P atients with advanced chronic kidney disease (CKD), including end-stage renal disease (ESRD), represent both an enigma and a challenge to cardiovascular specialists. A gradient of increasing hazard of all-cause mortality with advancing degrees of CKD is well recognized. Reported adjusted mortality rates (per 1,000 patient-years) for patients 65 years of age and older are 64, 109, and 266, respectively, for those with stage 3 CKD, with stage 4 to 5 CKD, and undergoing dialysis (vs. 54 for patients without CKD) (1). The largest contributor to increased morbidity and mortality in patients with advanced CKD or ESRD is a disproportionately high cardiovascular disease (CVD) burden (Figs. 1A and 1B). Less well recognized is that the factors contributing to increased CVD mortality transition from atherosclerotic causes in advanced CKD (a largely older population) to nonatherosclerotic causes in ESRD (Fig. 2). Arrhythmias and sudden cardiac death (SCD) account for 27% of all deaths (62% of cardiovascular deaths) among dialysis recipients; annual mortality rates of 5% to 7% are attributed to SCD alone, likely related to nonatherosclerotic mechanisms, such as left ventricular (LV) hypertrophy and myocardial fibrosis (2). Hakeem et al. (3) provide strong support for the importance of nonatherosclerotic mechanisms of cardiac death (rather than obstructive coronary artery disease [CAD]) in patients with advanced CKD. Patients with entirely normal myocardial perfusion single-photon emission computed tomographic studies had annual cardiac death rates of 0.4% for an estimated glomerular filtration rate (eGFR) of 90 ml/min/1.73 m², 0.9% for an eGFR of 60 to 89 ml/min/1.73 m², 2.2% for an eGFR of 30 to 59 ml/min/1.73 m², and 4.7% for an eGFR < 30 ml/min/1.73 m². Although it is tempting to ascribe these findings to the diminished sensitivity of stress nuclear imaging for detection of obstructive CAD in patients with severe CKD (4), the authors of this editorial believe that the key issue these data present (concordant with the attenuation of benefit found in randomized clinical trials of statins in dialysis recipients) is the large mortality hazard due to nonatherosclerotic disease in patients with advanced CKD, and especially those requiring dialysis.

Imaging modalities offer tremendous potential to improve understanding of this continuum of high CVD burden in advanced CKD, as discussed in 2 review papers in this issue of JACC. Edwards et al. (5) make a compelling argument for considering cardiac magnetic resonance (CMR) as the gold standard for evaluating “uremic” cardiomyopathy. The descriptors leading to current understanding of uremic cardiomyopathy (probably more accurately designated as “cardiomyopathy of CKD”) have been mainly derived using transthoracic echocardiography. These investigators (5) illustrate several advantages of CMR over transthoracic echocardiography, including better spatial resolution for estimation of LV mass and more accurate estimation of LV and right ventricular systolic function, but most importantly, they offer insights into the etiopathogenesis of cardiomyopathy by using tissue characterization.
Safe and accurate illustration of myocardial fibrosis promises to be the Rosetta Stone for deciphering the mystery of SCD in ESRD. Before the description of nephrogenic systemic fibrosis, 2 trends were evident in the literature pertaining to patterns of late gadolinium enhancement (LGE): 1) a higher volume of LGE was described among patients with progressively worsening CKD (associating with increasing LV mass); and 2) several distinctive patterns of LGE were noted, of which only a minority were related to infarction and the others were probably indicators of an inflammatory state. For clinicians, the obvious missing element from these smaller, cross-sectional studies is a systematic, prospective correlation of these LGE patterns with adverse clinical outcomes, particularly SCD.

The implication of gadolinium in the development of nephrogenic systemic fibrosis, a rare but devastating disease, has proven thus far to be a formidable barrier to further research in this area. Meanwhile, provocative clinical work has identified systemic inflammation, vascular inflammation, endothelial dysfunction, and myocardial fibrosis as possibly playing central roles in the high rates of SCD among patients with ESRD. The most recent example is a small but promising randomized trial in 309 hemodialysis recipients that was reported by Matsumoto et al. (6); it, showing that aldosterone blockade with low-dose spironolactone led to reductions in cardiovascular events and all-cause mortality. Because hypokalemia has been implicated in the pathogenesis of SCD in patients with ESRD, a possible confounder is that the “potassium-sparing” effect of spironolactone may itself have played a significant role. In the imaging arena, T1 mapping using CMR has shown promise in fibrosis evaluation by offering the distinct advantage of intrinsic tissue characterization in the absence of gadolinium-based contrast. Several technical wrinkles are being ironed out (7), and even though this technique may not yet be ready for universal use, the authors of this editorial hope that its use can be expanded to the population with ESRD in the near future. Most ideally, multimodality imaging (including CMR) would be prospectively incorporated into clinical trials such as the WED-HED (Wearable Cardioverter Defibrillator in Hemodialysis Patients) study, which is designed to evaluate the benefit of wearable external defibrillators in preventing SCD in hemodialysis recipients.

