# A Call to Action: Variability in Guidelines for Cardiac Evaluation before Renal Transplantation

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## Summary

**Background and objectives** Candidates for renal transplantation are at increased risk for complications related to cardiovascular disease; however, the optimal strategy to reduce this risk is not clear. The aim of this study was to evaluate the variability among existing guidelines for preoperative cardiac evaluation of renal transplant candidates.

**Design, setting, participants, & measurements** A consecutive series of renal transplant candidates ($n = 204$) were identified, and four prominent preoperative cardiac evaluation guidelines, pertaining to this population, were retrospectively applied to determine the rate at which each guideline recommended cardiac stress testing.

**Results** The rate of pretransplant cardiac stress testing would have ranged from 20 to 100% depending on which guideline was applied. The American Heart Association/American College of Cardiology (ACC/AHA) guideline resulted in the lowest rate of testing (20%). In our population, 178 study subjects underwent stress testing: 17 were found to have ischemia and 10 underwent revascularization. The ACC/AHA approach would have decreased the number of noninvasive tests from 178 to 39; it would have identified only 4 of the 10 patients who underwent revascularization. The three other guidelines (renal transplant–specific guidelines) recommended widespread pretransplant cardiac testing and thus identified nearly all patients who had ischemia on stress testing.

**Conclusions** The ACC/AHA perioperative guideline may be inadequate for identifying renal transplant candidates with coronary disease; however, renal transplant–specific guidelines may provoke significant overtesting. An intermediate approach based on risk factors specific to the ESRD population may optimize detection of coronary disease and limit testing.

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## Introduction

There is a severe burden of cardiovascular disease in patients with ESRD. Heart disease accounts for 40 to 50% of all-cause mortality in this population and remains the largest source of morbidity and mortality among patients who have undergone renal transplantation (1,2). The prevalence of atherosclerotic coronary artery disease (CAD) in the ESRD population is significantly greater than age-matched controls and higher than can be explained based on the Framingham risk factors alone (1–5). The prevalence of CAD in this population has led to interest in screening patients for CAD before renal transplant; however, selection of transplant candidates for screening remains controversial.

Practice patterns in screening for ischemic heart disease before renal transplant vary widely and are often unique to individual transplant centers (6). Lentine *et al.* (6) showed this variability in an analysis of Medicare beneficiaries undergoing renal transplantation from 1991 to 2004. In this analysis, the overall rate of pretransplant cardiac evaluation (defined as noninvasive stress testing or coronary angiogram) was 46.3%. A survey of transplant centers showed that 18% of centers perform no routine cardiac testing in renal transplant candidates, 8% perform routine coronary angiogram in all transplant candidates, whereas the majority of centers test selectively in high-risk groups (7). The preferred modality of screening for CAD varied widely, with 15% of centers using angiography as their primary screening method, 7% using exercise stress without imaging, and the majority of centers using a stress imaging modality as their primary screening method.

There are at least four distinct clinical guidelines addressing the preoperative cardiac evaluation of renal transplant candidates. Each of these guidelines proposes unique criteria for pretransplant cardiac evaluation:

1. American College of Cardiology /American Heart Association 2007 Guidelines on Peri-opera-

tive Cardiovascular Evaluation and Care for Noncardiac Surgery (ACC/AHA) (8)
2. Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients (KDOQI) (9)
3. Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient (Lisbon) (10)
4. The Evaluation of Renal Transplant Candidates, which appeared in a journal published by the American Society of Transplantation (AST) (11)

We questioned whether the observed differences in clinical practice derive from variation in the guidelines cited above. We hypothesized that application of these guidelines to a cohort of renal transplant candidates would show large variations in guideline recommendations for pretransplant cardiac testing. In addition, we sought to evaluate the performance of each guideline algorithm in predicting rates of abnormal stress test results and coronary revascularization procedures.

