The prevalence of hypertension is rising worldwide, and in Japan hypertension is estimated to be present in more than 40 million people. This represents approximately 45% of adult Japanese people ≥30 years of age. Uncontrolled hypertension is associated with high risk for cardiovascular events, stroke and chronic kidney disease across all ethnic and racial groups. Furthermore, these associated morbidity and mortality risks increase with increasing systolic blood pressure (SBP). While risks for coronary artery disease appear similar between Asian and Caucasian populations, Japanese hypertensive patients have approximately twice the risk for stroke as their Caucasian counterparts. These characteristics of hypertension illustrate the importance of strict BP control in Asia. Despite multiple options for pharmacotherapy and lifestyle interventions, however, the problem of uncontrolled hypertension persists and has prompted development of alternative device-based treatment options.

Renal artery denervation (RDN) using low-power radiofrequency energy delivery to ablate the renal nerves has been shown in several clinical trials to significantly reduce BP in patients with severe, uncontrolled hypertension. These early promising results led to the initiation and conduct of new, rigorously designed randomized trials including SYMPLICITY HTN-3 and SYMPLICITY HTN-Japan. SYMPLICITY HTN-3, the first randomized controlled trial of RDN in an Asian population, was underpowered for the primary endpoint analysis and did not demonstrate a significant difference in 6-month BP change between RDN and control subjects. (Circ J 2015; 79: 1222–1229)

**Key Words:** Ambulatory blood pressure; Asia; Renal denervation; Resistant hypertension
however, failed to demonstrate a significant BP-lowering benefit of RDN compared with sham procedure.\textsuperscript{15,16} The announcement in early January 2014 of the failure to meet the primary efficacy endpoint in SYMPLICITY HTN-3 resulted in the early discontinuation of the SYMPLICITY HTN-Japan randomized trial. Herein, 6-month primary results from the 41 subjects enrolled in the randomized controlled SYMPLICITY HTN-Japan trial are now reported.

\section*{Methods}

\subsection*{Study Design}
SYMPLICITY HTN-Japan is a prospective, randomized, controlled clinical trial comparing the safety and efficacy of RDN with standard of care medical therapy in subjects with uncontrolled hypertension. While there are many design similarities to SYMPLICITY HTN-3, subjects and clinical staff were not blinded to the treatment allocation and controls did not receive a sham procedure. The trial was conducted according to the Declaration of Helsinki at 17 sites in Japan. The trial was approved by the Institutional Review Board for each site and all subjects signed written informed consent for participation in the trial.

\subsection*{Subjects}
Eligible subjects were at least 20 years old and \(\leq 80\) years old at the time of informed consent. Subjects were required to have uncontrolled hypertension defined as office SBP \(\geq 160\) mmHg while on a stable anti-hypertensive regimen of at least 3 anti-hypertensive drug classes at maximum tolerated dose including a diuretic for a minimum of 6 weeks prior to enrollment; 24-h average ambulatory SBP was required to be \(\geq 135\) mmHg. Subjects were excluded if their estimated glomerular filtration rate was \(< 45\) ml/min/1.73 m\(^2\), using the modified calculation method for Japanese subjects.\textsuperscript{17}

Anatomical exclusions included main renal arteries \(< 4\) mm in diameter or \(< 20\) mm treatable length (ie, free of visible anatomic abnormality or atheroma), multiple renal arteries for which the main renal artery was estimated to supply \(< 75\)% of the kidney, renal artery stenosis (\(> 50\)% or renal artery aneurysm in either renal artery, history of prior renal artery intervention including balloon angioplasty or stenting and unilateral (functional or morphological) kidney.

Other exclusions included \(> 1\) inpatient hospitalization for a hypertensive crisis not related to confirmed non-adherence to medication within the past year, type 1 diabetes mellitus and \(\geq 1\) episodes of orthostatic hypotension not related to medication changes. Secondary causes of hypertension were also excluded (primary aldosteronism, pheochromocytoma, Cushing’s disease, coarctation of the aorta, hypothyroidism, hyperthyroidism, or hyperparathyroidism). The trial was designed to randomize 100 eligible subjects but was stopped early after randomization of 41 subjects due to the SYMPLICITY HTN-3 trial not meeting its primary efficacy endpoint.

