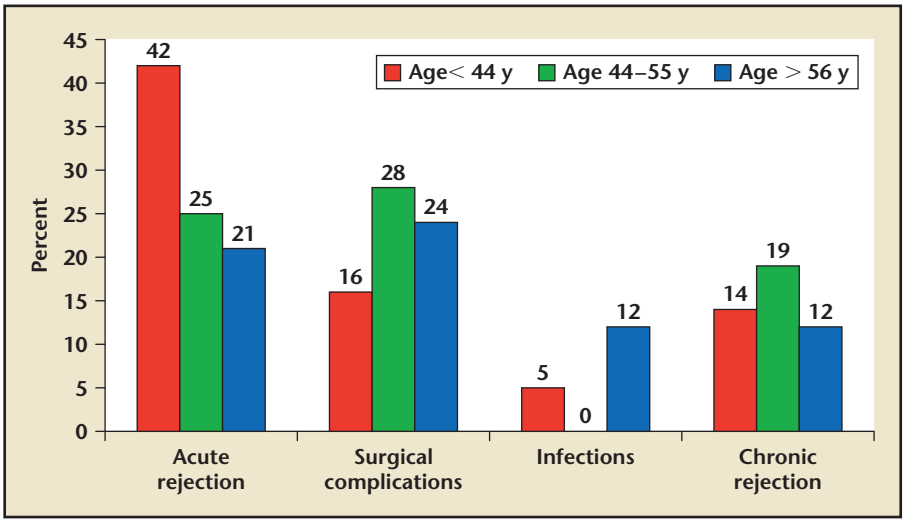


Figure 4. *Causes of graft failure (%) with relation to recipient age. Data from Roodnat J et al.*[36]

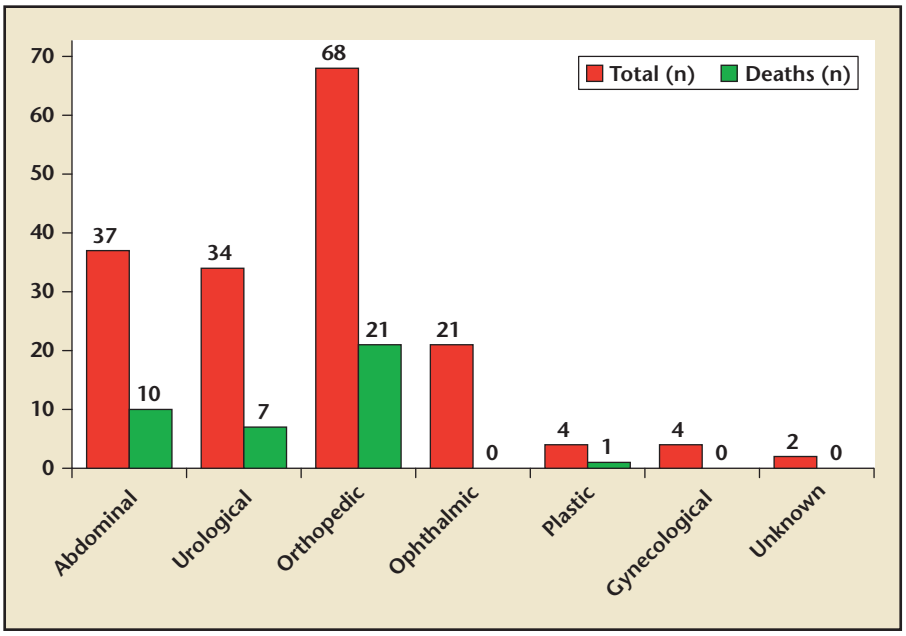


Figure 5. *Relationship between type of surgery and long-term mortality. Data from Juul AB et al.*[40]

cardiac disease or American Society of Anesthesiologists group, the difference was statistically insignificant ($P = .13$) (Figure 5).

