Update from the International Society on Hypertension in Blacks

Highlights from the 17th International Interdisciplinary Conference on Hypertension and Related Risk Factors in Ethnic Minority Populations
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The 2002 meeting of the International Society on Hypertension in Blacks focused strongly on the risks and consequences of uncontrolled hypertension and other risk factors, particularly in African Americans. Of note is the growing interest in chronic kidney disease (CKD) as a risk factor, or better stated, as a reflection of the underlying unique vascular pathobiology that leads to accelerated atherosclerosis, diastolic and systolic heart failure, arrhythmias, and sudden death. Importantly, the composite endpoint of worsening renal function, end-stage renal disease (ESRD) requiring dialysis, and all-cause mortality has emerged as a target for multiple intervention trials. It appears that attention to CKD as a high-risk state is leading to innovative diagnostic and therapeutic strategies in this growing population of patients.

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Chronic Kidney Disease and Cardiovascular Disease

In a plenary session titled "Reversing Cardiovascular Complication in Patients with Kidney Disease" Dr. Lawrence Y. C. Agodoa of the National Institutes of Health (NIH) presented an update on the CKD and ESRD epidemic. He highlighted that we are now witnessing a nonlinear, exponential growth in the number of new and existing ESRD patients. Importantly, in this renal population, 7 out of 10 of the leading causes of death are cardiovascular diseases, including myocardial infarction, heart failure, and cardiac arrest. Current estimates are that the number of ESRD patients in the United States will exceed the ability of a limited number of nephrologists and extended care providers to deliver ESRD care by 2010.

Dr. Peter McCullough, Chief of Cardiology at the University of Missouri-Kansas City School of Medicine, Truman Medical Center (at the time of the study), presented the scope of cardiovascular complications in patients with CKD. Based on the

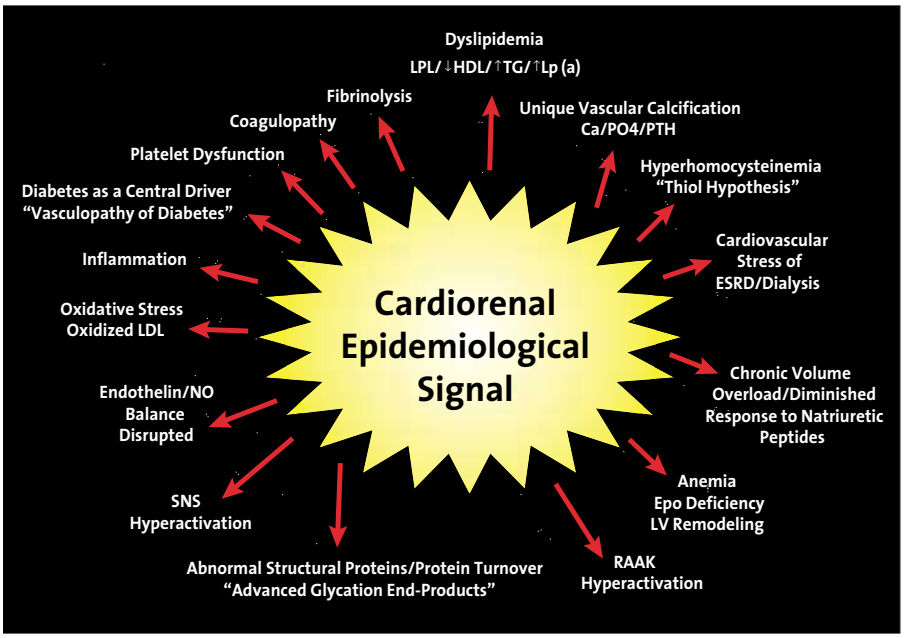

Figure 1. *The epidemiological signal of cardiorenal risk and the developing lines of hypothesis testing addressing the unique pathobiology of the chronic kidney disease state and its effects on the cardiovascular system. LPL, lipoprotein lipase; HDL, high density lipoprotein cholesterol; TG, triglycerides; Lp(a), lipoprotein (a); Ca, calcium; PO4, phosphorus; PTH, parathyroid hormone; ESRD, end-state renal disease; Epo, erythropoietin; LV, left ventricle; RAAK, renin–angiotensin–aldosterone–kinin system; SNS, sympathetic nervous system; NO, nitric oxide; LDL, low-density lipoprotein cholesterol.*