\subsection*{Procedure}
A stable anti-hypertensive regimen was required for \(\geq 6\) weeks prior to enrollment, and after enrollment subjects were further evaluated at 2 screening visits conducted at least 2 weeks apart (Figure 1). If all screening visit 1 criteria were met, subjects were asked to maintain a daily diary in which they recorded daily home BP measurements and anti-hypertensive medication use for \(\geq 2\) weeks. At the second screening visit, subjects were assessed and received 24-h ambulatory BP monitoring (ABPM) instructions. ABPM was required to be completed \(\leq 14\) days after screening visit 2, and 24-h SBP was required to be \(\geq 135\) mmHg in order for the subject to proceed to randomization.

After the suitability of renal artery anatomy was confirmed on angiography, subjects were randomized in a 1:1 ratio to receive RDN using the Symplicity\textsuperscript{TM} RDN system (Medtronic, Santa Rosa, CA, USA) or to the control group maintained on their established anti-hypertensive therapy. Randomization was stratified by study center. RDN was
performed according to the device instructions for use. The Symplicity generator is programmed to deliver individual ablations of 120s. Interventionalists were instructed to deliver 4–6 ablations in each renal artery, in a helical pattern, rotating as the catheter is pulled back from the distal portion to the proximal portion of the main renal artery.

Endpoints
The primary effectiveness endpoint was the change in office SBP from baseline to 6 months compared between the RDN and control groups. Secondary effectiveness endpoints included change in office-based diastolic blood pressure (DBP) at 6 months and change in SBP and DBP 6 months after randomization on 24-h ABPM and home BP measurement. The secondary safety endpoint was major adverse events (MAE), defined as the composite of 1-month all-cause mortality, end-stage renal disease, significant embolic event resulting in end-organ damage, renal artery dissection or perforation requiring intervention, vascular complications, hospitalization for hypertensive crisis or new renal artery stenosis >70% confirmed on angiography within 6 months after randomization.

Laboratory testing included blood tests for renal function (serum creatinine, blood urea nitrogen, cystatin C), serum electrolytes, spot urine albumin and creatinine, hemoglobin A1c, glucose, insulin, and C-peptide. Finally, anti-hypertensive medication use by class at baseline and 6 months with medication changes was analyzed.

Statistical Analysis
The trial was designed to compare the difference in office-based SBP change from baseline to 6 months between the RDN and control groups. Assuming a true difference between the mean SBP change values for the 2 groups the mean SBP values of 15 mmHg with a 25-mmHg standard deviation per group and a 1:1 randomization, a sample size of 50 subjects (45 evaluable) per treatment arm was required to yield 80% power to demonstrate a treatment difference with a 2-sided 0.05 level of significance. Utilizing the original assumptions for treatment difference and standard deviations, and using the final sample sizes of 41 (22 denervation and 19 control subjects), the power of the study to demonstrate a treatment difference at a 2-sided 0.05 level of significance dropped to 46%.

The analyses were performed according to the intent-to-treat principle. Continuous variables are presented as mean±SD and categorical variables are presented as number and percentage per treatment group. Between-group differences for continuous variables were compared using 2-sample t-test, and that for categorical variables using Fisher’s exact test. Two-sided 95% CI for the differences between treatment groups were also calculated. Differences in BP between baseline and follow-up were assessed using paired t-test. The variance in standard deviation for SBP change from baseline was compared using F-test. All data were analyzed using SAS version 9.1 or higher (SAS Institute, Cary, NC, USA).

Results
There were 84 subjects assessed for eligibility and 41 subjects were enrolled and randomized: 22 to RDN and 19 to the control group (Figure 2). Six-month follow-up was available for all subjects. Baseline characteristics for each treatment group were similar (Table 1), although there was a numerically, but not significantly, higher rate of diabetes among the control subjects (63.2% vs. 36.4%, P=0.12). Mean age was 56 years for control subjects and 60 years old for RDN subjects and the majority of subjects were men.

The mean number of ablation attempts for RDN subjects was 11.5±1.9 and the mean number of complete 120-s abla-
tions was 9.2±1.8. Most subjects (82%) received circumferential ablations in at least 1 renal artery. There was no difference in BP response based on the presence or absence of a circumferential ablation pattern or based on the number of ablations delivered.

