Screening and Risk Stratification of Coronary Artery Disease in End-Stage Renal Disease

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ABSTRACT

End-stage renal disease (ESRD) is a growing global health problem with major health and economic implications. Cardiovascular complication is the major cause of morbidity and mortality in this population. Clustering of traditional atherosclerotic risk factors, such as diabetes, systemic inflammation, and altered mineral metabolism, contributes to enhanced systemic atherosclerosis in patients with ESRD. Prevalence of obstructive coronary artery disease (CAD) on coronary angiography exceeds 50% in this population. Despite having extensive CAD and vascular disease, patients with ESRD often do not present with classic symptoms because of impaired exercise capacity and diabetes. Furthermore, clinical trial data are exceedingly lacking in this population, resulting in considerable clinical equipoise regarding the optimal approach to the identification and subsequent management of CAD in these patients. Traditional clinical screening tools, including conventional risk prediction models, are significantly limited in their predictive accuracy for cardiovascular events in patients with ESRD. Noninvasive cardiac stress imaging modalities, such as nuclear perfusion and echocardiography, have been shown to improve the traditional clinical model in identifying the presence of CAD. Furthermore, they add incremental prognostic information to angiographic data. Novel imaging techniques and biomarker assays hold significant promise in further improving the ability to identify and risk-stratify for CAD. This review focuses on the current understanding of the clinical risk profile of asymptomatic patients with ESRD with an emphasis on the strengths and limitations of various noninvasive cardiovascular imaging modalities, including the role of novel methods in refining risk prediction. In addition, issues and challenges pertaining to the optimal timing of initial risk assessment ("screening") and possible repeat screening ("surveillance") are addressed. We also summarize the current data on the approach to the patient with ESRD being evaluated for transplantation in the context of recent guidelines and position statements by various professional societies. (J Am Coll Cardiol Img 2014;7:715–28) © 2014 by the American College of Cardiology Foundation.
Patients with ESRD also have substantially worse outcomes after a cardiac event. For instance, as demonstrated in a landmark study of more than 34,000 patients on dialysis, the 1-, 2-, and 5-year survival rates of patients with ESRD who have an acute myocardial infarction (MI) were 41%, 27%, and 11%, respectively (5). Data from the GRACE (Global Registry of Acute Coronary Events) showed that patients with ESRD had 3-fold higher in-hospital and long-term mortality and MI compared with the population not receiving dialysis (6). Renal dysfunction also is a well-known prognostic factor after coronary artery bypass grafting. Patients with renal replacement therapy undergong coronary artery bypass grafting have a high operative and long-term mortality (7). Patients with ESRD form the highest-risk group with adverse cardiac outcomes, and CAD screening/risk stratification thus assumes paramount importance. However, traditional atherosclerotic risk factors, including diabetes, hypertension, and dyslipidemia, are significantly more prevalent in patients with ESRD, but they only partially explain the increased risk for CAD and coronary events (8), thereby significantly limiting the predictive ability of traditional risk estimate tools. Furthermore, the Framingham risk score, the most well-validated CAD risk prediction tool, does not incorporate renal function (9). Pooled analyses from large epidemiologic studies have demonstrated poor predictive accuracy of the Framingham risk model in cardiovascular risk prediction in patients with chronic kidney disease (CKD), underestimating risk by as much as 50% (10).

**SERUM BIOMARKERS FOR RISK ASSESSMENT**

The limited predictive accuracy of traditional risk prediction instruments in the population with renal failure has led to an extensive search for “novel” risk factors, including the role of various biomarkers to help refine risk assessment. These include markers of myocardial injury, systemic inflammation, endothelial dysfunction, sympathetic overactivation, oxidative stress, and vascular atherosclerosis. These novel markers are significantly more prevalent in patients with ESRD, in whom they seem to have a stronger association with cardiovascular events compared with patients without ESRD (11).

Among the wide array of extensively studied biomarkers, the cardiac troponin assay seems to be most promising. Troponin T is an extremely sensitive indicator of myocardial necrosis. A meta-analysis from 28 prospective studies involving approximately 4,000 patients with ESRD with no symptoms found that a positive troponin T level (>0.1 ng/ml) was a major predictor for increased all-cause mortality (relative risk: 2.64) and cardiac death (relative risk: 2.55) when adjusted for age, diabetes, left ventricular hypertrophy (LVH), and depressed left ventricular (LV) function (12).

