

Association of kidney disease measures with poor outcomes



Chronic kidney disease is a global public health problem. The classification of this disorder introduced by the Kidney Disease Outcome Quality Initiative (KDOQI) in 2002, provided a research focus for the past decade that has brought about a much improved understanding of chronic kidney disease and its complications, and an improved understanding of its effect on health-care resources.¹ With this understanding has come a modification of the original five-stage classification of chronic kidney disease by glomerular filtration rate (GFR) category to split stage 3 disease into 3A (45–59 mL/min per 1.73 m²) and 3B (30–44 mL/min per 1.73 m²) and a recognition of the importance of proteinuria in all categories of chronic kidney disease.² Most recently the Kidney Disease Improving Global Outcomes guideline development group have recommended classification of chronic kidney disease by cause, GFR category, and albuminuria category.³ These changes to the original KDOQI classification have been driven by prognostic data, showing that the risks of adverse outcomes associated with chronic kidney disease at all categories of GFR are affected by albuminuria category, and vice versa.

Adult (age 18 years and older) prevalence studies from around the world show a broadly similar prevalence of chronic kidney disease of between 10% and 16%.⁴ Age, hypertension, and diabetes are the key predictors of new onset chronic kidney disease. The main risk associated with chronic kidney disease is of increased cardiovascular events, leading to increased morbidity and mortality. Other important outcomes include acute kidney injury, infection, cognitive impairment, impaired physical function, and progression of kidney disease.⁵ Premature death often occurs as a result of complications of chronic kidney disease without progression of the disorder. The risk for any adverse outcome increases with lower GFR and is also increased by coexistent proteinuria. Nevertheless, controversy surrounds nomenclature and overdiagnosis of some populations with chronic kidney disease, particularly people with an isolated finding of GFR between 45 mL/min per 1.73 m² and 60 mL/min per 1.73 m², or with GFR higher than 60 mL/min per 1.73 m² and urine albumin-to-creatinine ratio (ACR) between 30 mg/g and 300 mg/g (about 3mg/mmol and 30 mg/mmol).⁶

Previous reports from the Chronic Kidney Disease Prognosis Consortium have described the risks of adverse events in people with this disorder, including acute kidney injury, cardiovascular disease, end-stage renal disease (ESRD), and mortality.^{7–9} These data show that both GFR and albuminuria are independent predictors of adverse outcomes. In *The Lancet*, Bakhtawar Mahmoodi and colleagues¹⁰ and Caroline Fox and colleagues¹¹ extend this work by presenting results from two related meta-analyses of more than 1 million individuals, exploring the associations of estimated GFR (eGFR) and albuminuria with mortality and ESRD by hypertensive status and diabetes status, respectively. These are important scientific contributions, strengthening the role of simple measures of kidney health—eGFR and albuminuria—as predictors of adverse outcomes independent of disease status.

Mahmoodi and colleagues¹⁰ examined data for 45 cohorts (25 general population, seven high risk, and 13 chronic kidney disease) with 1 127 656 participants, 364 344 of whom had hypertension. They showed that for both the combined general and high-risk cohorts and for the chronic kidney disease cohorts, low eGFR and high albuminuria were more strongly associated with mortality in individuals without hypertension than in those with hypertension, whereas the associations of low eGFR and increasing albuminuria with ESRD were much the same irrespective of hypertensive state. Fox and colleagues¹¹ analysed data for 1 024 977 patients

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from 30 general and high-risk cohorts and 13 chronic kidney disease cohorts, of whom 128 505 had diabetes. In the general and high-risk cohorts, mortality risks were 1.2–1.9 times higher in participants with diabetes than in those without diabetes across the ranges of eGFR and ACR. However, with fixed eGFR and ACR reference points in the diabetes and no diabetes groups, HR for mortality outcomes according to lower eGFR and higher ACR were much the same in participants with and without diabetes. Despite increased risks for mortality and ESRD with diabetes, the relative risks of these outcomes by eGFR and ACR were much the same irrespective of the presence or absence of diabetes, emphasising the predictive role of measures of kidney health independent of diabetes status.

Both studies have limitations, acknowledged by the investigators, including absence of standardisation of included measurements and assessments across all cohorts, under-representation of some ethnicities (particularly black people), and the possibility of residual confounding from observational data. Nevertheless, in the subgroups generating most controversy, in people without hypertension, HR for cardiovascular mortality was 1.72 (95% CI 1.32–2.24) at eGFR 45–59 mL/min per 1.73 m² with no proteinuria and ranged from 1.80 to 5.47 at GFR of 60 mL/min per 1.73 m² or more with ACR of 30–299 mg/g; in people without diabetes, HR for cardiovascular mortality was 1.52 (1.30–1.77) at eGFR 45–59 mL/min per 1.73 m² with no proteinuria and ranged from 1.79–4.00 at GFR of 60 mL/min per 1.73 m² or more with ACR of 30–299 mg/g.

These two studies underline the association of adverse outcomes with moderate reduction in kidney function and low levels of proteinuria, but we still need to know why this association occurs. Up to now, similar adverse outcomes have not been identified in kidney donors.¹² The medical community has yet to understand fully how some people come to have chronic kidney disease, why some people do not undergo disease progression despite having stable low rates of eGFR, what the precise role of episodes of acute kidney injury or acute kidney impairment (occurring both in hospital and in

the community) is in the development and progression of chronic kidney disease, and exactly which sections of the population doctors should be screening for early identification and prevention of chronic kidney disease. We think we know some of the factors in progression amenable to intervention to prevent associated adverse outcomes, such as control of diabetes and hypertension, but the two accompanying studies of effect modification by hypertension and diabetes disease status show us we still have a lot to learn.

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