Anti-hypertensive medication prescription was similar for all subjects: 4.9±1.5 for RDN subjects and 4.9±1.8 for control subjects at baseline. All subjects received a diuretic and no subjects received a vasodilator or direct renin inhibitor (Table 2). The proportion of subjects taking an aldosterone antagonist was relatively high in this Japanese population. Only 3 of 41 subjects (7.3%) had a change in anti-hypertensive medication based on randomization and the 6-month assessment: 2 were in the RDN group and 1 was a control subject (Figure 3).

BP Change
The SBP change in RDN subjects was not significantly different from the SBP change in control subjects (–8.6±11.9 mmHg; 95% CI: –21.1 to 3.8, P=0.169; Figure 4A). The RDN subjects had a significant reduction in office SBP from baseline to 6 months after randomization of –16.6±18.5 mmHg (P<0.001), while control subjects had a non-significant office SBP reduction of –7.9±±18.4 mmHg (P=0.091). A similar pattern of 6-month BP change was observed for home measurements with a –8.0±14.4-mmHg SBP reduction in the RDN group (P=0.016) and a –2.4±13.5-mmHg change in the control group (P=0.457). The difference in the 6-month home SBP reduction was −5.6 (95% CI: −14.5 to 3.2, P=0.205).

Data given as mean±SD or % (n). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

SBP at 6 months decreased significantly from baseline for the RDN subjects (–7.5±12.0 mmHg, P=0.008) but not for control subjects (–1.4±10.2 mmHg, P=0.563). The difference in the 24-h ambulatory SBP 6-month change was –6.2 (95% CI: –13.2 to 0.9, P=0.087; Figure 4B). Assuming the same means and standard deviations for the RDN and control groups, 27 subjects per group would have been required for statistical significance (P<0.05) of this difference. The reduction in 24-h DBP was –4.2±7.4 mmHg (P=0.014) in RDN subjects and –0.4±6.7 mmHg (P=0.817) in control subjects for a difference of –3.8 mmHg (95% CI: –8.3 to 0.6, P=0.091). A similar pattern of 6-month BP change was observed for home measurements with a –8.0±14.4-mmHg SBP reduction in the RDN group (P=0.016) and a –2.4±13.5-mmHg change in the control group (P=0.457). The difference in the 6-month home SBP reduction was –5.6 (95% CI: –14.5 to 3.2, P=0.205). Home DBP dropped at 6 months in the control group (–3.4±8.1 mmHg, P=0.066) but went up slightly in the control group.

Data given as mean±SD or % (n). ABPM, ambulatory blood pressure monitoring; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
Figure 3. Proportion of subjects with antihypertensive medication changes between baseline and 6 months. Medications change occurred more frequently in SYMPLECTITY HTN-3 than in SYMPLECTITY HTN-Japan (HTN-J). RDN, renal artery denervation.

Figure 4. (A) Primary effectiveness endpoint and (B) 24-h ambulatory systolic blood pressure (SBP) change at 6 months. The primary effectiveness endpoint of difference in office SBP change at 6 months was not reached. The 24-h ambulatory SBP change approached significance but because of early study suspension the trial was not sufficiently powered to detect a difference in the primary or secondary endpoints. ABPM, ambulatory blood pressure monitoring; RDN, renal artery denervation.
(1.4±7.8 mmHg, P=0.447) for a between-group difference of -4.8 (95% CI: -9.8 to 0.3, P=0.065).

Safety

The MAE rate, which includes any renal artery stenosis >70% as well as periprocedural complications, was 0.0% for both RDN and control subjects. One subject who received RDN had a 50% increase in serum creatinine at 6 months, but at 12 months the serum creatinine had declined and was no longer 50% above baseline. There was no significant difference in any measured laboratory parameter between the treatment groups at baseline or at 6 months.