In a small study, positive troponin T in patients with ESRD with no symptoms at the initiation of dialytic therapy was found to predict coronary stenosis on coronary angiography (sensitivity: 92%; specificity: 64%; area under the curve: 0.77) (13). Conversely, the association between troponin I and outcomes was less clear because of varying assays and cutoffs. The U.S. Food and Drug Administration currently approves the measurement of troponin T in patients with ESRD, which is supported by the Kidney Disease Outcomes Quality Initiative, although this is not formally recommended (14). A recent statement by the American College of Cardiology Foundation highlighted the utility of troponin for prognostication in patients with ESRD but emphasized unresolved issues regarding its clinical utility in guiding clinical practice (15).

Although biomarkers do predict events, they are limited by their lack of specificity. The specificity of troponin is limited because it is elevated in more than one-third of patients with ESRD (likely related to LVH, hypertension/hypotension, and silent ischemia). Furthermore, in the presence of other promising biomarkers, selecting the best 1 or combination thereof for refining risk prediction and integrating into part of a systematic approach for the management of patients with ESRD will require well-designed prospective trials.

**CHALLENGES OF CAD SCREENING IN PATIENTS WITH ESRD AND CARDIAC STRESS IMAGING**

A large proportion of the population with ESRD cannot exercise because of frequent noncardiac...
comorbidities, thereby necessitating the use of pharmacologic stress. Several cardiovascular abnormalities associated with ESRD could limit the diagnostic and predictive accuracy of established noninvasive cardiac stress imaging tools (16). Altered endothelial function with impaired coronary flow reserve in the absence of epicardial stenosis is well known in diabetic patients with ESRD and could decrease the sensitivity of vasodilator stress testing (17). The presence of severe LVH also could compromise the sensitivity of myocardial perfusion single-photon emission computed tomography (MPS) by missing small and mild perfusion defects because of the partial volume effect. Increased LV mass or concentric remodeling also limits the diagnostic sensitivity of dobutamine stress echocardiography (DSE) for subtle wall motion abnormality (WMA) (18). In addition, increased afterload due to hypertensive response could cause transient cavity dilation, flat inotropic response, and WMA in the absence of underlying epicardial CAD. Yet, invasive and noninvasive angiographic evaluations of epicardial stenosis are known to be limited in assessing the functional significance of noncritical coronary stenosis or microvascular function (19).

One-quarter of all deaths in the population with ESRD is thought to be due to sudden cardiac death (20,21). A large proportion of patients with ESRD with sickle cell disease do not have significant epicardial CAD. Factors such as microvascular disease, LVH, systolic dysfunction, autonomic instability, electrolyte, and volume shifts associated with dialysis are potential contributors. Therefore, screening for CAD would have only a modest impact in this regard.

Despite these limitations, a large amount of data have validated the effectiveness and clinical utility of these noninvasive stress imaging techniques in patients with ESRD. This is especially true in those being evaluated for renal transplantation as part of pre-operative risk assessment and to predict post-renal transplant outcomes. Several regulatory bodies and scientific councils have published guidelines for the appropriate cardiac workup in patients with ESRD who are awaiting renal transplantation. The approach to patients with ESRD at the start of dialysis or for the nontransplant candidate is less clear because of a less robust body of evidence.

### SCREENING AND RISK ASSESSMENT IN PATIENTS NOT BEING EVALUATED FOR TRANSPLANTATION

#### CORONARY ANGIOGRAPHY

The presence of epicardial coronary stenosis (>50% or 70%) using invasive angiography has been reported in 50% to 70% of

| First Author, Year (Ref. #) | Modality N Age, yrs Male, % DM, % Known CAD, % Follow-Up Duration, months Type of Events % Positive Scans Findings |
|-----------------------------|---------------------------------|---------|---------|--------|-----------------|-----------------|-----------------|
| Kim et al., 2004 (28)       | Thallium; dipyridamole 227 58.6 54 51 13 34 ACM 22.5% with positive thallium (reversible and fixed defects) | Age >60 yrs, DM, and CRP >0.5 mg/dl had >40% probability of positive test results vs. 4% in the absence of these 3 factors. | 96% event-free survival for patients with normal perfusion study results at 1 yr |
| Hase et al., 2004 (29)      | Thallium; IV ATP 49 64 69 61 12 12 (median) MI, CD 27% reversible defects | Perfusion defect independently associated with death and MI. Survival free of hard events was 97.5% for normal perfusion study results at 3 yrs. |  |
| Momose et al., 2009 (30)    | Thallium; 14 exercise, 41 dipyridamole 55 55 70 90 0 42 ACM, MI 22% reversible defects; 20% resting defect | |  |
| Kim et al., 2012 (31)       | 99mTc-tetrofosmin; adenosine 215 57 52 57 12 50 CD, ACS, CHF 45% of patients had perfusion defect or SSS >4 Annual event rate: 15% in the high-risk cohort with abnormal MPS findings, 4.5% in the high-risk cohort with normal MPS findings, and 1.2% in the low-risk cohort. | |  |

