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EDITORIAL COMMENT

# Atherosclerotic Versus Nonatherosclerotic Evaluation

## The Yin and Yang of Cardiovascular Imaging in Advanced Chronic Kidney Disease*

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Patients 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 $m^2$, 0.9% for an eGFR of 60 to 89 ml/min/1.73 $m^2$, 2.2% for an eGFR of 30 to 59 ml/min/1.73 $m^2$, and 4.7% for an eGFR <30 ml/min/1.73 $m^2$. 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.

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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 *iJACC*. 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.

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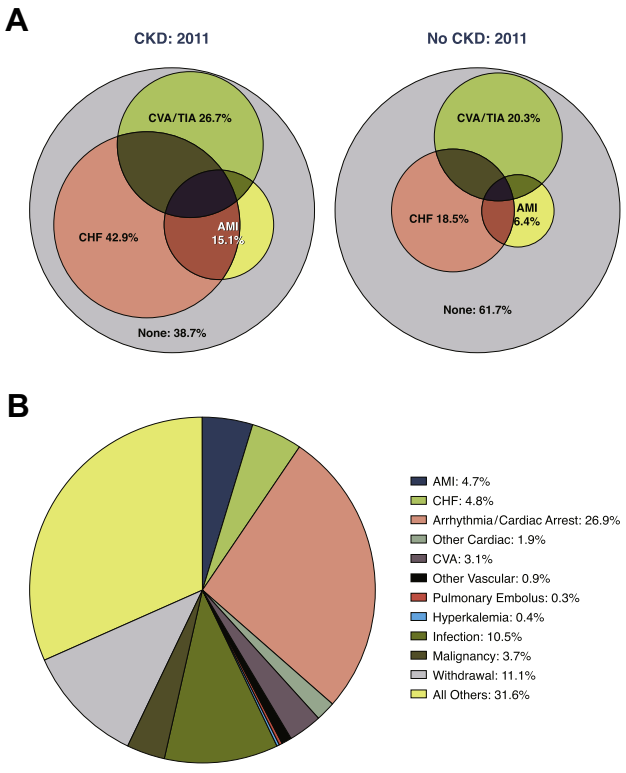


**FIGURE 1 Morbidity and Mortality in Patients With CKD or ESRD**

**(A)** Cardiovascular disease burden in Medicare patients 66 years of age and older with and without chronic kidney disease (CKD). **(B)** Causes of death among prevalent dialysis recipients in the United States, 2009 to 2011. AMI = acute myocardial infarction; CHF = congestive heart failure; CVA = cerebrovascular accident; ESRD = end-stage renal disease; TIA = transient ischemic attack. Adapted from U.S. Renal Data System (1).

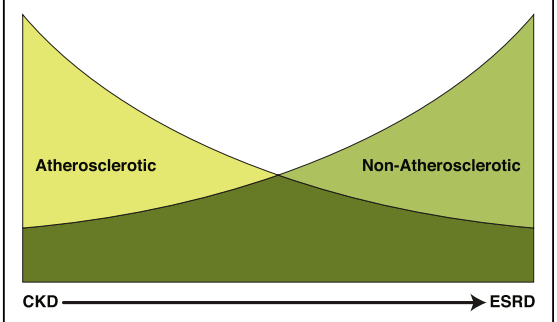


**FIGURE 2 Cardiovascular Disease Burden in Advancing CKD**

A conceptual framework of contributors to the cardiovascular disease burden in patients with advancing CKD. Abbreviations as in Figure 1.

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, $T_1$ 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 *iJACC*, 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