form cysts, yet cysts develop and enlarge only when under pressure from exogenous dDAVP. dDAVP increases cAMP within collecting duct cells, leading to activation of the BRAF/MEK/extracellular signal–regulated pathway for mitogenesis and increased numbers of epithelial cells. The dramatic results in this report are consonant with the view that epithelial cell growth is of paramount importance to the formation of the cyst as well to the overall increase of renal size in ARPKD.

In view of the fact that so many hormones with receptors in renal tubules have the potential to generate increased amounts of cAMP, why did the singular removal of AVP produce such a dramatic suppression of cyst formation? The answer probably rests in the physiology of terrestrial animals that must conserve water to survive. Of the hormones and autacoids capable of increasing cAMP production in collecting ducts, only AVP is persistently elevated in the plasma of free-range animals, including human. Where do the cysts form in ARPKD? In collecting ducts. Land-based animals are normally antidiuretic for most hours of the day and night, except for short periods when relatively large volumes of water are imbibed. Therefore, plasma AVP levels are usually elevated in the plasma of free-range animals, including human. Thus, cyst growth is “clamped” by vasopressin.

Recent studies have shown that cells cultured from the walls of renal cysts of patients with ADPKD and ARPKD respond to AVP in the range of plasma levels observed in patients. AVP, through the generation of cAMP, promotes epithelial cell growth and stimulates transepithelial chloride and fluid secretion in cyst epithelial cells. OPC-41061 inhibits with high affinity the formation of cAMP in response to AVP and decreases the rate of cellular proliferation caused by the hormone.

If rodent kidneys were human counterparts in all respects, then there would be no need to do a clinical trial to determine whether inhibition of AVP reduces renal volume in patients with ADPKD. Sadly, man does not mimic rodents in every way, and we shall not know for sure whether the AVP inhibitor works until an ongoing clinical trial is completed in a few years. Until then, nephrologists must grapple with a question that their highly informed patients will undoubtedly ask: How much water should I drink now? Patients have already figured out that if extra water decreases vasopressin and cAMP levels, then why isn’t plain old water a useful therapy? No one can give an informed, definitive answer to that question, but common sense leads me to think that sufficient water should be drunk to keep plasma vasopressin levels near a point that renders urine osmolality equal to or modestly lower than that of plasma. It would be impossible to meet the mark of the Brattleboro rat unless patients drank approximately 20 L of water daily. In the short term, a more moderate target would seem to be in order. To know for certain how much of the “water cure” is prudent therapy, a carefully controlled clinical trial seems justified.

What began approximately 25 yr ago as “blue-collar” science has progressed to optimistic clinical trials. With the assistance of more advanced molecular-based research strategies, we should expect to move much faster toward other highly targeted therapies for PKD.

**DISCLOSURES**

J.J.G. has consultancies with Otsuka Corp. and Genzyme Pharmaceuticals.

**REFERENCES**


In this issue of JASN, Smith et al. demonstrate an association between chronic kidney disease (CKD) and mortality in a cohort of patients hospitalized with acute myocardial infarction (AMI). Nearly 120,000 elderly patients with AMI (mean age 76 ± 7 yr) were followed for 10 yr, and all-cause mortality was stratified by baseline creatinine clearance (CrCl) or estimated GFR. The authors found a consistent and linear relationship between baseline renal function and mortality, with up to a 2.5-fold increased risk for death in patients in the lowest decile of CrCl. The relative contribution of kidney function to mortality risk equaled or eclipsed that of other key factors, such as age, BP, and systolic heart function. This is the first study to examine the impact of CKD on long-term mortality in patients with AMI and suggests that the degree of renal impairment should influence risk stratification after hospital discharge.

In a notable secondary analysis, the authors considered discharge medications in a subset of 93,000 patients. Those with worse renal function were less likely to have received aspirin and β blockers and more likely to have received angiotensin-converting enzyme inhibitors (ACEI). Adjustment for these differences did not have an impact on the magnitude of the observed associations, although potential changes in medications during the 10-y study period were not considered and is clearly a limitation. Regardless, the authors’ observations resonate with previous findings, in which patients who had CKD and high rates of coronary artery disease had curiously low rates of aggressive medication and interventional therapy. This disparity in care, which could represent therapeutic nihilism, may continue to translate into worse outcomes as the CKD population grows. Because few of these treatments have been specifically tested in patients with CKD, their potential for benefit is assumed on the basis of studies in the general population.