ACM = all-cause mortality; ACS = acute coronary syndrome; ATP = adenosine triphosphate; CAD = coronary artery disease; CD = cardiac death; CHF = congestive heart failure; CRP = C-reactive protein; DM = diabetes mellitus; IV = intravenous; MI = myocardial infarction; MPS = myocardial perfusion single-photon emission computed tomography; SSS = summed stress score.
asymptomatic patients at the start of dialysis, with multivessel involvement in 25% to 40% of studied populations (22–24). Diabetes mellitus is a major predictor of CAD. Because these studies are small and selective, they likely overestimate the true burden of disease. Regardless, the risk and cost of using invasive angiography as a screening tool would be prohibitive.

**Nuclear Imaging. Stress MPS imaging.** MPS has been well validated as a powerful prognostic tool in patients with CKD (25–27). Less data exist for patients at the initiation of dialysis therapy (28–31). A summary of these is provided in Table 1.

One prospective study assigned 215 asymptomatic patients at the start of dialysis into low- and high-risk groups using clinical and echocardiographic parameters (31). High-risk subjects then underwent screening MPS. With an average follow-up of 4 years, the annualized rate of adverse cardiac events was 15% in the high-risk patients with abnormal MPS findings, 4.5% in the high-risk patients with normal MPS findings, and 1.2% in the low-risk patients. Diabetes, perfusion defect, and left ventricular ejection fraction (LVEF) were independent predictors of adverse outcomes. An abnormal MPS finding carried a relative risk of 3.3 compared with patients with normal results. Furthermore, MPS data added incremental value to the baseline clinical/echocardiographic model (Fig. 1). However, because of the size limitation, no firm conclusions can be drawn in terms of potential clinical/therapeutic implications of different risk categories based on the size, type, and

![Figure 1](https://example.com/figure1.png)

**Figure 1** Incremental Prognostic Value of MPS Over Baseline (Clinical Only) and Baseline Plus 2D Echocardiographic Variables

(Top) Global chi-square. (Bottom) Receiver-operating characteristic curve analysis. Adapted with permission from Kim et al. (31). AUC = area under the curve; Echo = echocardiography; MPS = myocardial perfusion single-photon emission computed tomography; SPECT = single-photon emission computed tomography; 2D = 2-dimensional.
location of the perfusion abnormality. Nevertheless, these studies show that there is a high prevalence of perfusion defects (25% to 45%) and that the presence of perfusion defects, especially ischemia, is a strong predictor of cardiac outcomes. Therefore, they provide a solid base for using MPS to identify high-risk populations at the start of dialysis. The systematic approach of initial stratification using clinical and echocardiographic information could be cost-effective. Asymptomatic patients without LV dysfunction, risk factors, or long-standing diabetes are at relatively low risk and would not benefit from further stress testing (32). However, the risk of those with “high clinical echocardiographic risk” can be further refined by using stress MPS imaging (31).

Similar findings were observed in a study of 121 patients already receiving chronic maintenance dialysis. Abnormal MPS findings and depressed LVEF were both strong independent predictors of outcomes. Patients with a high summed stress score and summed difference score (≥4) had a >5 times higher risk of cardiac death (33).

