Chronic kidney disease (CKD), which is defined by the estimated glomerular filtration rate (eGFR) and/or albuminuria, is projected to affect approximately 10% to 16% of adults worldwide. Over the past 2 decades, there has been growing appreciation of the increased risk of mortality and adverse clinical outcomes in individuals with a decreased eGFR, compared with those with normal renal function. Cardiovascular disease (CVD) occurs prematurely among patients with CKD. The prevalence is several-fold higher than in the general population, and CVD contributes substantially to increased mortality. Traditional CVD risk factors are more common in these patients, but conventional models (e.g., the Framingham predictive instrument) consistently underestimate risk of future CVD events. A scientific statement by the American Heart Association in 2003 endorsed the position that patients with CKD [eGFR <60 mL·min\(^{-1}\)·(1.73 m\(^2\))] should be grouped with those at the highest risk for cardiovascular events (coronary risk equivalent); however, the increased CVD risk is neither well recognized nor integrated by the general medical community into the care of individual patients with decreased eGFR or albuminuria.

A new clinical practice guideline from the Kidney Disease: Improving Global Outcomes (KDIGO) group recommends altering the classification schema of CKD (Fig. 1A) (1). The new classification reflects an increasing recognition by nephrologists and cardiologists that urinary albumin excretion [defined by an albumin–creatinine ratio (ACR) >10 mg/g] is independently associated in a stepwise fashion with increased rates of all-cause and cardiovascular mortality. This risk appears to increase synergistically in concert with reduction in eGFR [<60 mL·min\(^{-1}\)·(1.73 m\(^2\))]. The new system, known as CGA, leaves intact the familiar eGFR (G in CGA) categories on which the prior system was focused and adds 2 dimensions: cause (C) and albuminuria (A). The goal is to improve the care of patients with CKD through a more precise classification system that provides inherent prognostic information regarding the risks of disease progression, cardiovascular mortality, and all-cause mortality. For example, Fig. 1B shows that the risk of cardiovascular mortality for a patient whose GFR value falls into the G3a stage increases from a value near the reference (green) to the highest risk (red) as albuminuria increases (2). In this context, we discuss 3 contemporaneous observational studies. Each study uses large data sets in an attempt to further define the increased risks associated with CKD.

Tonelli and colleagues (3) used population data from the Alberta Kidney Disease Network database to determine whether a reduced eGFR [<60 mL·min\(^{-1}\)·(1.73 m\(^2\))] merits consideration as a coronary risk equivalent. Using a population cohort of nearly 1.27 million patients [excluding patients with end-stage renal disease or an eGFR <15 mL·min\(^{-1}\)·(1.73 m\(^2\))] , the authors evaluated patients admitted to the hospital for myocardial infarction (MI) during a 48-month follow-up period. Patients were categorized into 4 mutually exclusive groups: known CVD, reduced eGFR alone, diabetes alone, or reduced eGFR and diabetes. Prior CVD was associated with the highest rates of incident MI (18.5 per 1000 person-years). In patients without prior CVD, unadjusted rates of incident MI were higher among those with reduced eGFR alone than among those with diabetes alone (6.9 vs 5.4 per 1000 person-years). After multivariate analysis, however, rates of hospital admission for MI and rates of all-cause death were lower in patients with reduced eGFR than in patients with diabetes. When CKD was defined as reduced eGFR plus severe proteinuria (ACR >300 mg/g or a urine dipstick value of 2+), the rates of incident MI were markedly higher than with diabetes alone (12.4 vs 6.6 per 1000 person-years). After multivariate adjustment, the risk of incident MI among patients with reduced eGFR and severe proteinuria was equivalent to the risk among patients with diabetes. These data, which are presented in a supplementary appendix to the article,
Fig. 1. (A), Nomenclature proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) group for CKD. This classification schema incorporates cause of CKD (present for >3 months), GFR, and albuminuria (1). (B), Summary of pooled relative risks of all-cause mortality and cardiovascular mortality derived from categorical metaanalysis, presented on the basis of the eGFR and the albumin-creatinine ratio (ACR). Boldface numbers indicate statistical significance (P < 0.05) (2). Colors represent increasing risk, from values near the reference (green) to highest risk (red). Reproduced with permission of KDIGO from the KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. [Fig. 1A is from (1); Fig. 1B, (2)].
demonstrate that the risk for MI and all-cause mortality increased with the simultaneous presence of decreased eGFR and increased proteinuria, as the new KDIGO system postulates. It would appear that a 2-dimensional definition represents the coronary risk associated with CKD better than reduced eGFR alone, as was hypothesized by the authors. This study demonstrates that reduced eGFR and proteinuria in concert confer a risk for MI and death similar to that of diabetes, an established coronary risk equivalent. In this light, patients with CKD would likely benefit from intensive CVD risk-reduction efforts and regular proteinuria screening.

