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 m².

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, Shlipak 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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REFERENCES


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 arterioles3 through the activation of systems that inhibit endothelial nitric oxide action.4


Aldosterone Blockade in Diabetic Nephropathy: Relative Risks and Potential Promise

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From a translational aspect, the synthetic pathways detailing aldosterone production offer the opportunity for studying genes such as \( \text{CYP11B2} \), which regulates production of \( 11\beta \)-hydroxylase, a key enzyme in corticosteroid production.\(^5\) Population studies of polymorphisms in the \( \text{CYP11B2} \) gene suggest that compensation for reduced activity of \( \text{CYP11B2} \), through modest increases in the release of ACTH, results in upregulation of other genetic pathways that can increase BP. The latter incorporates genes involved in aldosterone production, such as \( \text{CYP11B1} \), that are also sensitive to ACTH and that also have the potential to enhance the reactivity of aldosterone responses to other factors, such as angiotensin II.\(^6\) These pursuits are shedding light on common hypertension phenotypes, such as salt sensitivity,\(^7\) and informing alternative mechanisms of action of newer mineralocorticoid system–blocking drugs.\(^8\) Encouraging, too, is the resurgence of interest in aldosterone physiology in the clinical arena, such as the investigation of Mehdi \textit{et al.}\(^9\) in this issue of \textit{JASN}.

Mehdi \textit{et al.}\(^9\) randomly assigned patients who had diabetes, were receiving 80 mg/d lisinopril, and had a urine albumin-creatinine ratio (ACR) of \( >300 \) mg/g to placebo, losartan 100 mg/d, or spironolactone 25 mg/d for 48 wk. The role of diabetic nephropathy in ESRD and the formidable cardiovascular injury by the induction of reactive oxygen species. Recent data suggest that aldosterone possesses proinflammatory and profibrotic properties. Rats treated with aldosterone and volume-expanded with saline showed a downregulation in the expression of slit diaphragm proteins such as nephrin and podocin and upregulation of the podocyte marker desmin,\(^13\) and at least some of the proteinuria-potentiating effect of aldosterone is attributable to podocyte injury by the induction of reactive oxygen species.

Regarding the safety of aldosterone antagonism in patients who have diabetes and are already on an angiotensin–converting enzyme inhibitor, Mehdi \textit{et al.}\(^9\) note that increases in potassium blood levels were most prominent in the spironolactone-treated group, compared with placebo and losartan groups. People with impaired kidney function are known to rally nonexcretory pathways such as enhanced intracellular sequestration during potassium intake to defend the serum potassium concentration.\(^16\) The use of an oral potassium chloride challenge in a controlled environment is an innovative way to identify people who may be at risk for significant hyperkalemia.\(^17\) Nonetheless, hyperkalemia remains a serious concern with aldosterone antagonism in this setting.

How has the study of Mehdi \textit{et al.}\(^9\) moved us forward? There are several answers. First, the dosage of lisinopril used was large enough to remove any concerns about underdosing renin–angiotensin system blockade. Second is the 48-wk duration of this study when previous studies were often in the range of 12 to 24 wk. Third, goal BP was \(<130/80\) mmHg as per current recommendations. Fourth, the care taken to control for dietary and 24-h BP-related factors in the outcome variable (ACR) provides assurance that the reduction noted in ACR on spironolactone compared with placebo is a real finding. Last, there is the sobering reminder of the significant incidence of asymptomatic hyperkalemia (\( [\text{K}^+] >6.0 \) mEq/L on at least one occasion), which was highest in the spironolactone group (14 of 27 patients). Although manageable with dietary counseling and some use of kayexalate, it serves as a continuing reminder of the necessity for vigilance in the follow-up of patients for whom we use these potent medications.

Unanswered questions from this study include whether the antiproteinuric effect of anti-aldosterone agents select a group with better prognosis, coupled with whether longer term data using aldosterone blockade will slow the rate of loss of GFR and preserve life, as shown in large heart failure studies.\(^18,19\)

**DISCLOSURES**

None.

**REFERENCES**


See related article, “Addition of Angiotensin Receptor Blockade or Mineralocorticoid Antagonism to Maximal Angiotensin-Converting Enzyme Inhibition in Diabetic Nephropathy,” on pages 2641–2650.