Cardiovascular Risk Evaluation before Kidney Transplantation

Steven Fishbane
Winthrop University Hospital, Mineola, New York

J Am Soc Nephrol 16: 843-845, 2005. doi: 10.1681/ASN.2005020189

Candidates for kidney transplantation undergo an extensive evaluation of health status before surgery (1). An important component is a rigorous consideration of the subject's cardiovascular health. Among the reasons that cardiac disease is particularly relevant to the pretransplant evaluation is the need to fully assess and manage perioperative risk. There are excellent published clinical practice guidelines that link evidence to specific recommendations for the cardiac evaluation of patients undergoing noncardiac surgery (2). Although written for general patient populations, many of these principles can be applied directly to the potential renal transplant recipient.

Beyond perioperative risk, the potential transplant recipient has other characteristics that make cardiac evaluation important. First, cardiovascular disease is the major cause of death in this population (3). Almost half of deaths within 30 d of transplantation are due to cardiac events (4). Second, the long-term posttransplant need for immunosuppressive medications may complicate the process of atherosclerotic risk reduction (5). Both steroids and calcineurin inhibitors can increase BP and aggravate dyslipidemia. In addition, clinicians may tend to under-treat with statin drugs because of interactions with calcineurin inhibitors. Third, kidneys for living or cadaver transplants are a precious and scarce resource. Because cardiovascular death is a major reason for eventual graft loss, the balance of risk and benefit for decisions related to cardiac testing may be shifted with this difficult resource utilization/ethical issue in mind. In this editorial I will consider issues that affect the cardiovascular presurgical evaluation of patients who seek renal transplantation. I will place particular emphasis on difficult issues in clinical decision making with respect to the high-risk candidate.

The American College of Cardiology (ACC) recommends a stepwise approach to the selection of tests for risk assessment before noncardiac surgery (2). For elective surgery, physicians are asked to determine the level of clinical predictors of risk, much as discussed above, and to categorize patients as having minor, intermediate, or major predictors. It is recommended that patients in the major group go directly to coronary angiography; patients with intermediate predictors should be stratified on the basis of functional status; the ACC recommends that patients with good function proceed to surgery, with poor-function noninvasive stress testing recommended. The American Society for Transplantation has guidelines refined more specifically for pretransplant evaluation, recommending risk stratification and noninvasive stress testing for candidates at high cardiac risk (1).

Decisions as to selection of cardiac testing pathways involve consideration of the complex interplay of test performance characteristics applied to the individual patient. This is the discipline of analytic clinical decision making. The clinician must weigh (*1*) the accuracy of noninvasive tests (sensitivity and specificity), in light of (*2*) the individual patient's risk profile (pretest probability) to understand how well the test will be able to exclude the presence of significant disease (negative predictive value). Positive predictive value, the likelihood that a positive test result predicts actual disease, may be a less important characteristic when trying to rule out the presence of cardiac disease before transplantation.

Noninvasive cardiac tests (specifically dipyridamole thallium/sestamibi scintigraphy [DSS] or dobutamine echocardiography [DE]) have been fairly well studied in patients with ESRD. A recent meta-analysis found that transplant candidates with positive noninvasive stress tests may have a greater risk for future cardiac events. For prediction of cardiac death the pooled results indicated a sensitivity of 80%, but a specificity of only 59% (6). For prediction of coronary stenoses in this patient population, most studies have found these tests to have suboptimal accuracy, with sensitivity and specificity $<60\%$ (7–11), with some exceptions (12,13). It is my opinion that the study with the greatest evidentiary value was one recently reported by De Lima *et al.* (8). These investigators studied 126 renal transplant candidates, performing coronary angiography as well as both key noninvasive tests. The primary finding was that DSS had a sensitivity and specificity of only 58% and 67%, respectively, and DSE had a sensitivity of only 44%, with a better specificity of 87%. Furthermore, patients were followed for 4 yr to determine cardiac outcomes. But similar to the results for cardiac stenoses, the noninvasive tests performed with similar poor accuracy for the prediction of future cardiac events. Only coronary angiography was able to reasonably predict patients at risk. The authors concluded that noninvasive testing was probably insufficient for high-risk transplant can-

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Steven Fishbane, Associate Chairman of Medicine, Winthrop University Hospital, 200 Old Country Road, Suite 200, Mineola, New York 11501, Phone: 516-663-2169; Fax: 516-663-2179; E-mail: sfishbane@winthrop.org

ISSN: 1046-6673/1604-0843

didates (8). Taken together, the literature indicates that noninvasive cardiac stress tests perform with less than optimal accuracy in this patient population. It would probably be unreasonable to expect the tests to perform with either sensitivity or specificity of >70%. To estimate the tests' predictive value in an individual patient, however, we must first consider the patient's disease likelihood.