## Materials and Methods

### Study Population

We retrospectively identified a consecutive series of transplant candidates presenting to a single academic medical center using an internal appointment scheduling database. All patients with a visit code corresponding to an initial transplant evaluation over the 3-year period from April 1, 2004 through April 1, 2007 were included. From this initial cohort, patients were excluded for the following reasons: active cardiac conditions (active cardiac conditions per the ACC/AHA document include significant valvular disease, decompensated heart failure, significant arrhythmias, and unstable coronary syndromes), age $<18$ years old, simultaneous pancreas transplant, miscoding of the visit (*i.e.*, liver transplant), disabling noncardiac conditions, lack of need for near term renal replacement therapy (defined as GFR $\geq 20$ ml/min per 1.73 $m^2$), and patient preference not to pursue transplant after initial visit. Follow-up data through the initial transplant evaluation, including all recommended cardiac testing, was available for 100% of the study subjects. No formal protocol for cardiac evaluation was applied to this cohort; cardiac screening was obtained at the discretion of the treating physician.

### Data Analysis

The clinical data required to apply each of the four national guidelines were collected via chart review. The four guidelines were applied to each study subject to evaluate whether cardiac evaluation would have been recommended. Guideline recommendations were categorized as either (*1*) proceed to transplant without further cardiac evaluation or (*2*) further cardiac evaluation recommended. We determined the recommended rate of preoperative cardiac evaluation for each guideline and compared this to the actual rate of cardiac evaluation. We defined cardiac evaluation as noninvasive stress test with imaging or coronary angiography. The majority of the study subjects had undergone cardiac stress testing with imaging. This allowed for comparison of the guidelines ability to predict ischemia on stress testing.

### Summary of the Guidelines and Their Application in This Study

Figure 1 shows a summary of each guideline algorithm. We applied the guidelines as they are depicted. In the nondiabetic population, the Lisbon document provides a list of clinical risk factors for cardiovascular disease but does not specify the number of risk factors needed to trigger cardiac evaluation. For the purposes of our study, we used a threshold of three or more of the Lisbon risk factors to trigger further cardiac evaluation in the nondiabetic arm of the Lisbon algorithm (note the Lisbon document recommends cardiac evaluation in all diabetic transplant candidates).

### Statistical Analyses

Results are expressed as means and SD where appropriate. The guideline's negative and positive predictive value for predicting ischemia on stress test and subsequent revascularization were examined. The Fischer exact test was applied to compare the rates ischemia between groups. A single multirater free marginal $\kappa$ test was applied to compare overall agreement between all four guidelines in a single statistical measure.

## Results

### Study Population

The initial query of the scheduling database identified 320 subjects with an appointment for a new transplant