**Cardiac fatty acid metabolism radionuclide imaging.** The major source of energy for the normal myocardium is through myocardial fatty acid metabolism. Under conditions of myocardial ischemia, there is a switch from fatty acid metabolism to glucose as a primary source of energy. This change can be detected using fatty acid radiotracers, such as β-methyl iodophenyl-pentadecanoic acid (BMIPP). The impaired use by beta-oxidation leads to longer presence inside the cardiac myocytes, allowing it to be imaged (34). The imaging of this altered myocardial BMIPP metabolism at rest indicating changes triggered by the preceding ischemia has been termed “ischemic memory imaging.” Nishimura et al. (35) investigated the prevalence of CAD in patients on dialysis who underwent dual isotope thallium-201 and BMIPP single-photon emission computed tomography (SPECT) at rest followed by coronary angiography. An abnormal scan finding (BMIPP summed score of >6) predicted obstructive CAD with good diagnostic accuracy (sensitivity, specificity, and accuracy were 98%, 66%, and 90%, respectively.) The same authors also demonstrated the prognostic utility of dual isotope thallium-201 and BMIPP SPECT in 375 asymptomatic patients on dialysis with no history of CAD (36). After >3 years of follow-up, BMIPP summed scores ≥12 carried a >2-fold risk for cardiac death. Furthermore, BMIPP-thallium-201 mismatch (an indicator of ischemia) further refined risk stratification such that the cardiac death-free survival of patients with a mismatch score <7 was 96% as opposed to 53% in patients with a score >7 (Fig. 2). The results of this study show the potential of BMIPP SPECT in predicting cardiac death in asymptomatic patients on dialysis who do not have a history of CAD or MI. However, BMIPP is not yet approved in the United States.

**Coronary flow reserve assessment with positron emission tomography.** In patients with renal dysfunction, the severity of coronary vascular dysfunction, as assessed by positron emission tomography (PET), is a strong predictor of cardiac death. Murthy et al. (37) recently evaluated this hypothesis in 866 patients who underwent predominantly vasodilator stress PET imaging with rubidium-82 (17% ESRD) and were
followed for approximately 1 year. Those with abnormal coronary flow reserve (failure of myocardial blood flow to increase adequately on demand) had a significantly higher rate of cardiac mortality (10.7% vs. 3.2%/year in those with relatively preserved coronary vasodilator reserve, p < 0.0001). Identification of coronary vasodilator dysfunction improved risk stratification beyond comprehensive clinical assessment, LV systolic function, and semi-quantitative measures of myocardial ischemia and scar. A moderate net reclassification was seen after incorporating coronary flow reserve information, which was most notable in the intermediate-risk group (2% to 4% annualized of cardiac death). It appropriately downgraded 21% of them to low risk (0% annualized cardiac mortality) and upgraded 15% of them to high risk (9.8% annualized cardiac mortality) (37).

Therefore, the potential role of coronary flow reserve quantification may reside in risk-stratifying patients without overt regional perfusion defects with other imaging modalities and could be used to test medical therapy that could improve vasomotor function.

**Echocardiography-Based Assessment.**

Dobutamine stress echocardiography. Multiple studies using DSE have demonstrated its incremental prognostic utility over clinical data for demonstrating resting and stress-induced regional WMA. In 485 patients with CKD (one-half were on dialysis), a 25% increase in the percentage of segments with induced WMA by DSE was associated with higher all-cause mortality (hazard ratio: 1.40) after a mean follow-up period of 2.5 years (38). Similar results were demonstrated by combining clinical and stress echocardiography information (39). An abnormal DSE result had a hazard ratio of 4.3 (95% confidence interval: 1.8 to 10.0) for major cardiac events on multivariable analysis. This study substantiated a 2-tiered approach of initial stratification based on clinical variables followed by DSE for further risk refinement. DSE did not provide significant risk reclassification in the low-risk group. However, it did provide effective discrimination in the high-risk groups as defined by baseline clinical variables. These studies using DSE in patients with ESRD further support the approach of initial clinical risk factor evaluation to identify patients at risk who would be best discriminated by stress imaging.

Myocardial contrast echocardiography. Perfusion defects on rest myocardial contrast echocardiography without a stress component have been reported to have a modest positive predictive value and a high negative predictive value for detection of obstructive CAD (40). They also predicted cardiac death and revascularization (41). However, the small sample size together with the absence of stress imaging raises questions regarding the applicability of these data. The other major limitations of myocardial contrast echocardiography are image quality standardization and need of technical expertise to perform and interpret the study.

**Coronary Artery Calcium Measurement/Hybrid Imaging.**

Large epidemiologic studies have shown the correlation between a decrease in glomerular filtration rate and increased coronary artery calcium score (CACS) (42,43). When compared with subjects not on dialysis, patients with ESRD of different age groups and varying duration of dialysis have been reported to have a 2 to 5 times higher prevalence of coronary atherosclerosis as detected by CACS (44-46). In addition, they have a more severe burden of disease, because approximately 3 of 4 patients with ESRD had CACS >75th percentile for sex- and age-matched subjects without ESRD (46). Coronary calcification is often present and frequently progresses even in young adults (age 20 to 29 years) with ESRD who are receiving dialysis. The presence of coronary artery calcification was found in 80% of patients and among patients with calcification who underwent follow-up computed tomography (CT). CACS approximately doubled over a mean period of 2 years (45).

