Chronic Kidney Disease

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

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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 the study with an eGFR <60 mL/min per 1.73 m², which is considered moderate or more CKD. Consistent with many prior studies, this group at higher risk for CVD end points had a graded increase in mortality rate and CVD outcomes. Notably, those assigned to trandolapril had slightly lower adjusted hazard ratios for most of the end points compared with placebo. Thus, the overall benefit was a 27% risk reduction in total mortality with the ACEI in the CKD subgroup.

This analysis is important because PEACE was a trial that was influenced by changing clinical practice. The trial had difficulty in recruiting because many patients with diabetes and CVD were already being placed on ACEIs by their physicians and were not eligible for the trial. Nine months after starting the trial, the investigators reduced the sample size from 14,100 to 8,100, changed the primary end point to a secondary end point, and then expanded the original primary end point to include cardiovascular death, myocardial infarction, or coronary revascularization. The study randomly assigned patients from 1996 to 2000; in 2002, the investigators decided to allow 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 a calculated and clinical 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 the study with an eGFR <60 mL/min per 1.73 m², which is considered moderate or more CKD. Consistent with many prior studies, this group at higher risk for CVD end points had a graded increase in mortality rate and CVD outcomes. Notably, those assigned to trandolapril had slightly lower adjusted hazard ratios for most of the end points compared with placebo. Thus, the overall benefit was a 27% risk reduction in total mortality with the ACEI in the CKD subgroup.

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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.

Reframed 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).
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