In addition, at 24 months, 39% of patients experienced an office SBP of <140 mm Hg.

Through 24 months of follow-up, there were no serious periprocedural events in the EnligHTN I trial. Serious device- or procedure-related events included 1 case of worsening preexisting proteinuria, 1 case of symptomatic hypotension, and 2 events in 1 patient of worsening of preexisting renal artery stenosis with a new stenotic lesion.

Prof. Tsioufis concluded that data from the EnligHTN I trial indicate that renal denervation with the EnligHTN system is effective in lowering office BP with an acceptable safety profile.

Metabolic Syndrome Elevates Risk of Microalbuminuria Despite BP Control

Written by Emma Hitt Nichols, PhD

Fimasartan reduced blood pressure (BP) and albumin-creatinine ratio (ACR) in patients with or without metabolic syndrome; however, patients with metabolic syndrome at baseline and 3 months were at a greater risk of elevated ACR at 1 year. Jeong Bae Park, MD, Cheil General Hospital, Kwandong, Korea, presented 3-month and 1-year data from a 3-year multicenter study designed to evaluate the effect of early correction of metabolic syndrome on organ damage for patients with hypertension [K-METS]. The design of this study has been published [Kim C et al. *Pulse* 2013].

The antihypertensive agent fimasartan is derived from losartan and is expected to have greater efficacy and potency [Kim TW et al. *Bioorg Med Chem Lett* 2012]. In clinical trials of fimasartan, risk of cardiovascular disease was reduced with the correction of metabolic risk factors in addition to BP control. The purpose of the observational K-METS study was to determine the effect of the early correction of metabolic syndrome on organ damage, as well as the future development of diabetes and cardiovascular disease, for patients with hypertension.

In the prospective single-arm K-METS study, 5481 patients with hypertension received open-label fimasartan and are being followed for 3 years. At baseline, 17% of patients had diabetes, mean weight was 67.3 kg, mean body mass index was 25.3 kg/m^2, and the mean number of years taking an antihypertensive agent was 3.58. Baseline systolic and diastolic BPs (SBP and DBP, respectively) were 144 and 88 mm Hg, respectively. Metabolic syndrome was present in 57% of the study population.

The primary end point of the K-METS study is cardiovascular mortality, stroke, myocardial infarction, hospitalization for heart failure, and the development of diabetes at 3 years. At 3 months, patients with hypertension or metabolic syndrome received therapy for correction. At 1 year, BP, insulin resistance, diabetes, and cardiovascular events were assessed. At 3 years, incidence of diabetes and cardiovascular disease will be evaluated. Patients were categorized into 4 groups according to the presence of metabolic syndrome:

1. *Group 1:* metabolic syndrome at baseline and 3 months
2. *Group 2:* metabolic syndrome at baseline but not at 3 months
3. *Group 3:* no metabolic syndrome at baseline but metabolic syndrome developed by 3 months
4. *Group 4:* no metabolic syndrome at baseline or 3 months

At 1 year, SBP and DBP significantly decreased to 127 and 79 mm Hg, respectively ($p<0.0001$), as well as ACR from 41.2 to 26.6 mg/g ($p<0.0001$). The proportion of patients with metabolic syndrome also decreased to 44% ($p<0.0001$). Although all groups experienced a decrease in ACR, patients in Group 1 or 2 experienced the greatest decrease in ACR. Patients in Group 1 had the highest ACR rates compared with Groups 2, 3, and 4. In addition, patients in Group 1 were at a greater risk of ACR ≥30 mg/g compared with Groups 2, 3, and 4 (odds ratio, 1.62; 95% CI, 1.33 to 1.97).

Dr. Park stated that data from the K-METS trial suggest that fimasartan treatment results in a substantial decrease in BP and ACR at 3 months and 1 year.

Multiple Factors Examined for Contributing to SYMPLICITY HTN-3 Failure

Written by Emma Hitt Nichols, PhD

Multiple factors associated with the Renal Denervation in Patients With Uncontrolled Hypertension trial [SYMPLICITY HTN-3; NCT01418261] may have contributed to its failure to meet the primary endpoint of change in office blood pressure at Month 6, according to George L. Bakris, MD, University of Chicago Medicine, Chicago, Illinois, USA, who presented data from a subanalysis of this trial.