Urgent surgery was found to be a significant predictor of postoperative mortality ($P < .006$) according to Cox regression analysis. The long-term mortality among diabetic patients undergoing major noncardiac surgery in this study was found to be 24%, with the type of diabetes not being a significant risk factor. As Figure 6 illustrates, CVDs constitute a major cause of death.[40] Diabetes is associated with progressive and more extensive atherosclerotic CVD.[41] Autonomic dysfunction may add to perioperative blood pressure liability and increased risk of cardiac ischemic events in diabetic patients.[42-45]

The Diabetes Control and Complications Trial (DCCT)[46] has shown benefits of tight glycemic control in microvascular complications of diabetes. In fact, strict glycemic control has been shown to retard development of diabetic glomerular lesions in renal transplant recipients with type I diabetes mellitus.[47] The American Diabetic Association therefore recommends pancreas transplantation as an acceptable alternative to insulin therapy in diabetic patients with ESRD who have, or plan to have, a renal transplant.[48]

Use of Immunosuppressive Drugs

It is vital to review the cardiovascular impact of immunosuppressive therapy used so that prompt corrective action can be taken to decrease risk factors for development of atherosclerosis. Table 1 highlights the main adverse cardiovascular effects of the commonly used immunosuppressive drugs in the post-transplant period.[49]

Use of Diagnostic Modalities

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was used in a study by Mark and colleagues,[50] which showed 2 patterns of scarring: discrete subendocardial and diffuse. Both patterns were found to correlate with increased LV mass, but only subendocardial fibrosis was associated with coronary heart disease risk factors. Use of MRI is limited by cost and by possibility of a serious complication of nephrogenic systemic fibrosis (which is infrequent).[50]

Resting and Stress Echocardiography

LV structural changes are more prevalent in patients with ESRD.

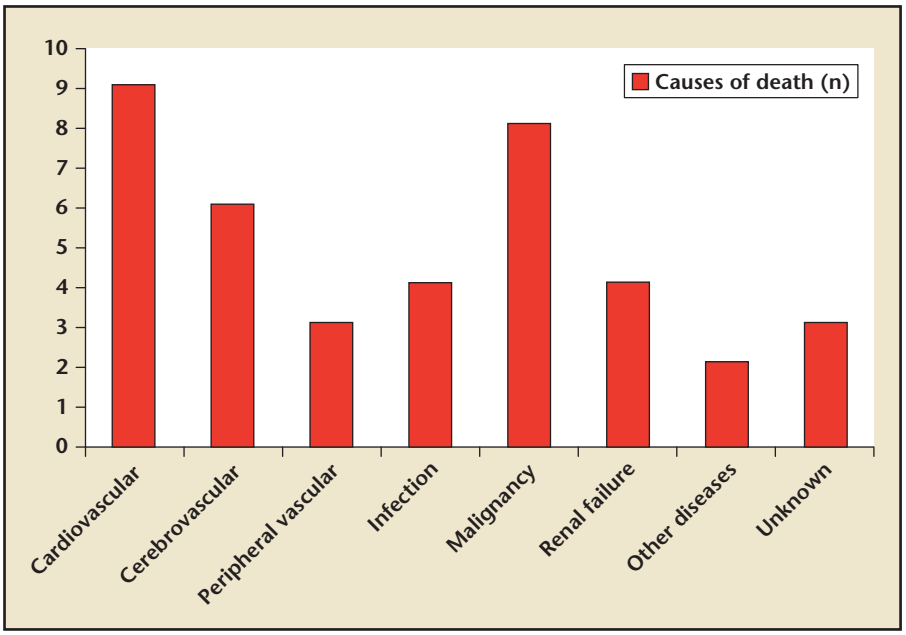


Figure 6. *Causes of postoperative death (total deaths 39 out of 170 diabetic patients). Data from Juul AB et al.*[40]

Presence of LV hypertrophy (LVH) is a strong predictor of adverse outcome. The type of LVH, concentric or eccentric, may also have prognostic importance.[51]

Foley and coworkers[52] studied 518 patients who survived at least 6 months from start of ESRD, out of whom 85 were excluded. At baseline and at yearly intervals thereafter, a clinical assessment was done. In addition, baseline and annual echocardiography was performed using M-mode and 2-dimensional echocardiography; 73.9% had LVH, 35.5% had LV dilatation, and 14.8% had systolic dysfunction. Cardiac failure at baseline was strongly predictive of overall mortality and mortality at 2 years. In patients who survived more than 2 years,

Table 1
Commonly Used Immunosuppressant Drugs and Their Cardiovascular Adverse Effects

