multiprotein cilia-destined cargo within the cell. Then through association of an adaptor molecule containing a cilia-targeting motif, perhaps such as cystin, multiple proteins deliver to the cilium. Further complexity in this model arises from the fact that not all proteins constitutively localize to cilia but require an external stimulus that promotes cilia entry. A good example of this is Hedgehog signaling. It was recently shown upon binding of Hedgehog to its receptor Patched, the protein Smoothened is targeted to the cilium[14]; therefore, multiple targeting motifs and adaptors likely regulate ciliary entry of proteins either in a constitutive manner or in response to a specific cue. Understanding these targeting signals will be key as we continue to unravel the mysteries of the cilia.

DISCLOSURES

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See related article, "Cystin Localizes to Primary Cilia *via* Membrane Microdomains and a Targeting Motif," on pages 2570–2580.

It's about Time: Extending our Understanding of Cardiovascular Risk from Chronic Kidney Disease

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It is widely accepted that chronic kidney disease (CKD) associates with accelerated cardiovascular disease and a higher rate of death than would occur otherwise.[1] These associations are based on studies of patients who had low renal function identified at a single point in time or, at most, two measurements separated by 3 mo to confirm chronicity. When caring for patients with CKD, we, too, generally estimate risk on the basis of single time point measurements of renal function. For example, a 65-yr-old man with a GFR of 80 ml/min per 1.73 m^2 has an estimated risk for death of 12% during the subsequent 5 yr; however, if his GFR is 40 ml/min per 1.73 m^2, then this risk is at least doubled.[1]

In this issue of *JASN*, Shlipak *et al.*[2] determined whether changes in kidney function during the first 7 yr of the Cardiovascular Health Study associated with increased cardiovascular risk during the subsequent 8 yr. The authors compared 1083 community-dwelling, ambulatory older adults with rapid declines in kidney function to 3295 adults without rapid decline. At baseline, participants were an average age of 72 yr, and 14% had diabetes. The incidence of cardiovascular disease was significantly higher in individuals with rapid declines in kidney function (defined as an annual decline in cystatin C–based eGFR >3 ml/min per 1.73 m^2), even after multivariable adjustment for demographics, aver-

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age kidney function, and established cardiovascular disease risk factors. Specifically, the hazard for heart failure increased by 24% for rapid decliners, whereas for myocardial infarction and peripheral arterial disease, the hazard was 42 and 67% higher, respectively.

Nephrologists naturally appreciate that a more rapid loss of kidney function over time associates with a greater risk for kidney failure. With these results, Shlipak *et al.*[2] advance the concept that patterns of kidney function over time can also be used to appreciate cardiovascular risk better: A more rapid loss of kidney function associates with greater risk for cardiovascular disease. Whether this is a causal relationship is still a matter of ongoing debate. Of note, patients enrolled in the Cardiovascular Health Study are those typically followed by primary care physicians and not nephrologists, because the average eGFR at the start of follow-up was 79 ml/min per 1.73 m^2.

Evaluating changes in an exposure, such as kidney function over time, also represents a change in modern epidemiology. Traditionally, exposures have been modeled as static conditions, assessed at a single point in time. In the case of CKD, people with declining kidney function are classified in the same risk group as those with diminished but stable renal function. However, exposures of interest to epidemiologists are, in truth, seldom constant.[3] Some studies have characterized exposure–response relationships as dynamic entities, changing in time.[4,5] Such studies typically require larger amounts of data over a longer period of time, which is increasingly possible with larger clinical studies and electronic medical records. There is also a growing sophistication to statistical analysis. Shlipak *et al.*[2] used traditional survival analysis methods, accounting for changes in renal function over time with fixed-covariate values. Others have used time-dependent covariates,[6] which can now be modeled for proportional hazards regression in most statistical software packages.[7]

Certainly, there are additional efforts required to characterize an exposure over time, yet the payoff for such efforts can be an improvement in our interpretation of evidence around exposure–disease relationships. With their study, Shilpak *et al.*[2] extend our mechanistic understanding of the kidney–cardiovascular relationship by acknowledging the importance of time and trajectory of kidney function decline. From an epidemiologic perspective, the Greek leader Pericles (perhaps, unknowingly) said it best: "Time may be the wisest counselor of all."

DISCLOSURES

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See related article, "Rapid Decline of Kidney Function Increases Cardiovascular Risk in the Elderly," on pages 2625–2630.

Aldosterone Blockade in Diabetic Nephropathy: Relative Risks and Potential Promise

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In the 1950s, electrocortin, as aldosterone was then known,[1] was a relatively novel hormone, the importance of which in human pathophysiology was established by reports of cases of aldosterone excess by Conn in 1955.[2] Despite more than 50 yr of study, the breadth of many actions of aldosterone continues to unfold in basic, translational, and clinical milieus.

From a basic aspect, aldosterone has typical genomic effects. After receptor binding, aldosterone exposure initiates transcriptional processes, which increase protein synthesis in pathways that enhance sodium retrieval from tubular lumens, salivary and sweat glands, and colon. Nongenomic aspects have been reported in which aldosterone infusion reduces the caliber of isolated afferent and efferent arterioles[3] through the activation of systems that inhibit endothelial nitric oxide action.[4]

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