Cardiovascular disease (CVD) is a cause of severe disability, poor quality of life, and death among populations with underlying CKD. Many factors contribute to both morbidity and mortality, and among them is electrolyte disturbances; first and foremost is dyskalemia. Potassium concentration in the blood is exquisitely regulated by many organs, including the gut, the kidney, and the brain, through multiple neurohormonal mechanisms that maintain potassium homeostasis and a transmembrane potential of about 85 mV in humans (1,2). This membrane potential is protected by the intricate and fine regulation of extracellular potassium concentration that is critical for cardiac and skeletal muscle function. Acute and chronic hypokalemia and hyperkalemia can cause deviations in membrane potential in skeletal myocytes and cardiac myocytes that can lead to muscle paralysis and fatal arrhythmias, respectively. Sudden cardiac death can be caused by dyskalemia and is a major cause of death in people with hypertension, diabetes, heart failure, and CKD.

Dyskalemiases are very common and strongly associated with both cardiovascular and all-cause mortality, including in those with CKD and heart disease. These diseases increase risk for hyperkalemia, largely due to impaired renal excretion of potassium (2–7). Risk factors for hyperkalemia include kidney disease, heart disease, diabetes mellitus, use of potassium-sparing diuretics, angiotensin converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, angiotensin receptor blocker nephriysin combinations, age, high-dietary potassium intake, muscle injury, and acidosis. Although it is well appreciated that hyperkalemia is common among people with CKD and heart disease, many of whom are treated with drugs that block the renin-angiotensin-aldosterone system and thereby, impair the kidney’s ability to excrete potassium, it is less well appreciated that hypokalemia is also associated with increased mortality risk among these populations. Korgaonkar et al. (8) recently reported that hypokalemia and low normal serum potassium among patients with CKD not on dialysis are associated with increased risk for mortality and progression to ESRD. They also found a U-shaped relationship between serum potassium concentration and all-cause mortality, but the strength of the association between hypokalemia and mortality was greater than that for hyperkalemia and mortality. Alderman et al. (3) reported that hypokalemia was associated with increased mortality risk and hyperkalemia with increased risk for cardiovascular events among those enrolled in the Antihypertensive and Lipid Lowering Treatment Study. Moreover, in a recent study of >100,000 people enrolled in the Prospective Urban Rural Epidemiology Observational Cohort, both low-and high-urinary potassium levels—a surrogate for dietary potassium intake—were associated with increased risk of death or cardiovascular events (9). Krogager et al. (4) recently reported on a cohort of nearly 2600 patients postmyocardial infarction, in which they observed a U-shaped relationship between serum potassium concentration on hospitalization and 90-day mortality. Alarmingly, they also found that low and high normal serum potassium were associated with markedly increased risk for mortality. Einhorn (10) showed a strong association between a hyperkalemic event (inpatient or outpatient), hyperkalemia, and death among those with and without CKD in the Veterans Administration health system. Taken together, these studies indicate that low- and high-potassium levels in the diet and the blood are associated with increased risk for mortality. Although these studies do not establish a causal link between dyskalemia and death, they augur for careful thought and surveillance of serum potassium, particularly in high-risk populations.

In this issue of the Clinical Journal of the American Society of Nephrology, Hughes-Austin et al. (11) examine the relationship between serum potassium and mortality among people enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). They focused on the associations of hyperkalemia in community-living populations and whether various comorbid conditions or medications affect associations between hyperkalemia and either CVD events or mortality. They correctly point out that most research regarding hyperkalemia and outcomes derives from the hospitalized setting or acute medical conditions. However, it seems that reports concerning hyperkalemia as a risk factor for adverse outcomes can be found everywhere these days: prospective observational studies in large populations, large-scale clinical trials (12,13), and retrospective reviews as well as selected populations (see above).

The key finding from the study by Hughes-Austin et al. (11) is that high serum potassium concentration is significantly associated with a higher risk for all-cause mortality independent of kidney function or other CVD risk factors. Moreover, they report that similar associations were observed for both CVD and non-CVD death overall. The association was strongest for those with a serum potassium of ≥5.0 mEq/L at baseline; however, it was
striking that risk for all-cause mortality (CVD and non-CVD) was increased even among those with serum potassium levels within the normal range of 4.0–4.9 mEq/L. Analyses also indicated that the associations were consistently stronger in those who were listed as taking any diuretic at baseline. The authors found no significant association between high-serum potassium level and sudden cardiac death. Although the authors found this surprising, it could represent a flaw in the methodology for assessing a relationship between long-term outcomes and a single baseline serum potassium level on which the analysis was based. Although the authors do not comment on this point, like other recent reports cited above, they also found (figure 1 in ref. 11) a U-shaped curve relating serum potassium concentration to mortality. Therefore, although they did not find significant associations between hyperkalemia and mortality in their fully adjusted Cox model, there is a trend toward higher mortality at lower serum potassium. I think this is an important point that should be emphasized. Specifically, we now have multiple studies that illustrate the increase in mortality with both low and high potassium concentration. Although the authors’ analyses revealed greater strength between high serum potassium and mortality, putting this study in context with others should raise awareness of the importance of serum potassium and outcomes in populations, such as those represented by the MESA and the CHS.

Significant strengths of this study include the large number of participants in two well conducted prospective, observational studies with long-term follow-up and centrally adjudicated events and statistical methods to help adjust for comorbidities. Another strength is that the MESA and the CHS were community-based observational studies, and although they do not reflect precisely the United States population, the findings are more generalizable than some clinical trials and retrospective analyses. Significant weaknesses include the exclusion of nearly one half of the participants in the CHS cohort who had a history of CVD at baseline, a single serum potassium level at baseline, lack of information on serum potassium at the time of adjudicated events, and no information on baseline electrocardiogram findings.

This analysis shines a light on the association between serum potassium and mortality. Although the MESA population was relatively young, the CHS population was older. Older people have higher rates of kidney and heart disease as well as lower plasma renin and aldosterone levels compared with younger individuals. The study used pooled data and did not examine the CHS separately, the inclusion of age in the fully adjusted model notwithstanding. Although this study does not establish causation, the data suggest that clinicians should pay close attention to patients with a serum potassium level above 5.0 mEq/L, because it may be a risk marker for both CVD and non-CVD mortality. Many questions regarding outpatient management of dyskalemia, especially in people with cardiac and renal disease, remain unanswered. These include how often we should measure potassium as well as what, when, and how best to treat deviations in serum potassium. Given the aging population and the high rates of diabetes, CKD, and heart disease, future research designed to provide answers to these questions is critical.

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See related article, “The Relation of Serum Potassium Concentration with Cardiovascular Events and Mortality in Community Living Individuals,” on pages 245–252.