Also in this issue of JACC, Hakeem et al. (8) tackle the vexing issue of “screening” for CAD, particularly risk assessment before renal transplantation. The existing literature is particularly confusing because it reports on a potpourri of imaging modalities without a consistent gold standard or rigorous clinical
endpoints. Central to this confusion are disagreements among premier institutions regarding the pursuit of “ischemia-based” evaluation (noninvasive risk stratification) versus “structural” evaluation (direct coronary angiography). Considering the large number of renal transplants performed worldwide and the 5-fold higher numbers of patients on waiting lists (17,671 transplants and 90,474 wait-listed patients in the United States in 2011), it is certainly not a matter of pride for the medical community that this subject has not been more systematically and deliberately addressed to date. In fact, the basic premise that screening for CAD and resultant prophylactic revascularization in asymptomatic patients with advanced CKD leads to improved post-operative and long-term outcomes has not yet been adequately tested. Importantly, this premise was tested and proven incorrect in the general population.

Several centers rely on cardiovascular biomarkers, particularly high-sensitivity troponins, to detect high-risk substrate (predictive of higher probability of short- and long-term mortality), rather than merely identifying obstructive CAD alone; this approach appears to be more plausible, on the basis of our knowledge of the high incidence of non-atherosclerotic causes of death among patients with ESRD. Another noteworthy limitation in the literature is the lack of validation data pertaining to the use of fractional flow reserve estimation in patients with ESRD and its predictive role in estimating long-term outcomes. Conceivably, lack of fractional flow reserve use in centers adopting a “direct” coronary angiography technique relying on qualitative estimation of CAD alone could result in “unnecessary” coronary revascularization procedures. Thus, overall, the authors of this editorial contend that an “ischemia-based” strategy is a more conservative intermediate step that can help direct the need for, and identify territories for, coronary revascularization while simultaneously obviating the costs and risks (including contrast nephropathy) of an invasive approach in most patients. This critical clinical issue will be addressed by the ISCHEMIA-CKD trial (NCT01985260).

In this quest to identify the most accurate noninvasive diagnostic modality in an “ischemia-based” strategy, 1 notable study that is conspicuous by its absence in the review by Hakeem et al. (8) is a meta-analysis by Wang et al. (4). Using a hierarchical
modeling strategy, Wang et al. (4) reported pooled sensitivity and specificity estimates, respectively, of 0.79 and 0.89 for dobutamine stress echocardiography (13 studies) and of 0.74 and 0.70 for myocardial perfusion imaging (9 studies); Figure 3 shows the receiver-operating characteristic curves. Dobutamine stress echocardiography was found to be more accurate than myocardial perfusion imaging (p = 0.02) when all studies were included; this difference was not evident when studies not using a standard reference for obstructive CAD ≥70% stenosis were excluded (p = 0.09). Factors hypothesized to explain the reduced accuracy of myocardial perfusion imaging include reduced coronary flow reserve in the context of LV hypertrophy, endothelial dysfunction, the possibility of “balanced ischemia,” and greater interobserver variability. The algorithm proposed by Hakeem et al. (8) is based on an approach extrapolated from the general population, not hitherto supported by evidence pertaining to patients with ESRD. We urge caution in implementing this approach, which could be viewed as overly simplistic, in this population.

In conclusion, an expanded diagnostic armamentarium in the contemporary era, including multiple complementary imaging modalities, can guide appropriate diagnostic and therapeutic evaluation of patients with advanced CKD or ESRD. The challenge for cardiovascular imaging specialists is to acquire fluency in the interpretation of these techniques, in the context of an accurate pre-test probability knowledge, to ensure that the appropriate research questions are asked and the appropriate clinical questions are answered.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Charles A. Herzog, Chronic Disease Research Group, Minnesota Medical Research Foundation, 914 South 8th Street, Suite S-406, Minneapolis, Minnesota 55404. E-mail: cherzog@cdrg.org.

REFERENCES


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