Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a cornerstone of treatment in patients with chronic kidney disease (CKD). Treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers has been shown to lower blood pressure, reduce proteinuria, and slow the progression of CKD caused by diabetes and other diseases. Approximately 50% of patients with CKD will incur cardiovascular disease (CVD); conversely, 20% of those with CVD meet a definition of CKD, most commonly an estimated glomerular filtration rate of <60 mL/min per 1.73 m², with no other signs of kidney damage (Figure). Clinical trials of patients with CVD often attempt to exclude patients with CKD, given their higher rates of study medication discontinuation, difficulty in clinical and experimental treatment, and potentially unique form(s) of CVD, which may add to variation in trial outcomes. We have learned in recent years that the serum creatinine alone is an insensitive indicator of reduced renal filtration, and the estimated glomerular filtration rate (eGFR) is best obtained from a calculation based on the creatinine, age, gender, and race. In the Prevention of Events with an ACE Inhibitor (PEACE) trial discussed in the present issue of Circulation, a serum creatinine level >2.0 mg/dL was an exclusion criterion. This worked to effectively exclude most patients with an eGFR <30 mL/min per 1.73 m². However, it allowed 1355 of 8280 (16.4%) of patients in the present analysis from PEACE into this PEACE substudy is important because PEACE was a trial that allowed open-label ACEIs instead of the treatment allocation in diabetics with overt proteinuria or hypertension with microalbuminuria, on the basis of new evidence showing benefit. All of these adjustments worked strongly toward a type II error, that is, failing to find a benefit attributable to trandolapril. Thus, this PEACE substudy is important, because with a single, simple variable now present as an automated calculation from the clinical laboratory, a reduced eGFR <60 mL/min per 1.73 m² can identify the patient with stable coronary disease and preserved left ventricular function who is likely to benefit from ACEIs. If approximately 16% of patients in PEACE “flew under the radar” and were not deemed to require an ACEI clinically, there probably are greater numbers in clinical practice who ultimately would benefit from RAAS inhibition.

Why does renal function prove to be such a good risk stratifier and help to target a subgroup for RAAS blockade? One explanation is that eGFR cutpoints in PEACE allowed identification of slightly older, sicker, more diabetic, and more hypertensive patients—the groups more likely to benefit from ACEIs. However, in PEACE, those in the lower eGFR groups had lower rates of myocardial infarction and higher rates of revascularization than the other groups. Another explanation is that CKD works through a variety of mechanisms to activate and intensify the action of the RAAS, thus promoting atherosclerosis, myocardial disease, and, ultimately, death. It is important to note that approximately 40% of patients in PEACE were not taking β-blockers; it is likely that very few were taking aldosterone-blocking drugs, and none were taking angiotensin receptor blockers. Thus, in many PEACE patients with CKD who were assigned to placebo, the sympathetic nervous system, RAAS, and the biological actions of aldosterone were unchecked. This translated into an unadjusted hazard ratio for death of 4.14 compared to 2.86 for those assigned to placebo and trandolapril, respectively (P<0.01). A recent meta-analysis (n=33,500) from 6 trials including PEACE targeting patients with preserved left ventricular function and random assignment to ACEI or placebo found a pooled 17% risk reduction in CVD mortality (P=0.01). If this analysis could be
refocused on the subgroup with an eGFR <60 mL/min per 1.73 m², data from the present PEACE analysis would suggest that the benefit would be nearly doubled.

In summary, patients with CKD present many difficulties to practicing cardiologists that trialists have attempted to avoid. However, understanding the eGFR in stable coronary artery disease offers an opportunity to find patients most likely to benefit from RAAS-modulating drugs—a proven strategy to reduce cardiac and renal end points (Figure).

Intersection between patients with CKD and patients with CVD shows that approximately half of patients with CKD have CAD, whereas 20% of those with CAD will meet a definition of CKD. Those with combined CKD and CAD have been shown to have the benefits of RAAS blockade, as shown. RAAS indicates renin-angiotensin-aldosterone system; CKD, chronic kidney disease; CAD, coronary artery disease; ESRD, end-stage renal disease.

Disclosures

None.

References


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Chronic Kidney Disease: Tipping the Scale to the Benefit of Angiotensin-Converting Enzyme Inhibitors in Patients With Coronary Artery Disease
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