The CACS in patients with ESRD is a combination of calcification in the intima (related to ischemic heart disease in the population without ESRD) and the media (not present in patients without ESRD) (47). This has been used as the explanation of limited specificity in predicting stenotic disease in a small study of 18 patients with ESRD (48). However, a recent publication using coronary computed tomography angiography (CTA) for assessment of coronary plaques showed that the calcium score correlated well with plaque burden, and the diagnostic association between the calcium score and the atherosclerotic lesions was good irrespective of ESRD status (49).

In the general population, a calcium score of 0 is rarely seen in patients with significant coronary stenosis. Absence of calcium has a high (>95%) negative predictive value for significant angiographic coronary stenosis in symptomatic patients with a high pre-test likelihood of CAD (50). Some data also exist for CACS as a predictor of future cardiac events in the population with ESRD (51-54) (Table 2). As in the general population, CACS offered an incremental
predictive value to clinical risk factors. Overall, the results of these studies support the notion that patients with ESRD have a higher burden of atherosclerosis and that CACS has a great potential for CAD screening and risk stratification.

In this context, there may be a role for hybrid imaging, incorporating CACS along with other stress modalities, to refine the process for evaluation of high-risk patients with ESRD (Fig. 3). The prevalence of abnormal MPS findings and obstructive CAD in the general population is directly related to the magnitude of CACS. In addition, CACS (especially when severe) provides incremental prognostic information to perfusion defects from MPS (55,56). The annual overall cardiac event rate is approximately 3% in those with normal MPS findings with an underlying severe CACS compared with 0.7% in those with CACS <10. However, the known excellent negative predictive value of a CACS of 0 in excluding significant angiographic CAD or ischemia on functional testing makes it an attractive tool in serving as a gatekeeper for invasive angiography or stress testing in asymptomatic patients without a history of CAD (56).

This approach is supported by a recently published study (57) that evaluated the role of hybrid imaging (CACS, epicardial adipose tissue [EAT], volume, and myocardial perfusion imaging) using SPECT-CT (97.5%) or PET-CT (2.5%) in 411 patients with ESRD (86% on dialysis) awaiting kidney transplant. Compared with patients with no perfusion defect, patients with abnormal scan results had higher median CACS (412 vs. 27.5) and EAT volumes (148.5 ml vs. 115.7 ml). Likewise, CACS and EAT were independently associated with abnormal perfusion in multivariate logistic regression analysis. On the basis of these findings, the authors propose using CACS and EAT as potential “filters” for downstream testing (57).

For a wider adoption of hybrid imaging in the pre renal transplant population, larger studies with hard clinical endpoints are needed. In addition, the cost-effectiveness of this approach along with establishing optimal cutoff values for CACS and potentially EAT as risk predictors will need to be studied systematically (58).

**CORONARY CTA.** Recent advances have made possible the noninvasive assessment of CAD with
graphic CAD, the potential role of CTA likely rests in normal CTA results in excluding significant CAD, making major obstructive CAD unlikely. Although the overall correlation between high CACS and obstructive disease was good, a significant number of patients with CACS between 400 and 2,000 had <70% stenosis, with many having <50% disease by CTA in the major coronary arteries. The main challenge of interpreting CTA in patients with ESRD is to overcome the adverse effect of the high calcific burden seen in this population. In the study by Mao et al. (62), 10% of the scans were deemed uninterpretable.

Yet, a recent publication (63) lends support to the potential role of CTA in patients with ESRD. In 70 patients with ESRD on long-term dialysis undergoing CTA, the prevalence of significant CAD (luminal narrowing >50%) was 43%. More than 90% of the segments were interpretable; 19 of the 54 interpretable segments were considered uninterpretable because of extensive calcification. The remaining 35 segments were considered uninterpretable for technical reasons, including motion artifacts and poor contrast arrival. After 2 years of follow-up, 36% of those with CAD had a cardiac event compared with none of the patients with no significant CAD (p < 0.01) (63). Further studies using the newer generation of multidetector CT are needed to see whether the new advances in CTA technologies (wide coverage, dual-source/energy detectors, perfusion, faster gantry, and new detector materials) can improve the diagnostic performance in this challenging population. In view of the known excellent negative predictive value of a CACS of 0 and normal CTA results in excluding significant angiographic CAD, the potential role of CTA likely rests in serving as gatekeeper for invasive angiography in those patients with submaximal, equivocal, or mildly abnormal stress testing results.

