Renal Denervation For Control of Treatment-resistant Hypertension

Denervation of the renal nerves has the potential to dramatically reduce hypertension in medication-resistant patients. That was the message from Henry Krum, MD, PhD, professor of medicine at Monash University in Melbourne, Australia, and lead investigator of the SYMPLICITY-2 trial, which compared renal denervation to no intervention in over 150 patients. Krum spoke about the trial in a Hot Topics session at Kidney Week 2011. “I don’t need to tell this audience that hypertension is a major problem, and this problem is only going to get worse,” Krum said. “The prevalence will grow to almost 50 percent in Western populations by 2025, with developing populations catching up very quickly.”

About 9 percent of the population is resistant to treatment, defined as having uncontrolled blood pressure despite being on three or more antihypertensive medications.

One critical driver of hypertension is sympathetic activity involving the renal nerve. Activation from the brain to the kidney stimulates release of renin and activation of the RAAS system, retention of sodium, and reduction of renal blood flow. Feedback to the brain via renal afferents also plays a part, driving blood vessel constriction and other effects. Renal denervation for hypertension dates back to the 1940s, but its success came with high rates of incontinence, impotence, and hypotension, due to off-target effects. Since then, precise targeting of the renal nerve has been accomplished with the “SYMPLICITY” system (Medtronic), in which a catheter is inserted into the renal artery via the femoral artery, which delivers radiofrequency energy to ablate the nerve.

The first major trial of the system, published in 2009, enrolled 57 patients with office systolic blood pressure of 160 mm Hg or greater, uncontrolled by three or more medications. In this open trial with no control group, blood pressure was reduced by 27 mm Hg systolic and 17 mm Hg diastolic, an effect maintained over the 12 months of the study.

Measures of muscle sympathetic nerve activity indicated that part of the effect was due to afferent denervation. “This opens up a new vista for treatment of renal hypertension,” Krum said, since it directly implicated an important role for the afferent system.

The recently completed SYMPLICITY-2 trial supported these initial results in a controlled, but not blinded, trial comparing denervation to best medical management in 153 patients over 24 months. The mean age of patients was 57 years, with a third of them experiencing diabetes mellitus. Baseline office blood pressure was 176/17, despite that more than three-quarters of patients were on an ACE inhibitor, a calcium channel blocker, and a beta blocker.

The results mirrored those seen in the first trial, with a reduction in blood pressure of 32 mm Hg systolic and 12 mm Hg diastolic, which emerged quickly and was sustained at 12 months.

There was little to no change in the control group. Relatively few patients have reached the 24-month follow-up, but initial findings in this smaller group are equally positive, Krum said. The treatment appeared to be safe and well tolerated.

A critical question is whether there is functional (as opposed to simply anatomic) reinnervation of the nerve over the long term. “Our data suggest that is not the case at 24 months,” said Krum.

A third trial is underway in the United States, with a placebo group undergoing a sham procedure in order to maintain a blind. “This will probably be the definitive answer in the refractory hypertension setting,” Krum predicted. Referring back to the evidence for involvement of the afferent system, he noted that sympathetic excess plays a role in many nondon hypertensive disorders, including heart failure. “Many of the disorders implicated in the progression of heart failure are adrenergically mediated,” including myotrophic hypertrophy, fibrosis, and renal disease itself.

Sympathetomy in animal models can reduce the adverse cardiac effects of several of these disorders. Based on that, a trial is underway to test the ability of renal denervation to reduce progression of heart failure in renal disease patients with left ventricular dysfunction. The initial aim is to demonstrate safety in this population, and to determine whether there is a physiologic effect on ventricular function.

While praising the studies performed so far, Gerald DiBona, MD, emeritus professor at the University of Iowa in Iowa City, noted that too little is known about long-term reinnervation. “For me, the big issue is what about the persistence of denervation.” Functional reinnervation occurs in weeks, and in months in dogs. In humans, the little data there are suggest it may occur over several years. “We need to know whether the effenter renal nerves are growing back after two or three years,” he said. “Is there afferent reinnervation? We have no direct data as of yet. It may be that they do not reinnervate.”