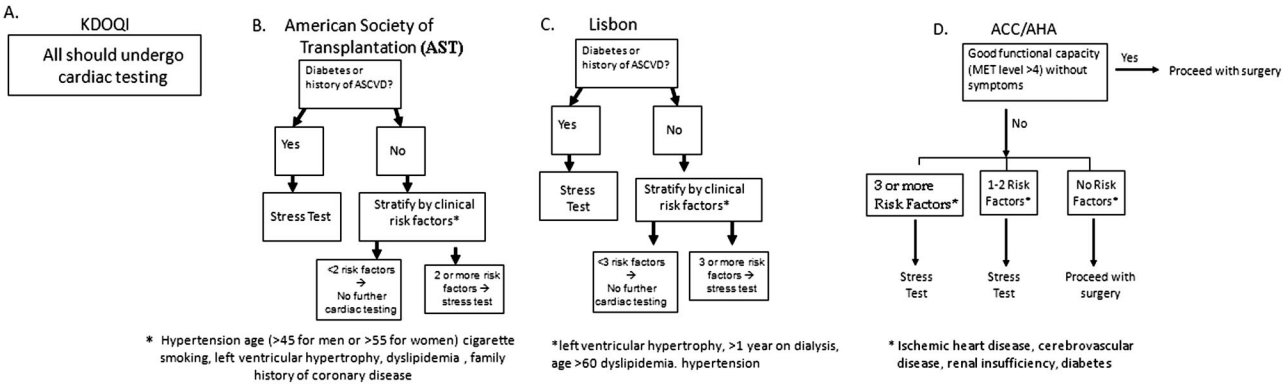


**Figure 1. | Overview of the four preoperative cardiac risk assessment guidelines.**

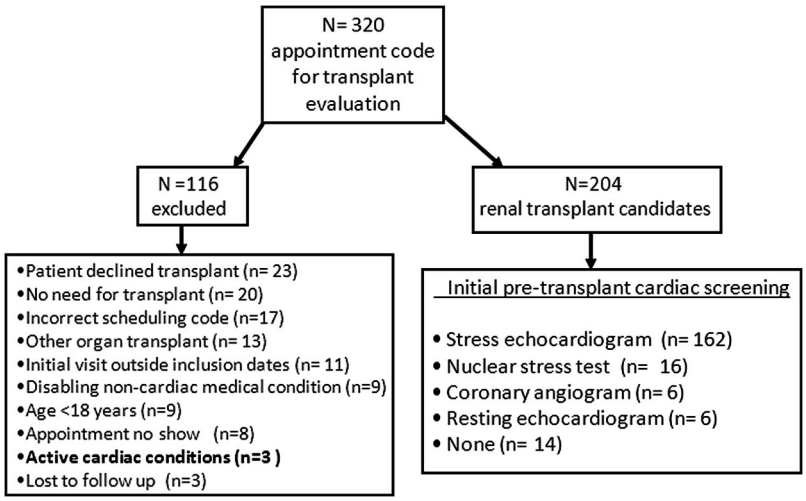


**Figure 2. | Overview of the study population.**

evaluation during the study's inclusion dates. One hundred sixteen patients were excluded (as detailed in Figure 2), yielding the study cohort of 204 viable renal transplant candidates. Noninvasive cardiac evaluation was obtained in 87% of the cohort (stress echocardiogram in 79%, nuclear stress test in 8%), whereas 3% ($n = 6$) underwent coronary angiography as their initial mode of cardiac evaluation (Figure 2). Table 1 shows the demographics of the sample population.

### Comparing Guidelines: Variation in Rates of Cardiac Evaluation

We retrospectively applied each of the four national guidelines to our series of consecutive renal transplant candidates to determine the rate at which each of the guidelines recommended cardiac evaluation. The recommended rate of cardiac evaluation was 100% for KDOQI, 92% for AST, 68% for Lisbon, and 20% for ACC/AHA (Figure 3). Our actual rate of cardiac evaluation in this same population was 90%. The renal transplant–specific guidelines (KDOQI, AST, and Lisbon) recommended cardiac evaluation at significantly higher rates than did the ACC guidelines (Fisher exact, $P < 0.0005$ for KDOQI *versus* ACC, AST *versus* ACC, and Lisbon *versus* ACC). Additionally, the overall agreement of recommendations for cardiac evaluation between the four guidelines was poor (free marginal $\kappa = 0.045$; free marginal $\kappa$: perfect agreement = 1, agreement equal to chance = 0, perfect disagreement = −1).

**Table 1. Demographics of the study population**

| | $n = 204$ |
|---|---|
| Age (years) | 52 |
| Male | 62% |
| History of coronary artery disease | 16% |
| History of revascularization | |
| percutaneous intervention | 10% |
| bypass surgery | 9% |
| Hypertension | 80% |
| Hyperlipidemia | 65% |
| Active tobacco use | 39% |
| Family history of coronary artery disease | 31% |
| Type I diabetes | 16% |
| Type II diabetes | 29% |
| Dialysis dependent | 54% |
| Duration of dialysis >1 year | 36% |
| Received transplant as of study end date | 49% |

