Putting the Comparison of 2008 and 2011 Appropriate Use Criteria for Stress Echocardiography in Perspective: Can Screening in Solid Organ Transplant be Appropriate?

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The study by Bhatia *et al.*,[1] "Comparison of the 2008 and 2011 Appropriate Use Criteria for Stress Echocardiography" in the current issue of *JASE* has identified a gap in the literature that at first seems insignificant but upon further examination has very important clinical and cost implications, particularly for academic centers with solid-organ transplantation programs. Patients being considered for solid-organ transplantation may seem a small niche population until one realizes that kidney transplantation alone in the United States has more than quadrupled since 1991. The most recent data from the US Department of Health and Human Services Organ Procurement and Transplantation Network report 23,360 kidney transplantations from January to October 2012 and 117,053 patients on the waiting list. All of these patients (plus those who are evaluated but not listed) will undergo some type of preoperative evaluation, and many will undergo cardiac testing for "screening" purposes. However, survey and registry data have demonstrated that significant variation exists from institution to institution with regard to the "standard" workup of asymptomatic transplantation candidates, ranging from routine coronary angiography to imaging stress testing to no testing at all.[2] Because waiting times before eventual transplantation can be years, repeat cardiac testing compounds the problem, as some professional societies have suggested routine surveillance of waitlisted patients. Suddenly, the numbers start to add up. The observations made in the study by Bhatia *et al.* at the Massachusetts General Hospital are probably not that far off from the situation at other large hospitals with dedicated solid-organ transplantation programs. The question is, who needs to change? Are clinical practice patterns out of step with appropriateness criteria? Or are appropriateness criteria a step behind with regard to good clinical practice?

In the retrospective chart review by Bhatia *et al.*,[1] the 2008 and 2011 appropriate use criteria were applied to a consecutive series of 252 clinically requested stress echocardiograms at a single large academic hospital (Massachusetts General Hospital; requesting providers consisted of 83 different health care providers, of whom 50% were cardiologists), and the appropriateness classifications were examined. An initial review of the results suggests that the 2008 guideline left too many studies unclassified, and the newer 2011 guideline classified a significantly larger number of studies. However, the authors noticed an important trend: the increase in "classifiable" studies was driven primarily by an increase in "inappropriate" studies. Furthermore, the increase in inappropriate studies was accounted for primarily by preoperative studies in patients being considered for solid-organ transplantation who were capable of ≥4 metabolic equivalents (METs) and were without cardiac symptoms. This difference in classification between the 2008 and 2011 guidelines is based on the following 3 details.

First, the 2011 guidelines include a series of 17 "general assumptions" that were not included in the previous version. Assumption 17 states, "As with other surgeries, the need for coronary artery disease (CAD) assessment prior to solid organ transplantation is related to patient and surgical risk. In general, solid organ transplantation should be considered in the vascular surgery category given that CAD is common in patients with diabetes mellitus who have end-stage renal disease."[3] It is not clear that this assumption is true, but this is one change that was made.

Second, the 2008 guidelines did include a section on preoperative assessment for noncardiac surgery and what the authors deemed "appropriate," but they did not include an "inappropriate" category for asymptomatic patients with moderate to good functional capacity (≥4 METs).[4] This is despite the fact that the published American College of Cardiology (ACC) and American Heart Association (AHA) 2007 guidelines on perioperative cardiovascular evaluation[5] would have been consistent with this recommendation. In the updated 2011 guidelines, categories are now included (Table 13, "Stress Echocardiography for Risk Assessment: Perioperative Evaluation for Noncardiac Surgery Without Active Cardiac Conditions") that classify studies as "inappropriate" for intermediate risk and vascular surgery in asymptomatic patients with moderate to good functional capacity. This is the category that allowed the significant increase in the ability to classify the stress echocardiographic studies (guideline recommendation 159).

Third, the 2011 guidelines downgraded the level of appropriateness for asymptomatic patients undergoing intermediate-risk surgery with poor or unknown functional status and one or more clinical risk factors from "appropriate" in the 2008 version to "uncertain." Therefore, this change would potentially take patients out of the "appropriate" category. The difficulty for clinicians is that this is inconsistent with the widely known ACC and AHA 2007 perioperative algorithm that states, "Consider noninvasive testing if it will change management" in these patients, although granted it is a class IIb recommendation, on the basis of level of evidence B.

With the changes between the 2008 and 2011 stress echocardiographic appropriateness criteria mentioned above, Bhatia *et al.*[1] make the following observations: The number of stress echocardiographic studies that could be classified increased from 42% to 88%. The absolute number of "appropriate" tests that were classifiable did not change (104 and 105, respectively). The absolute number of classifiable studies that were deemed "inappropriate" did change, from 11 to 105. Because their study was performed at a solid-organ