The sham arm of the SYMPLICITY HTN-3 trial demonstrated a greater than expected reduction in systolic

blood pressure (SBP) [Bhatt DL et al. *N Engl J Med* 2014]. This may in part explain the lack of efficacy for the primary endpoint of the trial. The purpose of this sub-analysis was to determine the significance of several potential confounders that may have driven the effect observed in the sham arm, including procedural changes, change in antihypertensive therapy, variability in adherence, and differences in patient populations according to different geographic regions.

In the prospective, sham-controlled, SYMPLICITY HTN-3 trial, 535 patients with severe resistant hypertension were randomly assigned in a 2:1 fashion to undergo renal denervation (RDN) or a sham procedure. Resistant hypertension was defined as patients who had been prescribed 3 or more antihypertensive medications at maximally tolerated doses. There was no significant difference in change in SBP between the 2 arms at 6 months, as the sham arm demonstrated a significant change in SBP from baseline ($p<0.001$).

In the sub-analysis, procedural variability was analyzed such that the mean number of ablations in patients who underwent RDN was matched 1:1 using propensity scores. Patients were categorized according to 4 quadrant ablations in both, one, or neither renal artery. As the number of ablations increased, there was a trend toward a progressive decrease in office SBP in the patients who underwent RDN. There was, however, a similar, trend in the patients who underwent the sham procedure, with BP decreasing with an increasing number of ablations.

Baseline predictors of BP improvement in patients in the sham arm included the use of alpha-blockers, higher baseline office BP readings, the use of aldosterone antagonists, and the total number of intervention attempts. However, vasodilator use was inversely associated with response in both the sham and RDN arms. A secondary analysis of potential racial differences demonstrated that black patients were less likely to improve in the sham arm compared with patients who were not black.

Geographic location also led to some notable differences. Patients who lived in the Northeastern United States (Boston-New York region) demonstrated a change in office BP, albeit to a lesser extent in ambulatory BP. However, the results for patients living in the Southwestern, Southern, or Western United States reflected that of the original trial. It is unclear as to why there was a difference based on geographic location.

Dr. Bakris concluded by stating that there were some limitations in the SYMPLICITY HTN-3 trial that may have led to the neutral results with RDN for the primary endpoint. He further suggested that the limitations discussed in his presentation were exploratory and were meant to be hypothesis-generating.

Renal Denervation Improves Systolic Ambulatory BP in Resistant Hypertension

Written by Emma Hitt Nichols, PhD

Systolic daytime ambulatory blood pressure (BP) was significantly decreased by renal denervation plus standardized medical treatment with the Symplicity catheter compared with standardized medical treatment alone in patients with confirmed resistant hypertension. Michel Azizi, MD, PhD, Hôpital Européen Georges Pompidou, Paris, France, presented 6-month data from the multicenter Renal Denervation in Hypertension study [DENER-HTN; NCT01570777]

The Symplicity catheter system delivers radiofrequency energy to target nerves through the renal artery wall to reduce sympathetic nervous system involvement in hypertension [Medtronic 2013]. The purpose of the open-label DENER-HTN trial was to evaluate the safety, efficacy, and cost-effectiveness of renal denervation with the single-electrode Symplicity catheter for patients with resistant hypertension.

In the parallel superiority DENER-HTN trial, 106 patients with resistant hypertension were randomly assigned to receive renal denervation or 4 weeks of standardized therapy alone, after 4 weeks of standardized therapy did not reduce BP to <135/85 mm Hg. Resistant hypertension was defined as office BP of 140/90 mm Hg despite stable antihypertensive therapy with ≥3 medications. All patients received new, standardized treatment for hypertension that included indapamide (1.5 mg), ramipril (10 mg, or irbesartan, if cough present), and amlodipine (10 mg) daily.

The primary endpoint of the trial was changes in daytime ambulatory systolic BP at 6 months. At baseline, the mean office BP was 163/95 mm Hg, and the daytime ambulatory BP was 153.9/93.0 mm Hg. The mean body mass index was 30.1 kg/m^2, and the mean glomerular filtration rate was 88.6 mL/minute. Patients were monitored with home BP; if the home BP was not <135/85 mm Hg at 2 months, then the patient received spironolactone (25 mg) daily. If BP was still not controlled by 3, 4, or 5 months, patients also received bisoprolol, prazosin, and rilmenidine, respectively.

Patients who underwent renal denervation experienced a significant decrease in systolic BP of 16 mm Hg and the treatment-only group experienced a decrease of 10 to 14 mm Hg, with a difference between the 2 arms of –5.9 mm Hg at 6 months (95% CI, –11 to –0.05; p=0.03). In addition, nighttime ambulatory BP decreased by 6 mm Hg. The proportion of patients who achieved