Drugs	Cardiovascular Adverse Effects	Action Required
CsA	Hypertension, dyslipidemia, DM, interaction with drugs metabolized by CYP450 isozyme system	CCBs and ACEIs are the preferred choice for hypertension; to treat dyslipidemia, consider lowering dose, change to FK506, diet control, and lipid-lowering drugs (usually a statin), with preference to pravastatin or rosuvastatin therapy; watch for statin-induced muscle toxicity/rhabdomyolysis; avoid toxic levels of CsA and monitor blood sugars closely; initiate early therapy for post-transplantation DM
FK506 (tacrolimus)	Hypertension, dyslipidemia, DM. interaction with drugs metabolized by CYP450 isozyme system	Treat hypertension with CCBs, ACEIs, or β-blockers; treat dyslipidemia with diet control plus lipid-lowering drug therapy (usually statins), with preference to use of pravastatin or rosuvastatin; watch for statin-induced muscle toxicity/ rhabdomyolysis; avoid toxic levels and monitor blood sugar levels closely; initiate early therapy for post-transplantation DM
Sirolimus	Dyslipidemia, no significant impact on hypertension or post-transplant DM, may interact with drugs metabolized by CYP450 isozyme system	Treat dyslipidemia with diet control plus lipid-lowering drug therapy (usually statins), with preference to pravastatin or rosuvastatin; consider lowering dose and/or change to alternative immune-suppressant drug if resistant dyslipidemia
Steroids	Hypertension, dyslipidemia, DM	Treat hypertension with CCBs/ACEIs or β-blockers; treat dyslipidemia with diet control plus lipid-lowering drug therapy; monitor blood sugar levels closely and initiate early therapy for post-transplantation DM; use lower dosing if possible
Mycophenolate mofetil and azathioprine	Both pose low cardiovascular risks	Monitoring for hypertension, DM, and dyslipidemia when used in conjunction with any of the above mentioned immunosuppressant drugs

ACEI, angiotensin-converting enzyme inhibitor; CCBs, calcium channel blockers; CsA, cyclosporine A; DM, diabetes mellitus.
Data from Miller LW.[49]

peripheral vascular disease, LV mass index, eccentric LVH, LV cavity volume, LV dilatation, fractional shortening, and systolic dysfunction were all associated with late mortality.[51]

Dobutamine Stress Echocardiography
Dobutamine stress echocardiography has adequate accuracy for diagnosing and predicting prognosis in renal transplant patients. Its limitation is suboptimal feasibility in renal failure patients due to a high prevalence of hypertension. Dialyzed patients are known to be at increased risk for complex ventricular arrhythmias. Dipyridamole has an advantage over dobutamine due to lack of hypertension-related limitation.[52-58]

Myocardial Perfusion Imaging
Myocardial perfusion imaging (MPI) is considered safe and accurate in diagnosing CAD and predicting mortality. Its advantages in renal patients are its lack of effect of resting electrocardiographic abnormalities on MPI findings and the fact that it can be combined with pharmacologic stress to enhance prognostic significance. Its limitation is the difficulty of using exercise stress in some ESRD patients.[59,60] Atkinson and colleagues[61] performed a study to determine the accuracy of MPI for detection of significant CAD in an unselected population of ESRD patients being considered for renal transplantation and to observe predictive value of MPI and coronary angiography in relation to long-term cardiovascular events and mortality in the group. All patients underwent a multi-gated acquisition (MUGA) scan at rest and MPI using dipyridamole-technetium 99m tetrophosmin single-photon emission computed tomography (CT), and subsequently coronary angiography (CA) was performed. MPI was found to be positive in 10 patients, 1 of whom had normal coronary arteries. However, 13 patients had negative MPI but positive CA indicating high false-negative rate (35%). Sensitivity of MPI in detecting angiographically significant CAD (> 50% stenosis in a major coronary artery) was 41%, specificity was 96%, positive predictive value was 90%, negative predictive value was 65%, and overall accuracy was 70%.[62]

Coronary Angiography
CA has been traditionally considered a gold standard in identifying patients with CAD. However, its limitations include cost, availability, the invasive nature of screening, the risk of nephrotoxicity, and its inability to provide functional significance of coronary artery stenosis. In the study by Atkinson and associates,[61] CA was found to have a positive predictive value of 95.7% and a negative predictive value of 54.2% for predicting combined outcome of death and cardiovascular events. Survival was found to be significantly longer in patients with negative MPI or CA.[61]