Discussion

SYMPLICITY HTN-Japan is the first randomized controlled trial of RDN in an Asian population. Analysis of the BP change in 41 randomized subjects demonstrated significant reductions in SBP 6 months after randomization according to office measurement, on 24-h ABPM and at home for subjects randomized to RDN. There were no significant reductions in SBP by any measure in the control subjects. The difference in office SBP change between the groups, however, was not significantly different and thus the primary effectiveness endpoint was not met. After the results of the SYMPLICITY HTN-3 trial were made public, enrollment in the SYMPLICITY HTN-Japan trial was discontinued. Because the subject enrollment was much less than the 50 per arm estimated to be needed to provide 80% power to show a difference between the groups, the trial is underpowered to detect significant differences in outcome. If subject accrual had continued and the BP change data followed the same trends as reported here, then the trial would have met the primary and secondary effectiveness endpoints.

The reduction in office SBP in the subjects randomized to RDN reported in this study is similar to the reductions seen in subjects randomized to RDN in the SYMPLICITY HTN-3 trial (Figure 5A). The SBP reduction in Japanese control subjects, however, who were not blinded and did not receive a sham procedure, was far less than the SBP reduction in the sham control subjects in SYMPLICITY HTN-3. Interestingly, the SYMPLICITY HTN-2 randomized trial that also compared RDN with an unblinded control group receiving only usual medical care, observed no reduction in office BP at 6 months after randomization in the control subjects. It has been postulated that the inclusion of a blinded sham procedure in SYMPLICITY HTN-3 led to a greater than expected placebo effect, as well as improved adherence to prescribed medications and lifestyle changes. In the SYMPLICITY HTN-2 trial and the current HTN-Japan trial, a placebo effect due to the blinded sham procedure was not possible. The role of changing adherence to drug therapy in subjects from these trials is unclear, but it is of interest that there were very few anti-hypertensive medication changes reported in the Japanese subjects, suggesting more uniform drug adherence and that subjects were on a much more stable medication regimen compared with subjects from SYMPLICITY HTN-3.

Because ABPM is captured over a 24-h period, the measurements are more likely to reflect true BP, and the possibility of a pronounced placebo effect is greatly reduced. The ABPM results of SYMPLICITY HTN-Japan differ from HTN-3 primarily in the control subjects, who had only a very small drop in 24-h SBP compared with the SYMPLICITY HTN-3 sham control subjects (Figure 5B). The 24-h ambulatory SBP decrease in subjects receiving RDN in the current trial was similar to that reported for subjects randomized to denervation in SYMPLICITY HTN-3. ABPM results from a larger cohort of patients (n=236) treated using the SYMPLICITY RDN catheter and with similar inclusion and exclusion criteria as used here, showed a 24-h SBP drop of 8.7 mmHg at 6 months, which is in line with the present results.

In the current trial, we observed less variance in BP measurements than reported in SYMPLICITY HTN-3, as evidenced by an office SBP standard deviation of 16.6 compared with 23.9 mmHg for 6-month change in office SBP in SYMPLICITY HTN-3 (P=0.049). The standard deviations for 24-h SBP were similar for the RDN groups (12.0 and 15.1 mmHg, P=0.206) but among the control subjects the HTN-Japan variance was significantly less (10.2 vs. 17.3, P=0.012). This observation, together with the small number of medication changes reported in the Japanese subjects, points to more uniform drug adherence and thus a more homogeneous management of medication in study subjects in Japan; this might explain the smaller changes in SBP in the control group in the current study and may account for the more encouraging numerical differences reported in this admittedly underpowered trial of
Japanese patients with uncontrolled hypertension.

A much higher proportion of treated subjects in the current trial were receiving an aldosterone antagonist (45.5%) compared with the RDN group from SYMPLECTIC HTN-3 (22.5%). A subsequent analysis of predictors of response to RDN in SYMPLECTIC HTN-3 showed that aldosterone antagonist use was positively associated with a greater reduction in SBP at 6 months.21 The authors speculated that there may be an additive effect of RDN to the known neurohormonal suppression of sympathetic nervous system activity by aldosterone antagonists.22 A review of the 6-month SBP change in the Japanese subjects receiving aldosterone antagonist showed a smaller SBP reduction than observed in the subjects not prescribed aldosterone antagonist, suggesting that this medication was not associated with a greater response to denervation in this trial. A much larger number of treated subjects in a randomized controlled trial would be needed to adequately address this question.

