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Chronic kidney disease and stroke outcomes: beyond serum creatinine

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Chronic kidney disease (CKD) is an increasingly recognized public health problem. With a worldwide prevalence approaching 10%,[1] CKD is a major risk factor for cardiovascular disease.[2] Though CKD is a putative risk factor for stroke,[3] the mechanisms by which CKD impacts stroke risk have proven difficult to elucidate, as many risk factors for CKD are also risk factors for stroke. Understanding the impact of CKD on outcomes after stroke poses similar challenges.

The Kidney Disease Improving Global Outcomes guidelines define CKD as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and/or proteinuria ≥1+ on urine dipstick.[4] These two variables, eGFR and proteinuria, represent the two separate but related aspects of CKD pathophysiology: kidney dysfunction and kidney damage, respectively. Prior studies have produced mixed results regarding the association between CKD and stroke recurrence, including studies that assessed both kidney dysfunction and kidney damage.[5,6] Clarifying the independent and joint contributions of kidney dysfunction and damage to stroke outcomes is a necessary step in the effort to better understand interorgan relationships in neurology.

Ueki and coauthors investigated the association of CKD with stroke recurrence and all-cause mortality in a prospective longitudinal cohort of Japanese patients with ischemic stroke.[7] In their analyses, they critically included both eGFR and proteinuria as predictor variables, investigating kidney dysfunction and kidney damage as simultaneous but independent determinants of stroke recurrence and mortality. Importantly, the authors had the foresight to evaluate the independent effects of eGFR and proteinuria while additionally assessing for synergistic effect modification by these factors. Their analysis was based on 12,576 Japanese patients with stroke, among whom 20% had recurrent stroke and 32% died over a median follow-up of 4 years. Ueki and colleagues found that worse eGFR and higher proteinuria were both independently associated with a higher risk of recurrent stroke and

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all-cause mortality. In other words, each factor was associated with stroke recurrence and death independent of the other factor. However, there were subtle differences; whereas worse eGFR was associated with an increased risk of recurrent stroke across the continuum of eGFR, only the highest level of proteinuria was associated with an increased risk of recurrent stroke. In their primary analysis, eGFR did not act synergistically with proteinuria to influence the risk of stroke recurrence or death by formal statistical criteria. But, close examination of their data reveals apparent synergy; patients with poor eGFR and high proteinuria had the highest adjusted risks of recurrent stroke and mortality.

One important limitation of this study is the exclusion of patients requiring renal replacement therapy, for whom anuria precluded proteinuria assessment. The authors addressed this limitation by performing a sensitivity analysis that included patients on renal replacement therapy, in which results were largely unchanged. However, patients requiring renal replacement therapy are a unique subset of patients with CKD,[8] so understanding the impact of CKD on stroke outcomes in such patients may require investigating factors not reflected by eGFR and proteinuria. Other limitations include an ethnically homogeneous study population and the lack of repeated measures of eGFR and proteinuria, but these limitations are counterbalanced by the study's other notable strengths, which include its large sample size, prospective data collection, and long follow-up period.

Limitations notwithstanding, this study is a valuable contribution to the literature. Specifically, as relates to CKD, this work establishes that kidney dysfunction and kidney damage both have significant and independent associations with stroke recurrence and post-stroke mortality. These data do not clarify whether kidney dysfunction and kidney damage, as opposed to upstream factors such as hypertension, are causally linked to post-stroke outcomes. However, the findings do justify asking whether different aspects of CKD pathophysiology may be targeted to improve stroke outcomes. While the authors' findings do not have immediate, direct clinical implications, it is noteworthy that when treating conditions linked with CKD, such as hypertension and diabetes, treatment options include drugs with nephroprotective properties. Whether such drugs should be used preferentially to improve post-stroke outcomes should be investigated.

Broadly, the authors should be commended for providing a model for the rigorous investigation of interorgan relationships. The authors' approach of analyzing individual and joint effects of multiple biomarkers that reflect different constituent processes underlying CKD may be generalized to other complex problems. For example, the burgeoning investigation of the liver-brain axis[9] would benefit from employing a similar approach that comprehensively evaluates the various biomarkers of liver function and liver injury. Such an approach could enrich work across the spectrum of neurological disorders, ranging from cerebrovascular conditions such as cerebral amyloid angiopathy to neurodegenerative conditions such as Alzheimer's disease.

Ueki and colleagues have made it clear that going beyond serum creatinine is necessary to more fully understand the impact of CKD on stroke outcomes. Evolving beyond reductionist approaches that isolate individual disease biomarkers will allow our field to develop a more comprehensive, and thus actionable, understanding of interorgan relationships in stroke.

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Non-standard Abbreviations and Acronyms

CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate

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