CT Angiography
High-resolution computed tomography (CT) has been used to provide a quantitative assessment of coronary artery calcification (CAC), called a CAC score (CACS). Magnitude of CAC is higher in patients with CKD compared with the general population. Because CACS was developed and validated in the general population, data regarding the reliability and significance of CACS are scarce.[62-67] Barraclough and coworkers[68] studied 33 patients with CKD who were not on hemodialysis, who underwent a high-resolution CT at baseline and after 1 year to assess CAC and its progression. The Agatston score is the best established measure of CAC. Progression of CAC is defined as change in CACS of more than 15%. The study found significant variability while comparing 2 scans on the same patient performed 30 minutes apart, with 27% of scores showing more than 15% change from baseline. It was observed that a significant change in CACS can occur simply with patient repositioning. Out of 33 patients, 8 had no CAC at baseline and 10 had severe CAC. Six patients with more than 30 baseline CACS had more than 15% change following repositioning. The study showed significant imprecision in high-resolution CT-derived CACS in CKD patients, and the author suggests a need for standardization of methods of CACS measurement with HRCT.

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Current Guidelines

According to the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, guidelines were suggested based upon presence or absence of active cardiac conditions, functional capacity, and clinical risk factors to help risk stratify patients before undergoing noncardiac surgical procedures. Figure 7 depicts an algorithm for preoperative cardiac evaluation and care for intermediate risk surgery.[69] Lewis and associates[70] suggested performing noninvasive cardiac testing for potential renal transplant candidates at increased risk for coronary heart disease based on their medical history. Subjects with an abnormal noninvasive test should undergo coronary angiography. Patients with critical coronary lesions should undergo revascularization. Manske and colleagues[3] studied