### Comparing Guidelines: Rates of Ischemia on Noninvasive Testing

Of the 204 patients who underwent preoperative cardiac evaluation, noninvasive evaluation for ischemia was available in 178 (87% of study population). Ischemia was identified in 17 of the 178 patients (10%). Figure 4 analyzes the rate of ischemia with the subjects grouped based on the guidelines recommendations for preoperative cardiac evaluation. The KDOQI and AST guidelines would have supported nearly universal stress testing and thus would have recommended stress testing in all patients who turned out to have stress-induced ischemia. The ACC/AHA guideline would have recommended stress testing in 39 of the subjects. If the ACC/AHA guideline were applied, 4 of the 17 patients who were found to have ischemia on stress test would have been identified for stress testing. An alternative strategy such as our adaptation of the Lisbon document would have recommended cardiac evaluation in 124 patients (69%) and identified 16 of the 17 patients with ischemia (94%). It is noted that the one patient "missed" by the Lisbon approach had a false-positive stress test based on angiographic data. Table 2 shows the performance characteristics of each of the guidelines in predicting ischemia on stress test and revascularization before transplant.

### Comparing Guidelines: Rates of Revascularization

There were 17 subjects in our cohort with ischemia on stress test: 14 of these patients had coronary angiograms and 10 of these patients underwent revascularization (Table 3), 7 patients did not undergo revascularization (1

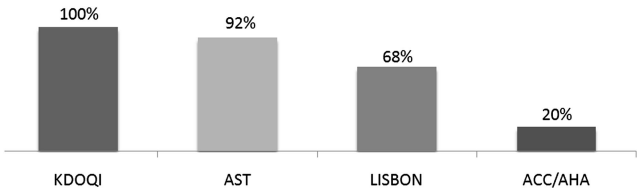


**Figure 3. | Predicted rates of cardiac evaluation in renal transplant candidates when the four national guidelines are applied.**

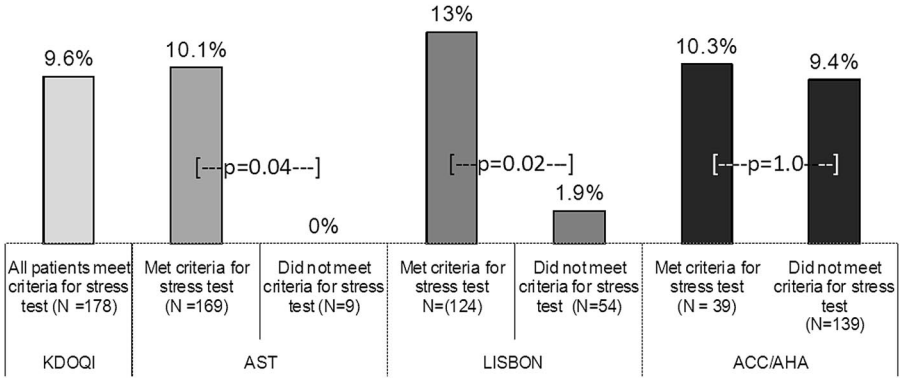


**Figure 4. | Rates of ischemia with stress testing in the 178 subjects who underwent preoperative stress testing.** Subjects are grouped based on each guidelines recommendation for cardiac evaluation.

**Table 2. Clinical guidelines performance in predicting positive stress tests**

| | KDOQI | AST | Lisbon | ACC/AHA |
|---|---|---|---|---|
| Positive predictive value | | | | |
| ischemia on stress test | NA | 10.1% | 12.9% | 10% |
| revascularization | NA | 5.9% | 8.1% | 10% |
| Negative predictive value | | | | |
| ischemia on stress test | NA | 100% | 98.1% | 90.6% |
| revascularization | NA | 100% | 100% | 91.1% |

Results refer to the guidelines positive and negative predictive value to predict ischemia on cardiac stress testing and need revascularization as a result of the stress testing. Results are based on the 178 patients who underwent stress testing. The KDOQI guideline recommends universal stress testing and thus was excluded from this analysis. NA, not applicable.

with single vessel disease not amenable to percutaneous intervention [PCI], 3 without significant coronary disease on angiogram, and 3 did not undergo angiogram for the following reasons: further noninvasive testing was negative, awaiting dialysis dependence before angiogram, and prior angiogram suggested inadequate targets for intervention). The ACC/AHA guidelines would have recommended cardiac evaluation in 4 of the 17 patients who had ischemia on stress test. All four of these patients underwent preoperative revascularization (one had three vessel coronary artery bypass grafting, one had two vessel PCI, and two had single vessel PCI). ACC/AHA guidelines would not have identified 13 of 17 subjects who had ischemia on stress test; of these 13 subjects, 6 underwent pretransplant revascularization (all single vessel PCI). The KDOQI, AST, and Lisbon guidelines would have recommended cardiac evaluation in all of the patients who underwent preoperative revascularization. There were five patients (three with ischemia on stress test and two who went directly to angiogram without stress testing) who had no significant coronary disease on angiogram.