**Cardiac Magnetic Resonance Imaging.** Myocardial scar pattern and burden on cardiac magnetic resonance (CMR) are well validated for risk assessment of ischemic heart disease in the general population. Such data do not exist in patients with ESRD. The presence of subendocardial scar by delayed hyperenhancement CMR in a small number of patients with ESRD has been related to CAD risk factors, depressed LVEF, and severe CAD on angiography (64). Unfortunately, the risk of gadolinium-induced nephrogenic systemic fibrosis in ESRD precludes the use of CMR (65). A safer contrast agent, such as ferumoxytol, has mainly intravascular distribution after administration, so it does not seem to have significant potential for scar assessment in this population (66).

**Screening and Risk Stratification of the Patient with ESRD Being Evaluated for Transplantation**

Patients being considered for renal transplantation generally undergo comprehensive cardiac assessment. Considering the limited organ availability and the ever growing demand, such risk assessment could help in determining transplant candidacy. In addition, CAD remains the major cause of death post-renal transplantation, with approximately one-third of all such deaths due to MI (67,68). Identifying patients who may benefit from pre-operative coronary revascularization might decrease perioperative and post-transplant cardiac events (69).

Almost all pre-transplant evaluation studies centered their efforts on identifying the presence of epicardial coronary stenosis in pre-renal transplant recipients using invasive coronary angiography or noninvasive stress imaging, such as MPS or DSE. Exercise electrocardiography (ECG) has been reported to have a low sensitivity (32%) in detecting CAD in this population (70). The often associated ECG abnormality (e.g., LVH) and reduced exercise capacity also make exercise ECG testing not suitable for screening purposes.

**Invasive Coronary Angiography.** Angiographic prevalence of CAD in patients undergoing pre-transplant evaluation (>50% or 70% luminal stenosis) ranged from 40% to 60%, with multivessel involvement in 20% to 33% of the studied populations (71–73). The presence of angiographic CAD also predicted cardiovascular events in 106 patients before renal transplantation. After 4 years, only 6%
of patients with <70% coronary artery stenosis had a cardiac event compared with those with >70% stenosis (71).

In a large study of 3,698 patients who were referred for MPS as part of renal transplant evaluation, significant CAD (>50% stenosis) was found in 62% of 260 patients who underwent invasive angiography (33% with 3-vessel disease). After a mean follow-up of 30 ± 15 months, depressed LVEF, myocardial perfusion defects on MPS, diabetes, and age >45 years were all predictors of worse outcome, whereas degree of angiographic CAD was not. In addition, revascularization improved survival only in the subset of patients with 3-vessel disease without previous coronary artery bypass graft surgery but not in others (72). Similar results were reported in a cohort of 222 patients (73). There was no apparent survival difference between patients who underwent angiography and patients who did not. Therefore, on the basis of these findings, routine invasive angiography before transplant is not recommended.

**NONINVASIVE CARDIAC STRESS IMAGING.** Several studies examined the “diagnostic performance” of MPS and DSE using coronary luminal stenosis on invasive angiography as the endpoint (defined as luminal narrowing >50% in any epicardial vessel). The sensitivity of MPS ranged from 29% to 100%, and specificity ranged from 31% to 88% (74–77). Stress-induced WMA on DSE had a sensitivity of 44% to 96% and a specificity of 60% to 100% (70,78–84) for identifying luminal stenosis >50%. In addition to challenges mentioned earlier, there are additional reasons that could explain this wide range of diagnostic accuracy. Balanced ischemia can be missed by MPS. The sample size of these studies was small, and there is significant verification bias because only positive studies undergo invasive angiographic correlation. Most important, a luminal stenosis of 50% or even 70% often can be physiologically and hemodynamically insignificant (19,85). In the landmark FAME (FFR vs Angiography for Multivessel Evaluation) trial, only 35% of stenosis in the 50% to 70% range (cutoff used in most diagnostic accuracy studies for stress tests) was functionally significant (fractional flow reserve <0.80) (85). Whether this applies to patients with ESRD is not clear. However, it would be reasonable to adapt the well-accepted approach of using hard clinical endpoints as outcome measures for reflecting the predictive accuracy of stress imaging rather than using anatomy as the endpoint. A large amount of data amassed over the past 2 decades have firmly established the prognostic value of both MPS and DSE in risk stratification of the pre-transplant patient (74–84,86). A pooled analysis of 12 studies (8 using thallium MPS and 4 using DSE) showed that the presence of ischemia conferred a 6-fold risk of MI and a 4-fold risk of cardiac death (87). Yet, the presence of scar or fixed defects only predicted cardiac death (relative risk: 4.7) but not MI. Normal MPS results conferred an event-free survival of 97.7% for MI and 96.9% for cardiac death at 1 year (87). A more recent study using MPS with technetium-99m also confirmed that the presence of reversible perfusion defects on MPS had an adjusted hazard ratio of 1.92 (95% confidence interval: 1.1 to 4.4) for mortality (88). More important, the functional information derived from MPS or DSE was a more powerful predictor of outcomes than the purely anatomic information from angiography (72,89,90).

