

traditionally utilized to study crescentic glomerular disease which is the type of renal disease characterized by podocyte migration. In this regard, it would be interesting to examine ET_AR blockade in the antiglomerular basement membrane model of kidney disease, which more closely mimics crescentic glomerular disease.

Taken together, the study by Buelli *et al.* has identified a signaling cascade that leads to impaired podocyte phenotype and function, thereby providing significant insights into our understanding of podocyte injury in proteinuric glomerular disease. The novel associations made between ET-1, ET_AR, β -arrestin-1, EGF receptor, and β -catenin now provide a number of promising targets for therapeutic intervention and will require further study in the future.

DISCLOSURES

None.

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See related article, " β -Arrestin-1 Drives Endothelin-1-Mediated Podocyte Activation and Sustains Renal Injury," on pages 523–533.

Cardiovascular Events after AKI: A New Dimension

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The possibility that AKI is a risk factor for subsequent cardiovascular disease is an intriguing one. Several studies have shown that survivors of AKI are at increased risk of death and CKD. Because cardiovascular disease is the leading cause of death in many countries, it would be useful to understand whether there is increased risk of cardiovascular events after an episode of AKI. Therefore, prospective studies, such as the National Institutes of Health–National Institute of Diabetes and Digestive and Kidney Diseases-sponsored ASessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury study, have specified *a priori* adjudicated cardiovascular events as outcomes of interest.¹

Although CKD and ESRD are now well accepted risk factors for cardiovascular disease, little is known about the connection between AKI and cardiovascular events. There are several potential pathophysiological mechanisms by which AKI may directly contribute to increased risk of cardiovascular disease, independent of its impact on CKD progression. There are limited data (mostly from children²) that AKI survivors have higher levels of BP, consistent with animal models showing that postischemic rats develop salt-sensitive hypertension.³ As discussed by Wu *et al.*, there is a growing literature linking AKI to abnormalities in mineral metabolism, especially elevations in levels of fibroblast growth factor-23,^{4,5} a novel biomarker that has garnered great interest recently as likely being directly cardiotoxic.⁶ Finally, AKI is associated with acute increases in inflammatory cytokine levels.^{7–9} As has been shown in other acute conditions characterized by inflammation (*e.g.*, acute

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infection), this AKI-associated inflammatory response may increase the risk of subsequent cardiovascular disease events.^{10,11}

Most published studies on the association between AKI and cardiovascular events after hospital discharge have been in the setting of coronary angiography. A recent meta-analysis suggests that AKI after coronary angiography is associated with an increased risk of cardiovascular events based on a composite end point of ischemic and nonischemic events.¹² In this context, the work in this issue of *JASN* by Wu *et al.*¹³ on the long-term risk of coronary events in a general hospital setting is very provocative and interesting. Analyzing the Taiwan National Health Insurance (NHI) database (which contains information on virtually all hospitalizations, outpatient visits, and procedures in Taiwan), Wu *et al.*¹³ showed that dialysis-requiring AKI was independently associated with a higher hazard ratio of 1.67 (95% confidence interval, 1.36 to 2.04; $P < 0.001$) for coronary events, defined as a composite of nonfatal myocardial infarction, coronary artery bypass graft, and coronary angiography. The strength of this association was similar across a number of subgroups and similar to the strength of association between diabetes mellitus (a well known cardiovascular disease risk factor) and subsequent coronary events.

In their statistical models, both CKD and ESRD were handled as time-dependent covariates, and therefore, the association of AKI with subsequent coronary events was independent of the development or progression of CKD/ESRD. However, the strength of the association was stronger when CKD/ESRD was not considered (hazard ratio, 2.04; $P < 0.001$), which is consistent with the hypothesis that some of the association between AKI and subsequent coronary event risk is mediated through development of CKD/ESRD after AKI. Furthermore, adjusting for interim coronary events attenuated the association between dialysis-requiring AKI and subsequent risk of death, supporting the hypothesis that coronary events are in the causal pathway linking AKI and mortality.