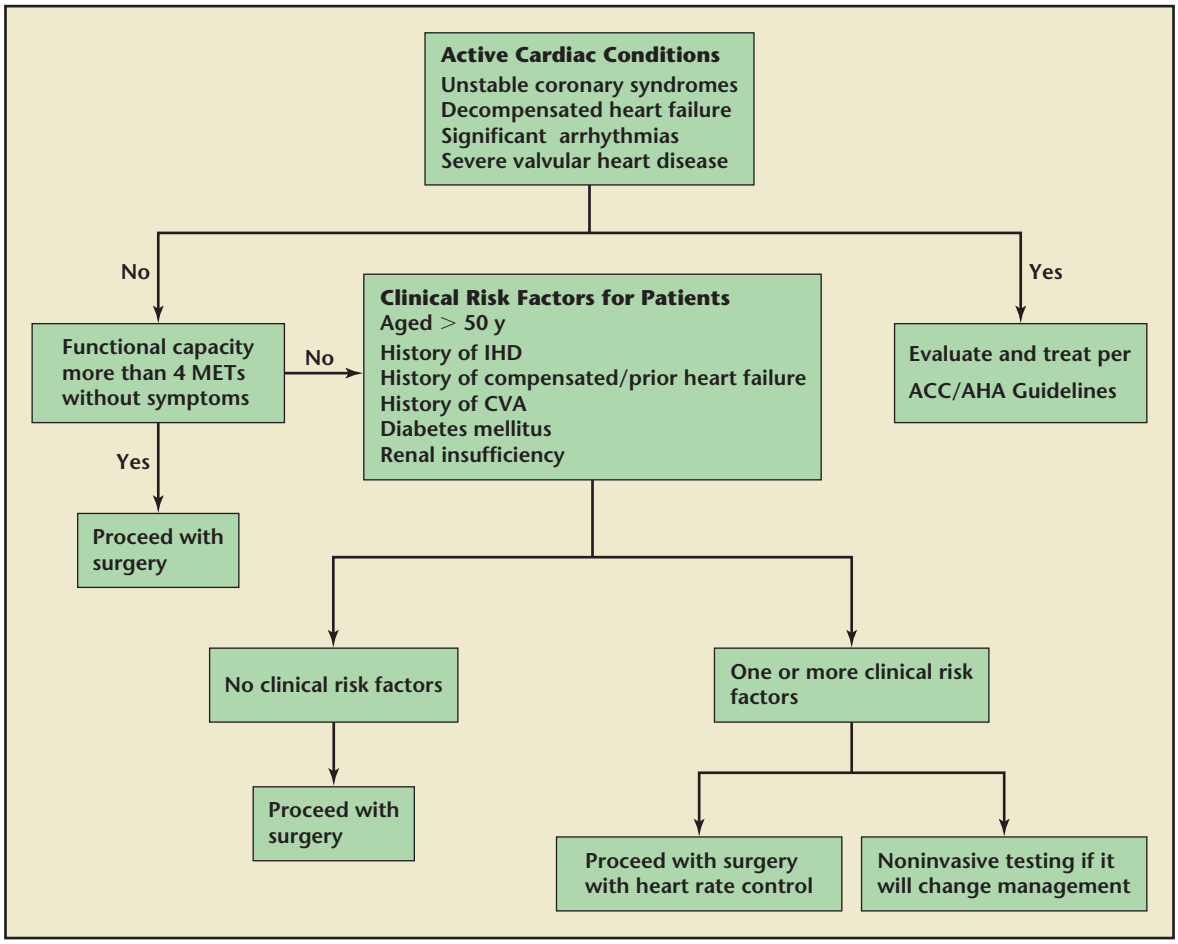

Figure 7. *Algorithm for preoperative cardiac evaluation and care for elective, noncardiac, and intermediate-risk surgery. ACC, American College of Cardiology; AHA, American Heart Association; CVA, cerebrovascular accident; IHD, ischemic heart disease; METs, metabolic equivalents. Reprinted from J Am Coll Cardiol. Vol. 50, Fleisher LA et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery, e159-e241, copyright 2007, with permission from Elsevier.*

26 asymptomatic diabetic patients with critical stenoses > 75%. The post-transplant cardiovascular events were fewer in the group randomized to revascularization before transplant than in the group managed medically.

Contrast Use in CKD

Contrast-induced acute kidney injury (AKI) is defined as an increase in serum creatinine of 0.5 mg/dl or a 25% increase from baseline within 3 days after use of contrast medium.[71] The residual renal function in patients with CKD is highly susceptible to decline after exposure to iodinated contrast.[72] Risk of AKI after exposure to contrast medium is increased in stage 3 to stage 5 CKD and further amplified in patients with diabetes mellitus.[73-75] Contrast-induced AKI after primary percutaneous coronary intervention (PCI) has been shown to increase both short- and long-term mortality.[76,77] Iso-osmolar contrast agents such as iodixanol have been shown to have the lowest risk for AKI in patients with diabetes mellitus and CKD.[78,79] Limiting contrast volume to < 30 mL for a diagnostic catheterization and < 100 mL for PCI is a reasonable goal to prevent contrast-induced nephrotoxicity.[80]

Risk of AKI after exposure to contrast medium is increased in stage 3 to stage 5 CKD and further amplified in patients with diabetes mellitus.

Conclusions

Upon review of several studies for cardiac risk stratification it is apparent that no single test gives complete diagnostic and prognostic information. A combination of clinical data and imaging studies (MPI and 2-dimensional echocardiogram with CA) provides a fairly accurate diagnosis of CAD and prediction of cardiovascular events and mortality in renal transplant patients. ■

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Main Points

- Cardiovascular disease has been identified as the leading cause of death with graft function among renal transplant recipients. No single test or diagnostic modality has been found to provide complete diagnostic and prognostic information. Hence, a combination of clinical, biochemical, and radiographic data is essential to risk stratify renal transplantation candidates.
- Coronary artery disease (CAD) is a major risk factor for increased morbidity and mortality in renal transplant recipients. It is of critical significance to identify patients with or at high risk for CAD prior to renal transplantation to prevent perioperative mortality.
- Numerous clinical factors, such as serum levels of C-reactive protein, calcium and phosphorous homeostasis, anemia, dyslipidemia, and obesity, must be taken into account when risk stratifying candidates for renal transplantation.
- A combination of imaging modalities, including magnetic resonance imaging, resting and stress echocardiography, myocardial perfusion imaging, and angiography, should be used to identify the presence of CAD and predict likelihood of cardiovascular events and mortality in renal transplant patients.

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