For example, aspirin has been used in the management of acute coronary syndromes for nearly 30 yr. Four landmark, randomized, controlled trials from the 1970s and 1980s, involving 3000 patients without CKD, show that aspirin decreased the rate of death, stroke, and MI during acute coronary syndromes or elective angioplasty. Similarly, a more recent meta-analysis of 287 randomized clinical trials that included 200,000 patients concluded that aspirin improved outcomes in patients with AMI, stable or unstable angina, transient ischemic attack or stroke, and intermittent claudication. In patients with acute coronary syndromes or those undergoing coronary artery bypass graft surgery, aspirin is prescribed less frequently for those with CKD than for those with normal renal function. Unfortunately, no randomized trials exist to confirm the benefit of aspirin in patients with both acute coronary syndromes and CKD.

ACEI and β blockers are also cornerstones for management of acute coronary syndromes in the general population. At least 35 randomized trials and multiple meta-analyses involving more than 12,000 patients proved that ACEI reduced the rate of death, stroke, reinfarction, and hospital admission in patients with AMI and either acute or chronic heart failure. Likewise, 51 randomized trials that included more than 31,000 patients showed that β blockers markedly decreased subsequent event rates after AMI. In patients with acute coronary syndromes and CKD, β blockers are generally neglected, whereas the data on ACEI use are mixed. Regrettably, no prospective, randomized trials have established the benefit of either ACEI or β blockers in patients with both acute coronary syndromes and CKD.

Last, percutaneous coronary intervention is a well-established and cost-effective therapy for AMI. A recent systematic review of 15 randomized trials that included more than 3500 patients showed that percutaneous coronary interventions decreased rates of mortality, stroke, reinfarction, and need for bypass surgery by 35 to 70% compared with thrombolysis. As with the previously discussed medications, coronary angiography, percutaneous coronary intervention, and bypass surgery all are offered less frequently to patients with AMI and CKD. Once again, no prospective trials exist to demonstrate the benefit of percutaneous coronary intervention in patients with AMI and CKD.

Considering only these studies, there have been at least 400 randomized trials, encompassing more than 250,000 subjects, to study treatments for acute coronary syndromes in the general population. Incredibly, there have been no such randomized trials in the CKD population. This omission is not coincidental: Patients with CKD have been systematically excluded from therapeutic trials.

CKD is associated with worse outcomes in almost every conceivable metric. Patients with CKD, compared with those without, experience twice the rate of cardiovascular disease, which progresses twice as rapidly. At baseline, patients with stage 5 CKD have six times the stroke rate and up to 36 times the mortality of age-matched control subjects. In the intensive care unit, patients with ESRD have twice the mortality of risk-matched control subjects. After coronary revascularization, those with stage 3 or higher CKD also have twice the mortality of control subjects. In a cohort of nearly 120,000 patients who were admitted with acute decompensated heart failure, even those with stage 1 CKD had twice the risk for death of patients without CKD, whereas those with stages 4 to 5 CKD had six to seven times the risk for death.
Should we as a nephrology community merely assume that because of these worse outcomes (high event rates), the benefit of therapy would be equivalent in patients with CKD and those with normal kidney function? The 4D trial suggested that this may not be a safe assumption. Arguably, it is more likely than not that these treatments provide at least some benefit to the CKD population; however, the extent of the benefit still should be defined. Clearly, there are more aggressive and nontraditional aspects of the atherosclerotic process among people with CKD that are not factors in those with normal kidney function. In assuming that traditional treatments offer the same benefit, are we missing opportunities to note potentially poorer therapeutic effects and test strategies more focused on our patients’ unique pathobiology?

The CKD population is expanding, patients with CKD bear a heavy burden of cardiovascular morbidity and mortality, and therapies in this group of patients remain unproved. This incongruity should be a call to arms. More randomized trials are desperately needed, and we as a medical community should feel an ethical responsibility to establish the efficacy of available treatments in this sizable and growing minority of patients. What proportion of the worse outcomes in CKD can be attributed to the health services delivery problem of decreased use of secondary prevention as compared with the potentially flawed care? What proportion of the worse outcomes in CKD can be attributed to the health services delivery problem of decreased use of secondary prevention as compared with the potentially flawed care? Without squarely asking that question, we cannot consider ourselves to be practicing true evidence-based medicine.

DISCLOSURES

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REFERENCES


See related article, “Renal Impairment Predicts Long-Term Mortality Risk after Acute Myocardial Infarction,” on pages 141–150.

Cardiovascular Disease, Chronic Kidney Disease, and Type 2 Diabetes Mellitus: Proceeding with Caution at a Dangerous Intersection

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