**GUIDELINES**

Several regulatory bodies and scientific councils, including the recent American College of Cardiology and American Heart Association guidelines, have emerged to provide a framework for the appropriate workup of the patient with ESRD awaiting renal transplantation (91–95). A summary of these guidelines is provided in Table 3. The common theme in the recommendations is against routine invasive coronary angiography for CAD screening. Asymptomatic patients with 3 or more risk factors (diabetes mellitus, previous CAD, >1 year on hemodialysis, LVH, age >60 years, smoking, hypertension, and dyslipidemia) should receive a noninvasive stress test regardless of functional status. Although none of the guidelines specify which stress imaging modality to use, the general opinion is that the modality with the best local expertise and experience should be used. In general, the indication for invasive coronary angiography and revascularization should be similar to that for the general population. Routine angiography and then prophylactic coronary revascularization before transplantation surgery in stable patients without established indications to improve symptom or survival are not recommended.

**REPEAT OR SURVEILLANCE TESTING**

In regard to the issue of repeat stress testing (surveillance), there is no consensus between the different guidelines (91–95). According to the 2012 American Heart Association/American College of Cardiology document, the value of the practice to reduce cardiac events in the pre-transplant population is uncertain (94). On the contrary, the 2005
TABLE 3 Summary of Guidelines for the Appropriate Workup for the Patient With ESRD Awaiting Renal Transplantation

<table>
<thead>
<tr>
<th>Guideline (Ref. #)</th>
<th>Recommendations</th>
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<tr>
<td>2012 ACC/AHA Scientific Statement (94)</td>
<td>Noninvasive stress testing may be considered in those with no active cardiac conditions: presence of multiple CAD risk factors regardless of functional status (Class IIb, Level of Evidence: C). Relevant risk factors include diabetes mellitus, prior cardiovascular disease, &gt;1 yr on dialysis, LV hypertrophy, age &gt;60 yrs, smoking, hypertension, and dyslipidemia. The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers ≥3 to be reasonable. The usefulness of periodically screening asymptomatic subjects for myocardial ischemia while on the transplant waiting list to reduce the risk of MACE is uncertain (Class IIb; Level of Evidence: C).</td>
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<tr>
<td>2007 Lisbon Conference (92)</td>
<td>Noninvasive and/or invasive testing should be considered in highest risk patients with the following conditions: diabetes, prior CV disease, and multiple cardiac risk factors, e.g., &gt;1 yr on dialysis, LV hypertrophy, age &gt;60 yrs, smoking, hypertension, and dyslipidemia. Does not specify the number of risk factors to justify testing.</td>
</tr>
<tr>
<td>2005 NKF/KDOQI Guidelines (91)</td>
<td>Noninvasive stress testing recommended for all patients with diabetes; repeat every 12 months; prior CABG, repeat every 12 months; if prior PCI, repeat every 12 months; if prior CABG, repeat after first 3 yrs and then every 12 months. Repeat testing every 24 months in “high-risk” nondiabetic patients, defined as ≥2 traditional risk factors, known history of CAD, LVEF ≤40%, peripheral vascular disease.</td>
</tr>
<tr>
<td>2001 AST Guidelines (93)</td>
<td>Noninvasive stress testing recommended for patients at “high risk,” defined as renal disease from diabetes, history of ischemic heart disease, or ≥2 risk factors. Coronary angiography for possible revascularization before transplantation recommended for patients with a positive stress test result. Revascularization before transplantation recommended for patients with critical coronary lesions.</td>
</tr>
<tr>
<td>2000 European Best Practice Guidelines (95)</td>
<td>Thallium scanning recommended for patients with history of MI or “high-risk” clinical features. Coronary angiography recommended if thallium scanning is positive; revascularization advised if lesions are suitable.</td>
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ACC/AHA — American College of Cardiology/American Heart Association; AST — American Society of Transplantation; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CV — cardiovascular; LV — left ventricular; LVEF — left ventricular ejection fraction; MACE — major adverse cardiac events; MI — myocardial infarction; NKF/KDOQI — National Kidney Foundation/Kidney Disease Outcomes Quality Initiative; PCI — percutaneous coronary intervention.