## Discussion

Multiple expert groups have published guideline recommendations for preoperative cardiac assessment of patients being considered for renal transplantation (8–11). Our study showed the wide variability between these guidelines; we found that rates of stress testing range from 20 to 100% depending on which of these guidelines is followed. The national society guidelines and their varying recommendations are a major contributor to the variability in clinical practice. The guidelines that were produced by renal-specific societies (KDOQI, AST, and Lisbon) promote a more aggressive approach (essentially screening all candidates with stress testing) compared with the more conservative approach of the ACC/AHA guidelines, which

**Table 3. Description of renal transplant candidates with positive stress tests**

| Age (years) | KDOQI | AST | Lisbon | ACC/AHA | Angiogram | Intervention |
|---|---|---|---|---|---|---|
| 64 | + | + | + | − | Yes | None/single vessel disease |
| 50 | + | + | + | − | No | |
| 54 | + | + | + | + | Yes | Three vessel CABG |
| 53 | + | + | + | − | Yes | Single vessel PCI |
| 56 | + | + | + | − | Yes | Single vessel PCI |
| 49 | + | + | + | − | No | |
| 46 | + | + | + | + | Yes | Two vessel PCI |
| 44 | + | + | − | − | Yes | Clear coronaries |
| 66 | + | + | + | − | No | |
| 61 | + | + | + | − | Yes | Single vessel PCI |
| 48 | + | + | + | − | Yes | Single vessel PCI |
| 52 | + | + | + | − | Yes | Nonobstructive coronary disease |
| 56 | + | + | + | − | Yes | Clear coronaries |
| 51 | + | + | + | + | Yes | Single vessel PCI |
| 62 | + | + | + | − | Yes | Single vessel PCI |
| 36 | + | + | + | + | Yes | Single Vessel PCI |
| 37 | + | + | + | − | No | |

+ indicates guideline recommended stress testing; − indicates guideline did not recommend stress test. CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.

require the presence of either cardiac symptoms or poor functional status to consider stress testing. The increased rate of stress testing as advocated by the renal-specific societies might be justified given the scarcity of donor kidneys; however, the assumption that greater rates of stress testing results in better or safer outcomes may not be true. In some cases, the opposite may be true, with a false-positive stress test leading to unnecessary invasive procedures and complications.

Our data provide some insight regarding the optimal guideline screening strategy. During the 3-year study period, 90% of all viable renal transplant candidates had some form of cardiac evaluation (79% stress echo, 8% nuclear stress test, 3% direct to coronary angiography) that provided the denominator for our comparisons. Although the KDOQI guideline approach would have captured all subjects with abnormal stress tests and revascularizations, this comes at the cost of obtaining a stress test in all patients. In contrast, the ACC/AHA guideline approach would decrease the rate of stress testing significantly (by 80%), but this approach would have only identified 4 of 17 (24%) patients who had an abnormal stress test and only 4 of 10 (40%) who underwent revascularization. It is noted that the ACC/AHA approach would have identified the one patient who required coronary artery bypass grafting and the one patient who required two vessel PCI. All other interventions were single vessel PCI. Although the ACC/AHA guideline would have "missed" some of the patients with single vessel CAD, the benefit of PCI beyond medical therapy in these patients is not clear (12). In addition, the 1-year commitment to thienopyridines with drug-eluting stents may complicate or delay transplant surgery. The cost-effectiveness of routinely screening all renal transplant candidates for CAD is a controversial topic. There are currently 105,000 patients in the United States on the renal transplant waiting list. Assuming an average cost of $2000 for a stress test with imaging, applying the KDOQI guidelines to the transplant waiting list would cost $210 million. The ACC/AHA guidelines would result in an 80% reduction in cost, whereas the Lisbon approach would yield a 32% reduction in cost. This cost analysis refers only to the cost of the initial cardiac evaluation and does not include the cost of subsequent testing and revascularization procedures.