totality of evidence, two concepts have emerged in recent years: 1) CKD and ESRD are the two highest cardiovascular disease (CVD) risk states in human medicine, and 2) most of the CVD risk attributed to diabetes is really driven by underlying diabetic nephropathy and is signaled by the presence of microalbuminuria, gross proteinuria, and of an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.[1–2] He pointed out that careful attention to "cardiorenal risk" has led to the development of important new hypotheses being tested in translational models and clinical trials (Figure 1). Among the strategies in these trials are blockade of the renin–angiotensin–aldosterone–kinin (RAAK) system, treatment of erythropoietin deficiency and correction of anemia, correction of calcium–phosphorus imbalance, and homocysteine reduction.[3] Of note, the basic blocking and tackling of cardiovascular risk should be done with the highest degree of attention in CKD and ESRD, which means meticulous blood pressure (BP) control, for a target of ~125/75 mm Hg, control of diabetes, and reduction in low-density lipoprotein (LDL) cholesterol to an appropriate target level of 100 mg/dL, which would apply to most of the cardiorenal patient population.

From the African American Study of Kidney Disease and Hypertension (AASK), Dr. Janice Douglas and Yvette Baxter Hall, RN, highlighted published and unpublished findings. Dr. Douglas reminded the audience that this multicenter, NIH-sponsored trial was designed from 1991 to 1994, enrolled patients from 1995 to 1997, and carried out follow-up from 1997 to 2001. It recruited African Americans ages 18–70 years who were nondiabetic and had hypertension and evidence of CKD, with eGFR 20–65 mL/min/1.73 m^2. Importantly, the AASK excluded patients with severe proteinuria, defined as a urinary protein/creatinine ratio > 2.5. It is important to point out that 47% of AASK participants had household incomes of less than $15,000 per year, and therefore this study represents the lowest socioeconomic population ever recruited and retained in a clinical trial. In AASK, participants were not blinded to their compliance; in fact, it was just the opposite, as they received regular feedback about their compliance with study medications and their resultant blood pressure control. This feedback was a key tool in getting subjects in AASK to achieve the pre-specified target blood pressures.

The first important inference from this trial is that the tight BP control group (mean BP = 127/77) had similar outcomes to that of the less-tight BP group (mean BP 140/85 [P = .85]), for the difference in the composite of a decline in eGFR, ESRD, or death. This may be attributed to the fact that there were not enough patients with severe degrees of proteinuria in the trial. In terms of the three drugs tested in the randomized arms, the published and soon-to-be published results are clear: the best reductions in the composite endpoint were found with ramipril (R) (relative risk reduction 22%, P = .04; R vs M), followed by metoprolol (M) (relative risk reduction 19%, P = .19; M vs A),

Chronic kidney disease and end-stage renal disease are the two highest cardiovascular disease risk states in human medicine.

and then followed by amlodipine (A). In the patients at highest renal risk, with urine protein/creatinine ratios > 0.22, there were convincing reductions in the composite endpoint with ramipril (relative risk reductions 46% and 37%, R vs A, $P = .004$, and R vs M, $P = .003$, respectively). The messages from AASK are fairly clear: target blood pressure goals can be reached in the majority of this difficult population by the use of a multidrug approach, and specifically, the base of antihypertensive and cardiorenal protection should be an angiotensin-converting enzyme inhibitor.

Dr. Errol D. Crook from Wayne State University School of Medicine presented more supportive information regarding cardiorenal risk. In particular, recent analyses from the Hypertension Optimal Treatment Trial and the Heart Outcomes Protection Study both indicate that patients from these trials with baseline eGFR < 60–65 mL/min/1.73 m^2 had higher risk for incident CVD and CVD death across all blood pressure groups. Again, this implies that CKD or the underlying vascular pathobiology in the cardiac and renal systems is driving hard endpoints in the high-risk hypertension population. He also pointed out the importance of lipid control once patients reach ESRD. According to a recent article by Seliger and colleagues,[4] statin use in the United States Renal Data System (USRDS) was found to be at 10% for the entire population. Those treated with statins, however, appeared to benefit with a reduction in total mortality. Because total and LDL cholesterol decline with malnutrition in ESRD, it is important that clinicians learn to identify which patients with ESRD will benefit from statins, and hence, this is a call for clinical trials in this population.