To determine the patient's pretest probability of cardiac disease, we begin by recognizing that in the ESRD population the general risk for cardiac disease is very high. Several investigators have performed coronary angiography in asymptomatic ESRD patients, and have found the proportion with significant coronary artery stenoses to be approximately 37% (14–18). In this issue of *JASN*, Ohtake *et al.* put a finer point on this issue. They performed coronary angiography on 30 new ESRD patients with no known cardiac history (19). Remarkably, even in this asymptomatic incident population, 16 of 30 patients (53.3%) had significant coronary artery stenotic (CAS) lesions. Among diabetic patients, 10 of 12 patients (83.3%) had significant stenoses. While the general incident dialysis population might have slightly different characteristics than transplant candidates, these results still serve as an important reminder of the high probability of occult coronary disease in patients with advanced kidney disease.

The unfortunate combination of inaccurate diagnostic tests and a population of patients with a high pretest probability of disease ensures that the number of falsely negative test results will be unacceptably high. For simplicity sake, I will approximate the data presented above to estimate that noninvasive cardiac tests have a sensitivity and specificity of approximately 70%, and that the population pretest probability of occult coronary disease in transplant candidates is 40%. With these estimates, the general negative predictive value (the ability to exclude significant coronary disease) of noninvasive testing would be an acceptable 80%. However, as the patient's risk profile increases, test performance suffers (Table 1). If we consider a hypothetical higher-risk patient, such as one with diabetes and peripheral vascular disease, the pretest probability of coronary disease may be 75% or higher (20). In this patient, the negative predictive value is only approximately 40% (60% of all negative results will be falsely negative). The test adds less value than a coin toss; a cardiac angiogram will be required even with a negative noninvasive stress test. In fact, many candidates for renal transplantation have diabetes and other risk factors that raise the pretest probability of coronary disease to >50%. In such patients, negative noninvasive stress test results will have >30% false negative results. To the extent that the data of Ohtake *et al.* (19) are representative of the general diabetic transplant candidate, the high prevalence of occult coronary disease found (83.3%) indicates that noninvasive testing may not be helpful for the majority of high-risk transplant candidates. Failure to diagnose occult coronary artery disease may have a great impact on outcomes. Bennett *et al.* studied 11 dialysis patients with occult CAS, and found that 8 were dead within a mean of 19.8 mo (14). Intervention may improve outcomes; Manske *et al.* randomized 26 asymptomatic diabetic pretransplant patients with coronary disease to treatment by medical management or revascularization by surgery or angioplasty. Revascularization resulted in significantly fewer ischemic heart disease events after transplantation (21).

Table 1. Pretest probability of coronary disease

	PPV	NPV
10%	21%	95%
20%	37%	90%
30%	50%	84%
40%	61%	80%
50%	70%	70%
60%	80%	61%
70%	84%	50%
80%	90%	37%

In this table, noninvasive cardiac stress tests are assumed to have a sensitivity and specificity of 70% when applied to renal transplant candidates. The positive and negative predictive value (PPV and NPV) of the test result are presented based on the patient's pretest probability of disease. Accordingly, the ability to satisfactorily exclude significant coronary disease (NPV > 75%) will only occur if the pretest disease probability is 40% or less.

Only coronary angiography can reasonably exclude the presence of significant coronary artery disease in many high-risk transplant candidates. But the risks of this test include radiocontrast-induced nephropathy (RCIN) (22), atheroembolic disease (23), and other important complications (24). For the patient on dialysis who is undergoing pretransplant evaluation, the risk for RCIN may be less important, and coronary angiography would be a reasonable starting test for many high-risk patients. In contrast, the high-risk candidate who seeks preemptive living donor transplantation before dialysis poses a difficult problem. The risk for RCIN may be great enough that the patient may reach ESRD as a result of the procedure. Thus, the clinician is left with two disappointing choices: Wait for coronary angiography until the patient starts dialysis, or proceed and confront the risk of inducing RCIN and premature ESRD.

In conclusion, noninvasive cardiac stress tests are probably not accurate enough to sufficiently exclude significant coronary artery disease in high-risk renal transplant candidates. They provide a false sense of security, but leave many patients undiagnosed, with continued exposure to excessive cardiac risk and with a lost opportunity for beneficial therapeutic interventions. Better noninvasive tests are needed and improved technology should lead the way to a better future in this difficult area of clinical decision-making. The ideal test would be highly accurate and would not require the use of radiocontrast media. Until such a test is available, clinicians must use great care in the cardiac evaluation of high-risk renal transplant candidates.