The comparison of renal-specific guidelines to the ACC/AHA perioperative guideline seems particularly important because the ACC/AHA guideline is the one guideline that most cardiologists and internists are familiar with. The renal-specific guidelines are less well known outside of the transplant community. The Lisbon guideline resulted in an intermediate approach recommending preoperative cardiac evaluation in 68% of the study subjects. Using the Lisbon approach, nearly all of the patients with abnormal stress tests were identified with the added benefit of requiring fewer tests.

With the growth of clinical guidelines, discrepancies in recommendations from different societies have been noted. Gordon *et al.* (13) described a conflict between the perioperative guidelines by the American College of Physicians and the AHA/ACC as "guideline chaos." Ultimately, the American College of Physicians stopped publishing an independent guideline. The guidelines applicable to renal transplant candidates seem to have similar conflicts, and resolution among societies is recommended. Multiple single-center studies have shown the ability of stress testing techniques to predict adverse events in the renal transplant population (14–16). However, there are no randomized trials that show identification of coronary disease by screening the asymptomatic patient results in better outcomes. There are a few studies that have evaluated this concept outside of the transplant population. The Detection of Ischemia in Asymptomatic Diabetics study showed no significant benefit to revascularization in asymptomatic diabetic patients with ischemia on nuclear perfusion scans (17). Given the high prevalence of diabetes in the transplant population, the Detection of Diabetes in Asymptomatic Diabetics may have relevance when considering em-

piric revascularization in asymptomatic renal transplant candidates. Randomized trials comparing PCI to medical therapy in patients preparing for vascular surgery have not been able to show a significant difference in perioperative events despite the presence of ischemia on preoperative stress testing (18,19). Although PCI has not been shown to have a clear benefit beyond medical therapy, in the absence of randomized data specific to the renal transplant candidates, some authors have tried to propose a rational approach to PCI once an angiogram has been obtained (20). This algorithm emphasizes that patients with high-risk anatomy (left main or equivalent) should be triaged to bypass surgery and the importance of optimal medical management in all patients with CAD. Our study suggests that selective screening based on clinical risk factors might be an effective strategy with regards to balancing clinical testing, diagnostic yield, and interventions.

There were limitations to our study. Patients with overt cardiac symptoms were not included in the study cohort, and our results should not be extrapolated to this group. It was our intent to evaluate the cardiac screening process in asymptomatic patients with multiple risk factors. Although the study size limited our ability to evaluate hard clinical endpoints such as death and myocardial infarction, we believe a strength of our study is that 90% of our cohort underwent at least some form of objective cardiac testing (stress test with imaging or angiography) for risk stratification. We were able to use the surrogate endpoints of presence or absence of ischemia on stress testing and rates of revascularization as indicators of how the various guideline algorithms would have performed. It is also acknowledged that we do not have angiographic data for all of our study subjects, and it is possible that some of the normal stress tests could be false negatives. A long-term follow-up study will be needed to address some of the hard clinical endpoints noted above. It is the hope of the investigators that this study serves to stimulate the debate regarding how aggressive renal transplant programs should be in their evaluations for coronary disease in patients without overt cardiac symptoms. Future studies that prospectively compare diagnostic strategies and their associated clinical outcomes should be encouraged.

In conclusion, there are multiple national guidelines that can be applied to the renal transplant candidate. There are stark differences in these guidelines that result in large variations between guideline recommendations for cardiac evaluation. Further efforts should be made at resolving these discrepancies because it seems the rate of stress testing can be safely lowered based on clinical risk factors with no decrease in the rates of detected ischemia or revascularization.

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**Disclosures**

None.

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