It is well established that patients with ESRD are a very high-risk group for CAD and often do not have a typical presentation of myocardial ischemia. Although strategies incorporating clinical and stress imaging information have been used with an overall good degree of accuracy to detect CAD and risk-stratify these patients, multiple challenges remain regarding CAD screening in the asymptomatic patient with ESRD.

It seems reasonable to be more aggressive in screening transplant candidates for CAD considering the surgical risk and the need to ensure the best use of a limited organ supply. As opposed to the pre-transplant population, no formal guidelines exist for screening and risk stratification in patients on dialysis who are not being considered for transplant. The wide array of screening tools and lack of randomized trial data make clinical decision-making challenging. Furthermore, a high-risk cohort and accurate testing modalities do not automatically justify routine and/or early aggressive screening as evidenced by lessons learned from the DIAD (Detection of Ischemia in Asymptomatic Diabetes) study (97). The hypothesis of identifying and treating high-risk patients with ESRD could lead to improved survival, and the cost-effectiveness needs to be rigorously studied in randomized trials.

The realistic expectation of screening and risk stratification that could have a meaningful impact on patient outcomes would be to identify patients at high risk for coronary events and cardiac death. In addition to intensive risk factor modification, the next step would be to identify those with severe and extensive flow-limiting CAD (left main or 3-vessel disease), whereby revascularization has the potential to improve outcomes as suggested by some observational data (98) and a small randomized trial involving 26 patients more than 2 decades ago (69). Therefore, we propose that patients with ESRD with high clinical risk (patients with diabetes, known vascular disease, biomarker evidence of subclinical myocardial injury, or LV dysfunction) and patients...
without high clinical risk but with a high burden of coronary calcium could best benefit from further risk refinement with stress imaging modalities of choice. Patients who have high-risk stress findings should be further assessed with coronary angiography and treated accordingly (Fig. 4). Patients with high clinical risks or non-zero CACS who have mildly abnormal or equivocal findings could be further assessed with coronary CTA to exclude the presence of severe diseases (left main or multiple-vessel disease) because their condition could be underestimated by noninvasive imaging. The issue of repeat testing is relevant in patients with ESRD in view of a shorter “warranty period” after a normal stress test result and increasing risk with longer duration of dialysis therapy. Thus, there is a great need for innovative strategies, such as hybrid imaging to refine temporal risk prediction, and vigilant monitoring of these patients for any symptom.

**BEYOND CAD SCREENING**

Screening and risk stratification for CAD are important but only partial components in improving the overall cardiovascular outcomes of patients with ESRD. In addition to CAD, the presence and severity of LVH, LV dilation, and dysfunction are also independent predictors of cardiovascular death in these patients (99). More than 70% of patients with ESRD have ECG or echocardiographic evidence of LVH (100) in response to chronic hypertension and fluid overload, anemia, oxidative stress, and hyperparathyroidism (101). Moreover, LVH regression or progression after treatment of these risk factors is predictive of cardiovascular event outcomes (102,103). Therefore, early detection of both CAD and LVH in conjunction with aggressive risk factor modification should be part of the integral management for patients with ESRD.

In addition, sudden cardiac death due to non-ischemic causes, such as uremic cardiomyopathy, vascular inflammation, and arrhythmic risk related to LV systolic dysfunction and electrolyte shifts, is unfortunately part and parcel of ESRD/dialysis and cannot be reversed even with successful coronary revascularization unless transplantation has been undertaken.

Finally, limited evidence is available on the appropriate management of heart disease in patients with ESRD because virtually all randomized clinical trials have excluded patients with ESRD. Therefore, well-designed clinical studies to provide guidance for both the risk stratification and the management of the growing number of these high-risk patients are urgently needed.

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