Mahmoodi and coworkers (4) examined whether the presence or absence of hypertension was associated with an altered risk for mortality or progression to end-stage renal disease in patients with CKD. This meta-analysis used data from 45 study cohorts (1.12 million participants) in the Chronic Kidney Disease Prognosis Consortium. Patients were excluded if baseline information regarding eGFR, albuminuria, or hypertension was not available. Interestingly, the association of hypertension and mortality was different, depending on the eGFR and proteinuria cutoffs. With a preserved eGFR and absence of significant proteinuria, hypertension was associated with a modestly increased risk of mortality. As anticipated, there was a graded increase in mortality with decreasing eGFR or increasing albuminuria. Surprisingly, the hazards for all-cause and cardiovascular mortality were consistently lower among hypertensive patients than among their nonhypertensive counterparts for stages G3b through G5 [eGFR <45 mL/min\(\cdot\)(1.73 m\(^2\))] for example, the adjusted all-cause mortality hazard ratio (HR) for an eGFR of 45 mL/min\(\cdot\)(1.73 m\(^2\))^\(-1\) [relative to an eGFR of 95 mL/min\(\cdot\)(1.73 m\(^2\))^\(-1\)] was 1.77 (95% CI, 1.57–1.99) in nonhypertensive patients and 1.24 (95% CI, 1.11–1.39) in hypertensive patients (P for overall interaction = 0.003). A similar pattern occurred for ACR: Hazards for all-cause and cardiovascular mortality were higher in nonhypertensive patients as ACR values increased. With an ACR of 300 mg/g (reference, 5 mg/g), the adjusted HR of all-cause mortality was 2.3 (95% CI, 1.98–2.68) in nonhypertensive patients and 2.0 (95% CI, 1.84–2.35) in hypertensive patients (P for overall interaction = 0.019). The highest rates of all-cause and cardiovascular mortality occurred among patients without hypertension in the lowest eGFR and highest ACR categories. These somewhat counterintuitive findings of a “protective effect” of hypertension have been noted in prior observational studies. These findings may reflect unmeasured confounding associated with antihypertensive treatment. Antihypertensive medications are known to reduce proteinuria (e.g., angiotensin-converting enzyme inhibitors) and mortality in patients with left ventricular dysfunction (e.g., angiotensin-converting enzyme inhibitors and \(\beta\)-blockers). Another possibility is that a reduced eGFR, increased ACRs, and hypertension are “collinear” variables in the hazards model (i.e., they are not independent variables, so the predictive value of eGFR is diminished in a multivariate model). Of note is that progression to end-stage renal disease was not influenced by hypertension status in this study. This study emphasizes the adverse prognosis imparted by reduced eGFR and albuminuria, even in the absence of hypertension. It supports the assertions that traditional risk factors incompletely quantify risk in patients with CKD and that models incorporating eGFR and ACR may provide superior risk estimation.

A second study by Mahmoodi and colleagues (5) assessed the risk of venous thromboembolism (VTE) in patients with CKD by pooling data from 5 general population cohorts (n = 95 154). Although rates of VTE events are low in the general population, nephrotic-range proteinuria is an established risk. The metaanalysis was prompted by the findings of 2 component studies [Atherosclerosis Risks in Communities (ARIC) and Prevention of Renal and Vascular End-Stage Disease (PREVEND)] that demonstrated associations of decreased eGFR and albuminuria, respectively, with VTE in post hoc analyses. From a data set that included approximately 600 000 person-years of follow-up, 1178 VTE events were identified. The findings suggest a graded increase in the risk of VTE in association with higher levels of albuminuria and, to a lesser extent, reduced eGFR. The highest risk of VTE [reference, eGFR >90 mL/min\(\cdot\)(1.73 m\(^2\)) and ACR <30 mg/g] occurred in patients with the highest ACR (>300 mg/g) but a lower eGFR stage (G2; adjusted HR, 4.38; 95% CI, 2.64–7.26), but not in patients at the lowest eGFR stage (G4) with an ACR >300 mg/g (adjusted HR, 2.33; 95% CI, 0.74–7.34). The combination of a low eGFR and a high ACR was not consistently synergistic, a finding that probably reflects lower power in certain subgroups. Nonetheless, these results emphasize the significant association between reduced eGFR, increased ACR, and adverse events involving the venous circulation.

It is imperative to interpret these studies in the context of methodologic limitations related to their observational design (including concerns about underrepresentation of minority populations and lack of clinical data regarding treatment), but the large sample sizes, the robust statistical methodology, and the incorporation of laboratory information to complement observational data are important strengths. These studies illustrate that the risk associated with CKD is better conceptualized in 2 dimensions (i.e., a reduced eGFR
and the degree of albuminuria), as suggested in the new KDIGO guidelines. Furthermore, these studies illustrate that eGFR [calculated with the CKD Epidemiology Collaboration (CKD-EPI) equation] and albuminuria/ACR increase risk synergistically, and the studies refine our understanding of the global risk associated with CKD.

A substantial amount of work lies ahead. We must routinely assess eGFR and urinary albumin excretion, so that patients with CKD can be treated according to risk and interventions can be tested in more homogeneous, high-risk groups. Moreover, we must move from retrospective to prospective studies to identify interventions that will decrease the rates of CVD in patients with CKD. We hope that a more nuanced understanding of the factors that confer cardiovascular risk will improve our ability to do so.

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