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transplantation center and with a significant number of referring physicians from hepatology or nephrology (19% and 16% of the referral base physicians, respectively), the authors report a very high percentage of patients who were referred as part of routine preoperative solid-organ transplantation evaluation (42% of the overall stress echocardiographic volume during this time period, or 106 studies). When the solid-organ transplantation patients were excluded from analysis, the rates of appropriate, inappropriate, and uncertain studies were 69%, 22%, and 9%, respectively. Among the studies not involving solid-organ transplantation, there is not much discussion of what contributed to the 31% deemed inappropriate or uncertain. However, the authors express concern about the "growing population [of solid-organ transplantation patient evaluations] in academic medical centers [that] is a significant driver of stress test utilization." The authors state that "the majority of inappropriate [stress echocardiographic] studies in the current analysis were performed in patients with moderate to good functional capacity (≥4 metabolic equivalents) being evaluated for noncardiac solid-organ transplantation." It is noted that the MET level was determined by chart review and thus based on activity levels self-reported by the patients; this is a potential methodologic flaw. Nonetheless, the point is taken: is it "appropriate" for these tests to be performed if the MET level is true? It is also noted that the percentages of inappropriate and appropriate stress echocardiographic studies that affected clinical management were not significantly different," suggesting that tests that would have been deemed "inappropriate" may still result in meaningful clinical decisions. Last, the clinical outcomes (revascularization procedures, changes in medical management, change in transplantation status, etc.) are not clearly linked back to appropriate or inappropriate tests. The authors do acknowledge a relatively new AHA and ACC scientific statement from 2012 on cardiac disease evaluation and management among kidney and liver transplantation candidates,[2] which has endorsement from the national professional transplantation societies and the National Kidney Foundation (NKF), which tries to address some of these issues. Bhatia *et al.* also support further studies to investigate outcomes related to perioperative evaluations in the solid-organ transplantation population.

Although the percentage of stress echocardiographic studies performed at the Massachusetts General Hospital for solid-organ transplantation candidates seems disproportionately high (42% of a consecutive series study population), it seems reasonable to postulate that at hospitals with solid-organ transplantation programs across the United States, this population may represent the highest percentage of asymptomatic patients who are potentially being "screened" for the presence of coronary disease with noninvasive imaging stress tests. In a limited query, it appears that our volume for stress echocardiography in asymptomatic solid-organ transplantation candidates in 2012 at Dartmouth Hitchcock Medical Center (a significantly smaller center than Massachusetts General Hospital that performs about 75 kidney transplantations per year) was roughly 4% of the overall stress echocardiographic volume and 8% of the dobutamine stress echocardiographic volume (the total echo volume for 2012 was roughly 15,000 studies of which 2,016 were stress echocardiograms).

The fundamental dilemma as to whether stress echocardiography might be considered appropriate in a high-risk asymptomatic population is not easy to reconcile. In the remainder of this editorial, I focus on kidney transplantation candidates because they account for the vast majority of solid-organ transplantation in the United States, and the burden of subclinical coronary disease is highest in this subgroup. It is noted that resting echocardiography can be particularly useful in liver transplantation candidates because of the high prevalence of pulmonary hypertension and arteriovenous shunting.

A review of the available literature and guidelines on the "appropriate" preoperative cardiovascular evaluation of kidney transplantation candidates can be confusing because different professional societies have made significantly different recommendations. This ranges from the fairly conservative ACC and AHA perioperative guideline algorithm mentioned above to the more aggressive "screening" approach of the 2005 NKF guidelines[6] and the American Society of Transplantation.[7] For many years, our own institution adopted an approach that followed the NKF's recommendations, and essentially almost all renal transplantation candidates underwent "screening" imaging stress tests; however, plans were made to look at the outcomes of this strategy in a more critical manner.

We retrospectively applied four different society guidelines to a consecutive series of almost 200 asymptomatic patients without any active cardiac symptoms who were being evaluated for renal transplantation[8] and observed the following results: The ACC and AHA perioperative guideline would have tested only 20% of the study population, whereas the NKF guideline would have tested 100%. However, although the ACC and AHA perioperative guideline led to less testing, it did not discriminate those with and without ischemia, as only four of the 17 patients found to have ischemia would have qualified for testing (of the 17, 10 were treated with revascularization). The "Achilles' heel" of the ACC and AHA perioperative algorithm in these patients seemed to be that moderate or good functional status (≥4 METs) without overt cardiac symptoms did not guarantee a lack of ischemia on noninvasive testing. We postulated that there are confounding factors for these patients. They tend to be younger compared with the more elderly patients presenting for hip and knee surgery (the upper age limit for kidney transplantation is generally about 70 years, with most patients being evaluated in their 50s and 60s), which may provide them with more "reserve." In addition, the MET level is based on self-reported activities and thus subject to bias; many have diabetes, which may mask symptoms; and many spend 3 days a week undergoing dialysis, and their symptoms may be nonspecific (a drop in blood pressure, muscle cramps, etc.). On the other hand, the overall rate of ischemia was low (10%), and continuing with testing in all renal transplantation candidates seemed excessive. A compromise approach on the basis of risk factors specific to the chronic kidney disease population resulted in a reduction of overall testing to 69% of the study population, and this approach would have been able to identify 16 of the 17 patients with ischemia on noninvasive testing (the one patient "missed" was later found to be a false-positive).

In the absence of current randomized controlled data, the compromise proposed by the writing committee in the 2012 AHA and ACC Foundation scientific statement on cardiac disease evaluation and management in kidney and liver transplantation (which was endorsed by the American Society of Transplant Surgeons, the American Society of Transplantation, and the NKF) was to use risk factors specific to the chronic kidney disease population as a guide to reduce unnecessary testing in asymptomatic transplantation candidates, while still not missing significant ischemia, as patients are evaluated to receive a resource that is not only limited but also very sensitive to contrast dye exposure. The risk factors identified included diabetes, prior cardiovascular disease, >1 year on dialysis, left ventricular hypertrophy, age > 60 years, smoking, hypertension, and dyslipidemia. The recommendation was for an imaging stress test if three or more risk factors were present, although the writing committee acknowledged that this was a class IIb recommendation, based on level of