Prevent Kidney Disease to Lower High Level of Cardiovascular Risk

By Daniel M. Keller

With the incidence and prevalence of cardiovascular disease (CVD) increasing worldwide and its connection to chronic kidney disease (CKD), the new president of the European Renal Association – European Dialysis and Transplant Association outlined in a news conference at the association's 48th Congress in Prague several steps by which physicians can help to alleviate the personal and economic burdens of CVD. CVD is responsible for about 10 percent of all illness and 30 percent of all deaths in the world.

Raymond Vanholder, MD, PhD, professor of medicine at the University of Ghent and clinical head of the nephrology division of the Ghent University Hospital in Belgium, said the most prominent risk factors for CVD are type 2 diabetes, hypertension, hypercholesterolemia, smoking, and overweight. Among other negative outcomes, obesity often leads to hypertension and disturbances in blood glucose and lipid metabolism. Besides poor diet, other unhealthy lifestyle factors such as physical inactivity, stress, alcohol consumption, and smoking increase the risk of CVD.

While the connection between CKD and CVD has been recognized only fairly recently, Vanholder made the point that it is significant and unmistakable. Even minor renal dysfunction confers a significantly greater risk of CVD, and a published community-based population study (Go AS et al. *N Engl J Med.* 2004; 351:1296–1305) on more than one million people with a mean age of 52 years has shown an independent association between a rising glomerular filtration rate (GFR) and mortality, cardiovascular events, and hospitalizations.

At the extreme end of the spectrum—people with end-stage renal disease on hemodialysis – the mortality risk may be hundreds-fold higher compared to the general public. Vanholder showed data that patients on dialysis aged 25 to 34 years have 375-fold higher risk of death compared with their healthy counterparts. The elevated risk compared to the general population decreases for older groups but is still significant. "Even for people 75 to 84 years old, which is people who have not much to go anymore, even there the mortality risk is five times higher in the patients on hemodialysis," Vanholder showed.

For people who started on dialysis as children, their coronary artery calcification scores, a marker of atherosclerosis, remained fairly low until age 20 years but then increased exponentially. By age 30, "they show a calcification pattern that is worse than in normal people of age 80 or 90," he said. (See Goodman WG et al. *N Engl J Med*. 2000; 342(20):1478–83). For patients who underwent follow-up measurements, their calcification scores nearly doubled over a mean period of 20 months.

Next he showed that the age-adjusted risk of death from any cause is directly related to the GFR. With a GFR of 60 mL/min/1.73 m^2 or greater, the risk of death was 0.76/100 person-years. At a GFR of 45–59, essentially a loss of at least half one's kidney function, the rate rose to 1.08/100 person-years. But as the GFR dropped below 45, the death rates rose precipitously, and with a GFR below 15, the death rate was 14.14/100 person-years.

Vanholder noted that dialysis is begun with a GFR below 15, so the increased risk of death persists for years even before dialysis is initiated. His own work has shown that mortality risk begins to increase as the GFR drops below 75 mL/min/1.73 m^2.

"The big problem is that these people do not feel bad… and some people appear [at the nephrologist] only at the moment they need dialysis," he said. "So screening is really something which is very necessary." Estimates are that at least 10 percent of the global population has a GFR of 60 mL/min/1.73 m^2 or below. Most will die before they ever reach the stage of dialysis.

What to do

Vanholder said there needs to be better recognition of the association between CKD and CVD among the general population, politicians, and especially among physicians. Screening allows earlier referral to nephrologists and the potential to slow the progression of CKD.

Albuminuria is an early indicator of CKD, and so is the serum creatinine level. In the Heart Outcomes and Prevention Evaluation (HOPE) trial (Mann JF et al. *Ann Intern Med*. 2001; 134:629-–636) of patients with pre-existing vascular disease or diabetes plus an additional risk factor, at a serum creatinine level of 1.40 mg/dL there was a 40 percent higher cardiovascular risk. This level "is not much, [and] many doctors would even consider this number as a normal number," Vanholder noted. For comparison, he said male sex, often seen as a significant risk for CVD, raised the risk by only 2 percent.

Many preventive interventions are inexpensive or free. Smoking decreases kidney function, so smoking cessation is a cheap (and even money-saving) beneficial lifestyle change. Vanholder called salt "very toxic for the kidneys," so salt restriction, both on a per-patient and population basis, is highly recommended. Additional inexpensive measures are correction of body mass index, exercise, treatment of hypertension, and use of aspirin to treat blood hypercoagulability.

More expensive but effective interventions apply to diabetes, dyslipidemia, and anemia. Specific to the nephrologist are treatment of volume status, maintenance of nutritional status, and calcium/phosphate metabolism.

Vanholder said the best use of resources is to focus on the groups at highest potential risk. Some that are generally addressed are people with diabetes, hypertension, a family history of renal disease, previous renal damage or risks for it, and proteinuria. "What is perhaps more important are the ones we do not necessarily think of," he emphasized. These include smoking, infectious diseases such as hepatitis B or C and HIV, age above 60 years, and CVD, "and most of all, obesity or what we call the metabolic syndrome," he said. "I think the most important thing is that medical doctors have to be aware that these are the risk factors, and they have to check the kidney function attentively in those people, and from the moment there is an alarm sign, they have even more even reasons to try to convince these people to be careful.

"The earlier you start, the better. With most of these measures you cannot return the whole picture [of kidney function], but at least you can stabilize it and prevent the kidney function from going down further, and very much in parallel with this, the cardiovascular system will also be better protected."

Nighttime drugs

Greater Cardiovascular Risk Reduction With Antihypertensives at Bedtime Than in Morning

One simple, no-cost change appears to lower cardiovascular (CV) risk among patients with resistant hypertension. By taking their antihypertensive medications at bedtime instead of in the morning, patients in a Spanish trial significantly reduced their cardiovascular risk.

Researchers have known that sleep-time blood pressure (BP) better predicts CV risk than does either the awake or 24-hour BP means. However, all previous studies relied on a single baseline ambulatory blood pressure monitoring (ABPM) profile on each participant at the beginning of the study. Thus, they could not detect changes in the pattern or level of BP if they occurred.

Reporting at the 48th Congress of the European Renal Association—European Dialysis and Transplant Association in Prague, lead investigator Ramón Hermida, PhD, director of the laboratory of bioengineering and chronobiology at the University of Vigo in Vigo, Spain, told *ASN Kidney News* that his study tested the hypothesis that bedtime dosing of at least one blood pressure medication would more effectively reduce CV disease (CVD) risk than would conventional morning dosing of all of a patient's antihypertensive medications. He pointed out that bedtime dosing is a cost-effective and simple strategy to achieve adequate asleep BP reductions and to re-establish a normal 24-hour pattern of BP reduction at night ("dipping pattern") if it is missing.

Hermida reported the results of a substudy of a larger study of people with hypertension, which was prospective, randomized, and open-label. In the substudy, 776 participants with resistant hypertension had a mean age of 61.6 years, an approximately equal number of men and women, and were randomly assigned to take all their prescribed BP medications upon awaken-