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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.

End-stage renal disease (ESRD) represents advanced dysfunction of the glomerular filter apparatus (glomerular filtration rate <15 ml/min/1.73 m^2), which being essentially irreversible, warrants renal replacement (1). More than one-half million patients in the United States have ESRD according to 2010 data from the U.S. Renal Data System, with an annual incidence of >100,000 new cases reported in 2008 (2). The estimated annual economic cost of ESRD is approximately $47.5 billion (2).

CARDIOVASCULAR MORBIDITY AND MORTALITY IN ESRD: RATIONALE FOR SCREENING AND RISK STRATIFICATION

Patients with ESRD are 8 times more likely to die compared with the general U.S. population (1), and cardiovascular causes account for >40% of all deaths (3). Atherosclerotic coronary artery disease (CAD) is a large proportion of the cardiovascular disease spectrum in patients with ESRD, with the prevalence being several-fold greater than in age-matched

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ABBREVIATIONS AND ACRONYMS

BMIPP = β-methyl iodophenyl-pentadecanoic acid

CACS = coronary artery calcium score

CAD = coronary artery disease

CKD = chronic kidney disease

CT = computed tomography

CTA = computed tomography angiography

DSE = dobutamine stress echocardiography

EAT = epicardial adipose tissue

ECG = electrocardiography

ESRD = end-stage renal disease

LV = left ventricular

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

MI = myocardial infarction

MPS = myocardial perfusion single-photon emission computed tomography

PET = positron emission tomography

SPECT = single-photon emission computed tomography

WMA = wall motion abnormality

subjects without ESRD. This high prevalence of CAD can be partially explained on the basis of the clustering of traditional atherosclerotic risk factors in ESRD (1). Furthermore, patients with ESRD who have documented CAD often are asymptomatic, likely because of the presence of diabetic or uremic neuropathy or impaired exercise capacity (4).

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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 undergoing 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