The African American Study of Kidney Disease and Hypertension represents the lowest socioeconomic population ever recruited and retained in a clinical trial.

This year's meeting had multiple presentations of original data in "Blue Ribbon" sessions that addressed cardiorenal risk in ethnic populations. James H. Jackson, IV, PharmD, representing the National Hypertension Quality Improvement Program, a consortium of managed care organizations, evaluated 440 high-risk African American hypertension patients and found a rate of control (BP < 140/90) of 36.9%.[5] Importantly, the diabetic subgroup (n = 138) had only a 20.3% rate of long-term control. In multivariate analyses, diabetes itself was a risk factor for poor control, again implicating the importance of the hyperactivation of the RAAK and CKD driving this pervasive problem.

Dr. William B. White presented the first of two randomized, double-blind, placebo-controlled trials of the selective aldosterone-receptor blocker eplerenone (EPL) in the treatment of hypertension.[6] When compared to placebo, EPL had reductions in systolic BP of 5.7 mm Hg at 25 mg, and graded decreases in systolic BP up to 10.4 mm Hg at 100 mg of EPL. These were supported by casual and ambulatory blood pressure monitoring data. Of note, both aldosterone and renin levels increased markedly in patients assigned to EPL.

A prospective, comparative trial of EPL versus losartan (LOS) in a mainly (63%) African American hypertensive population was presented by Elijah Saunders, MD.[7] In this trial of 551 subjects, the treatment arms were EPL escalating from 50 to 200 mg per day, LOS from 50 to 100 mg per day, and placebo. The bottom line was that EPL had consistently better

Main Points

- In patients with chronic kidney disease (CKD) and end-stage renal disease, 7 out of 10 of the leading causes of death are cardiovascular diseases, including myocardial infarction, heart failure, and cardiac arrest.
- The messages from the African American Study of Kidney Disease and Hypertension are fairly clear: target blood pressure goals can be reached in the majority of this difficult population by the use of a multidrug approach, and specifically, the base of antihypertensive and cardiorenal protection should be an angiotensin-converting enzyme inhibitor.
- In a comparative trial, eplerenone had consistently better blood pressure reductions than losartan (systolic BP −12.8 vs −6.3 mm Hg, $P < .001$) at every dose level, and the effects were more pronounced in African Americans than in Caucasians.
- It appears that attention to CKD as a high-risk state is leading to innovative diagnostic and therapeutic strategies in this growing population of patients.

blood pressure reductions than LOS (systolic BP −12.8 vs −6.3 mm Hg, $P < .001$) at every dose level, and the effects were more pronounced in African Americans than in Caucasians. Again, both aldosterone and renin levels were elevated, this time with both LOS and EPL. Of note, urinary albumin excretion dropped as expected with LOS and EPL by 15%–30%. The conclusion of this trial was that EPL was superior to LOS in the control of BP in this mainly African American population. It appears from these trials and others that EPL will have a role in the treatment of hypertension and perhaps other cardiovascular disorders in the African American population.

Commentary

There are four basic explanations that have been put forward for the cardiorenal risk relationship: 1) excess comorbidities in CKD patients, 2) lesser use of beneficial therapies in CKD patients, or "therapeutic nihilism," 3) excess toxicities, from conventional therapies used, and 4) special biology of the chronic renal failure state, which leads to accelerated and more severe cardiovascular disease. This meeting brought out all of these forces at work. The good news is that convincing evidence is now emerging for blockade of the RAAK as the base of therapy in both Caucasians and African Americans. Importantly, trials are underway to give clinicians the needed evidence base to appropriately risk stratify and treat patients at cardiorenal risk. ■

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