These analyses of administrative data were complemented by an analysis in a smaller, prospectively collected cohort (the National Taiwan University Hospital Study Group on Acute Renal Failure [NSARF] study), which has key laboratory measurements, such as serum creatinine. Using this dataset, Wu *et al.*¹³ showed that, similar to the NHI cohort, dialysis-requiring AKI was an independent risk factor for subsequent coronary events in hospitalized patients.

In addition to the innovative focus on cardiovascular disease after AKI, a major strength of this study is its national scope. The analyses examining how much adjustment for interim CKD/ESRD attenuated the strength of the AKI–coronary event association and how much adjustment for interim coronary events attenuated the strength of the AKI–mortality association are useful. Another strength is the analysis of the NSARF study to complement the national insurance administrative dataset.

However, these results should be interpreted with several caveats in mind. First, in the main analysis, important covariates, such as CKD, are defined by administrative codes only. There are no data on proteinuria, even in the NSARF analysis, and proteinuria is known to be a strong risk factor for both AKI and cardiovascular disease.^{14,15} Thus, residual confounding and misclassification are likely.

Second, there is a paucity of information about many coronary disease risk factors. Even in the smaller NSARF cohort, data on coronary disease risk factors beyond diabetes and hypertension are lacking. Classic Framingham risk factors, such as family history of coronary disease, cigarette smoking, cholesterol level, and actual BP level, are not ascertained. Also absent is information on use of key medications, such as aspirin.

In addition, it is notable that there was a very high risk of nonrecovery from dialysis dependency (11,985/17,106 of survivors or 70.1%). Based on prior studies of nonrecovery, this result suggests that these patients had stage 4 or higher baseline CKD (< 30 ml/min per 1.73 m²).¹⁶ At the same time, the in-hospital death rate for these patients who suffered dialysis-requiring AKI was low (4192/28,497 or 14.7%). Thus, this population seems to be a very different population from what one usually thinks of when considering dialysis-requiring AKI (encompassing continuous RRT), especially in the critical care setting, where the mortality for these patients exceeds 50%. Although Wu *et al.*¹³ do note that a significant proportion of the cohort (7199/28,497 or 25.3%) died within 30 days of hospital discharge, the meaning of this finding is unclear—perhaps more patients were discharged home with hospice than in the United States. Even so, it seems unlikely that, for example, critically ill patients would be able to be discharged home to die. The low in-hospital death rate is also consistent with these patients having relatively advanced baseline CKD before the AKI hospitalization, which has implications for the generalizability of these findings to patients with less-severe baseline CKD.

Thus, future studies are certainly needed to replicate these results. An important requirement of future studies will be better capture of traditional cardiovascular disease risk factors as well as capture of baseline and subsequent renal function trajectories with actual laboratory data, including serum creatinine and urine protein quantification. It would be very advantageous if mechanisms linking AKI to cardiovascular disease events could be evaluated through, for example, the measurement of key biomarkers. This evaluation would strengthen the case that any observed association between AKI and cardiovascular disease is not spurious (*e.g.*, because of confounding or other bias) but rather, real and linked by causal mechanisms. Future studies should also expand to examine other cardiovascular disease outcomes other than coronary disease, such as heart failure, cardiac arrhythmias, cerebrovascular disease, and peripheral arterial disease. Because the incidence of nondialysis-requiring AKI is much higher than the incidence of dialysis-requiring AKI, examining the impact of more mild degrees of AKI on subsequent cardiovascular events would be important. Hopefully, this

study is the first of many in the field to examine the impact of AKI on cardiovascular disease, an exciting new dimension.

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C.-y.H. declares no conflict of interest. K.D.L. has been a member of a Data Safety Monitoring Board for Cytopherx and a member of the Clinical Events Adjudication Committee for Astute. K.D.L. has previously done consulting work for Abbvie and Complexa and owns stock in Amgen. K.D.L. has received gifts of reagents for biomarker assays from Abbott and CMIC.

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See related article, “Long-Term Risk of Coronary Events after AKI,” on pages 595–605.

If Oxidative Stress Is an Appropriate and Specific Target, What Reagent Should We Choose?

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Cardiovascular disease is prevalent in a disproportionately high percentage of patients on maintenance hemodialysis (MHD) and is responsible for much of the mortality in this population.¹ In addition, MHD patients express markers of oxidative stress and inflammation at significantly higher levels than

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