References

1. Kasiske BL, Cangro CB, Hariharan S, Hricik DE, Kerman RH, Roth D, Rush DN, Vazquez MA, Weir MR; American Society of Transplantation: The evaluation of renal transplantation candidates: Clinical practice guidelines. *Am J Transplant* 1[Suppl 2]: 3–95, 2001

2. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr; American College of Cardiology; American Heart Association: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery–executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 39: 542–553, 2002
3. Stewart G, Jardine AG, Briggs JD: Ischaemic heart disease following renal transplantation. *Nephrol Dial Transplant* 15: 269–277, 2000
4. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK: Long-term survival in renal transplant recipients with graft function. *Kidney Int* 57: 307–313, 2000
5. Kramer BK, Zulke C, Kammerl MC, Schmidt C, Hengstenberg C, Fischereder M, Marienhagen J; European Tacrolimus vs. Cyclosporine Microemulsion Renal Transplantation Study Group. Cardiovascular risk factors and estimated risk for CAD in a randomized trial comparing calcineurin inhibitors in renal transplantation. *Am J Transplant* 3: 982–987, 2003
6. Rabbat CG, Treleaven DJ, Russell JD, Ludwin D, Cook DJ: Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: A meta-analysis. *J Am Soc Nephrol* 14: 431–439, 2003
7. Le A, Wilson R, Douek K, Pulliam L, Tolzman D, Norman D, Barry J, Bennett W: Prospective risk stratification in renal transplant candidates for cardiac death. *Am J Kidney Dis* 24: 65–71, 1994
8. De Lima JJ, Sabbaga E, Vieira ML, de Paula FJ, Ianhez LE, Krieger EM, Ramires JA: Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension* 42: 263–268, 2003
9. Marwick TH, Steinmuller DR, Underwood DA, Hobbs RE, Go RT, Swift C, Braun WE: Ineffectiveness of dipyridamole SPECT thallium imaging as a screening technique for coronary artery disease in patients with end-stage renal failure. *Transplantation* 49: 100–103, 1990
10. Holley JL, Fenton RA, Arthur RS: Thallium stress testing does not predict cardiovascular risk in diabetic patients with end-stage renal disease undergoing cadaveric renal transplantation. *Am J Med* 90: 563–570, 1991
11. Schmidt A, Stefenelli T, Schuster E, Mayer G: Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. *Am J Kidney Dis* 37: 56–63, 2001
12. Herzog CA, Marwick TH, Pheley AM, White CW, Rao VK, Dick CD: Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. *Am J Kidney Dis* 33: 1080–1090, 1999
13. Boudreau RJ, Strony JT, duCret RP, Kuni CC, Wang Y, Wilson RF, Schwartz JS, Castaneda-Zuniga WR: Perfusion thallium imaging of type I diabetes patients with end stage renal disease: Comparison of oral and intravenous dipyridamole administration. *Radiology* 175: 103–105, 1990
14. Bennett WM, Kloster F, Rosch J, Barry J, Porter GA: Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. *Am J Med* 65: 779–784, 1978
15. Weinrauch LA, D'elia JA, Healy RW, Gleason RE, Takacs FJ, Libertino JA, Leland OS: Asymptomatic coronary artery disease: angiography in diabetic patients before renal transplantation. Relation of findings to postoperative survival. *Ann Intern Med* 88: 346–348, 1978
16. Braun WE, Phillips DF, Vidt DG, Novick AC, Nakamoto S, Popowniak KL, Paganini E, Magnusson M, Pohl M, Steinmuller DR, *et al.*: Coronary artery disease in 100 diabetics with end-stage renal failure. *Transplant Proc* 16: 603–607, 1984
17. Lorber MI, Van Buren CT, Flechner SM, Cameron L, Leatherwood J, Walker WE, Smalling RW, Kahan BD: Pretransplant coronary arteriography for diabetic renal transplant recipients. *Transplant Proc* 19: 1539–1541, 1987
18. Manske CL, Wilson RF, Wang Y, Thomas W: Prevalence of, and risk factors for, angiographically determined coronary artery disease in type I-diabetic patients with nephropathy. *Arch Intern Med* 152: 2450–2455, 1992
19. Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, Saito S: High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: An angiographic examination. *J Am Soc Nephrol* 16: 1141–1148, 2005
20. Valentine RJ, Grayburn PA, Eichhorn EJ, Myers SI, Clagett GP: Coronary artery disease is highly prevalent among patients with premature peripheral vascular disease. *J Vasc Surg* 19: 668–674, 1994
21. Manske CL, Wang Y, Rector T, Wilson RF, White CW: Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. *Lancet* 340: 998–1002, 1992
22. Lindholt JS: Radiocontrast induced nephropathy. *Eur J Vasc Endovasc Surg* 25: 296–304, 2003
23. Saklayen MG, Gupta S, Suryaprasad A, Azmeh W: Incidence of atheroembolic renal failure after coronary angiography. A prospective study. *Angiology* 48: 609–613, 1997
24. Ammann P, Brunner-La Rocca HP, Angehrn W, Roelli H, Sagmeister M, Rickli H: Procedural complications following diagnostic coronary angiography are related to the operator's experience and the catheter size. *Catheter Cardiovasc Interv* 59: 13–18, 2003

See related article, "High Prevalence of Occult Coronary Artery Stenosis in Patients with Chronic Kidney Disease at the Initiation of Renal Replacement Therapy: An Angiographic Examination," on pages 1141–1148.