Two new studies show that when it comes to hemoglobin A1c in dialysis patients, Goldilocks had it right—the best level is not too high, but not too low either. Both studies show that the lowest mortality occurred in patients with intermediate levels, ranging between 6.5 percent and 9 percent, and that dropping below that was associated with worse patient outcomes.

The guidelines for control of blood sugar in the Kidney Disease Outcomes Quality Initiative (KDOQI), dating to 2007, state that the target A1c level for people with diabetes “should be less than 7 percent, irrespective of the presence or absence of chronic kidney disease.” However, according to Kamyar Kalantar-Zadeh, MD, professor of medicine and pediatrics and epidemiology at the UCLA David Geffen School of Medicine in Los Angeles, “There is no consistent evidence to support these targets for dialysis patients.” Kalantar-Zadeh was lead investigator on one of the new studies. Previous large observational studies have come to different conclusions about the effect of A1c on mortality in dialysis patients. But these studies have generally been relatively short-term, he said. To determine the long-term effect of A1c, he and his colleagues examined outcomes in over 54,000 dialysis patients with diabetes over a seven-year period.

They found that mortality from all causes followed a U-shaped curve in relation to time-averaged A1c. The lowest rate of mortality occurred when A1c was between 7 percent and 8 percent. In line with previous studies, it rose sharply above that, with the hazard ratio rising to approximately 1.4 when A1c was in the 9 percent to 10 percent range. Surprisingly, though, the hazard ratio also rose when A1c was below 7 percent, increasing gradually when the level was between 6 percent and 7 percent, and then steeply as the level dropped below 6 percent. The risk of death at an A1c level of 5 percent was higher than at levels between 9 percent and 10 percent.

The same U-shaped curve was found for mortality from cardiovascular events, again with a nadir at A1c levels between 7 percent and 8 percent, with approximately similar magnitudes of risk on either side. Kalantar-Zadeh also analyzed mortality as a function of glucose levels directly, using random glucose samples in over 50,000 patients. The lowest mortality was seen in patients with time-averaged glucose in the 150–200 mg/dl range, with the risk increasing from either more, or less, glucose.

A second study, part of the Dialysis Outcomes and Practice Pattern Study (DOPPS), reached similar conclusions, according to investigator Fritz Port, MD, of Arbor Research in Ann Arbor, Michigan. In this prospective study of over 6000 dialysis patients with diabetes from 12 countries, after fully adjusting for a range of variables affecting mortality, the lowest mortality occurred in patients with A1c levels between 7 percent and 7.9 percent.

“The desirable range for diabetic dialysis patients is 7 percent to 9 percent,” Port said, “which is higher than the guidelines for the general diabetes population.” To improve patient survival, he said, diabetes medications could be reduced in patients with low blood sugar, a step that may be particularly important for patients with poor nutritional status.

“I think the take-home message is that the target may need to be reconsidered in diabetic dialysis patients,” Kalantar-Zadeh said, suggesting 6.5 percent to 8 percent as the appropriate range. Importantly, “the target has a lower threshold, not just an upper threshold.”

“It also has practical implications,” he said. “Patients do not need to be pressured all the time to achieve the same very low levels as in the general diabetes population. We may be satisfied with patients reaching the middle range.”

The reason that dialysis patients differ from other diabetic patients is not clear. One reason may be that dialysis patients have adapted to moderately high glucose, reaching a new normal, and so for them, lowering glucose below 6.5 percent or 7 percent is not beneficial.

While the findings of the two studies coincide, neither was a randomized trial comparing different target glucose levels. Thus, Kalantar-Zadeh said, there is a need for controlled trials to further confirm these findings.

The findings were presented at Kidney Week 2011.