The effectiveness of RDN in lowering BP has been predicted on the reduction of sympathetic nervous system overdrive that occurs following ablation of the afferent and efferent nerves lying outside the renal artery.23 It is therefore expected that RDN would be most effective in treating hypertension associated with high level of sympathetic activation. These promising results, however, were obtained in a Japanese hypertensive population characterized primarily by high salt intake, high salt sensitivity and a greater risk for stroke than their Caucasian counterparts.7,24–27 Furthermore, the association of increasing SBP and stroke is steeper for Asian than Caucasian patients, which highlights the importance of even a small reduction in SBP.28 According to estimates from epidemiological studies in Japan, a 2-mmHg reduction in mean SBP is associated with a 6.4% decrease in stroke and a 5.4% decrease in ischemic heart disease.2 Furthermore, in an estimation of the results from an earlier ABPM prospective study, 24-h SBP reduction of 10 mmHg accounts for a 38% reduction in stroke in Japanese hypertensive patients.29 Thus, the difference in 24-h SBP change (0.1 mmHg, P=0.87) between RDN and control groups may have clinical relevance in Asian populations.

There are several limitations to this trial, foremost being the small number of subjects and lack of adequate power to show a difference between the treatment groups. The operators did not have prior RDN experience and there was no objective measure to show that the renal arteries were sufficiently denervated. It is possible that some of the observed reduction in BP in both arms of the trials reflects the effect of close observation and patient follow-up, termed the Hawthorne effect, which has been postulated by other investigators.30 The trial did not include a blinded sham control, which may have affected the control group response and there was no objective measure to confirm that adequate RDN was achieved. There was also no measure of medication adherence, although the small number of changes in anti-hypertensive medication during the trial indicate that changes in medication use during the trial, suggested as a confounding factor in the SYMPLECTIC HTN-3 trial, may have been less important in this trial.

Conclusions

The SYMPLECTIC HTN-Japan randomized controlled trial did not demonstrate a significant difference in 6-month SBP change between RDN and control subjects. The study, however, was underpowered to show a significant different in effectiveness because of the small number of enrolled subjects. This is the first randomized controlled trial of RDN in an Asian population. Given the importance of BP reduction to reduce cardiovascular and stroke risk in Asian patients with uncontrolled hypertension and the disparate results of recent RDN clinical trials, further well-designed clinical studies using ABPM are needed.

Acknowledgments

The authors gratefully acknowledge all of the HTN-Japan Co-investigators; Daiki Yasuhara, for excellent study management; Martin Fahey, MS, and Mingwei Liu, PhD, from Medtronic for statistical support; Colleen Gilbert, PharmD, for assistance with the manuscript; and Sandeep Brar, MD and Myra Fan for study support and expert review. This work was supported by Medtronic Japan (ClinicalTrials.gov NCT01646404). The institutions and primary investigators for the SYMPLECTIC HTN-Japan study are listed in Appendix.

Disclosures

Dr Kario has received consultant honoraria from Medtronic and grant support for participation in the trial. All other authors received grant support for participation in the trial.

References


KARIO K et al


Appendix

Institutions and Primary Investigators for the SYMPLICITY HTN-Japan Study
Shonan Kamakura General Hospital, Shigeru Saito, Kanagawa; Jichi Medical University Hospital, Kazuomi Kario, Tochigi; Osaka University Hospital, Yuji Okuyama, Osaka; Kyoto University Hospital, Takeshi Kimura, Kyoto; Hirosaki University School of Medicine and Hospital, Ken Okamura, Aomori; University of Tsukuba Hospital, Kazutaka Aonuma, Ibaraki; Chiba University Hospital, Yoshio Kobayashi, Chiba; Kurume University Hospital, Takafumi Ueno, Fukuoka; Kumamoto University Hospital, Hisao Ogawa, Kumamoto; Sapporo Medical University Hospital, Tetsumi Miura, Hokkaido; Tokyo Women’s Medical University Hospital, Atsuhiro Ichihara, Tokyo; Ehime University Hospital, Takafumi Okura, Ehime; Kyushu University Hospital, Yohitaka Hirooka, Fukuoka; Mitsui Memorial Hospital, Kengo Tanabe, Tokyo; Asahikawa Medical University Hospital, Naoyuki Hasebe, Hokkaido.