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Safety and performance of the next generation EnligHTN™ renal denervation system in patients with drug-resistant, uncontrolled hypertension: The EnligHTN III first-in-human multicentre study

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ABSTRACT

Background/objectives: Catheter-based renal denervation for the treatment of drug-resistant hypertension has been intensively investigated in recent years. To date, only limited data have been published using multi-electrode radiofrequency ablation systems that can deliver lesions with a pre-determined pattern. This study was designed to evaluate the safety and efficacy of the next generation EnligHTN™ renal denervation system. Six-month primary endpoint data are presented here.

Methods: We conducted this first-in-human, prospective, multi-center, non-randomized study in 39 patients (62% male, mean age 63 years, and mean baseline office blood pressure 174/93 mm Hg) with drug-resistant hypertension. The primary safety and efficacy objectives were to characterize, from baseline to 6 months post-procedure, the rate of serious procedural and device related adverse events, as adjudicated by an independent Clinical Events Committee, and the reduction of office systolic blood pressure.

Results: Renal artery denervation, using the next generation EnligHTN multi-electrode system significantly reduced office blood pressure from baseline to 1, 3, and 6 months by −19/7, −26/9 and −25/7 mm Hg, respectively ($P \leq 0.0005$). No serious device or procedure related adverse events affecting the renal arteries or renal function occurred through.

Conclusions: Renal sympathetic denervation using the next generation EnligHTN renal denervation system resulted in safe, rapid, and significant mean office blood pressure reduction that was sustained through 6 months. Future studies will need to address the utility of this system against an appropriate placebo based comparator.

1. Background/objectives

Hypertension is the leading attributable risk factor for cardiovascular morbidity and mortality around the world [1–3]. Resistant hypertension, as defined by the inability to achieve target blood pressure despite three or more antihypertensive agents remains a treatment dilemma, with an incidence of between 10 and 12% [4,5]. Furthermore, this group of patients has a three fold increased risk of cardiovascular events over the group of patients with hypertension that is treated to target blood pressures [3].

A number of novel device based therapies are emerging with the potential to improve blood pressure in patients with treatment resistant hypertension [6–8]. The most studied of these remains catheter based radiofrequency renal artery denervation. Initial observational trials showed this therapy to be associated with approximately a 25 mm Hg BP reduction at 6 months in resistant hypertension patients and led to a consensus opinion for clinical appropriateness in treatment resistant hypertension [8–11]. Controversy now exists over the incremental value of this technology with the recent SYMPLICITY HTN-3 trial failing to meet its primary efficacy endpoint versus sham control [12]. However, this technology utilized a first generation single-tip electrode radiofrequency ablation catheter that requires significant operator manipulation with point by point ablation. Therefore, there is a higher risk of producing an inadequate ideal geometric distribution of lesions in the renal artery. Furthermore, fewer lesions were created in trials of the

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SYMPLICITY system than other systems and this may have a relationship with BP reduction. In fact, a SYMPLICITY HTN-3 subgroup analysis showed that more robust response was related to more lesions and four-quadrant positioning [16].

The EnligHTN renal denervation system has a multi-electrode platform with a predefined geometric orientation facilitating a more favorable lesion creation pattern for the purpose of interrupting renal artery nerve traffic [7]. The system can be positioned once and deliver four lesions prior to movement. The EnligHTN I Study, a multicenter, first-in-human observation safety and efficacy study utilizing the first generation EnligHTN renal denervation system (St. Jude Medical, MN, USA), reported a 26 mm Hg reduction in office systolic BP at the 6 month primary endpoint [9]. However, the first generation of this system required each electrode to deliver therapy sequentially, and therefore the procedure was time consuming. The next generation EnligHTN system allows for simultaneous delivery of all four electrodes and includes modifications in the temperature, including rate of rise over time and duration, based on extensive preclinical testing, to optimize renal artery lesion creation. The EnligHTN III trial was designed to allow comparisons to be made with the first generation, and therefore test both the safety and efficacy of this next generation system. We present the primary endpoint, the 6-month safety and efficacy data from the multicenter, first-in-human EnligHTN III trial.

2. Methods

2.1. Study population

Patients from 18 to 80 years of age who had been referred for management of resistant HTN by a primary healthcare practitioner or specialist at six participating centers (4 in Australia and 2 in New Zealand) were screened for participation. The protocol was based on the previously published EnligHTN I trial [9]. In brief, patients needed to have an office Systolic BP that remained ≥160 mm Hg despite the stable use of ≥3 anti-hypertensive medications concurrently at maximally tolerated doses. At least one of the anti-hypertensive medications was required to be a diuretic, unless there was documented intolerance. Patients also had to have a mean daytime systolic Ambulatory BP >135 mm Hg. In all participating patients the anti-hypertensive drug regimen was to remain stable for a minimum of 14 days prior to the procedure and through the 6-month follow-up.

2.2. Study design

The EnligHTN III study is a first-in-human, prospective, multi-center, non-randomized study to evaluate safety and efficacy of a new generator and algorithm with the same multi-electrode catheter used in the EnligHTN I trial, allowing simultaneous delivery of therapy from all four electrodes, for the purpose of renal artery sympathetic denervation in patients with drug-resistant hypertension. The primary safety objective was to characterize the rate of serious procedural and device related adverse events from date of procedure through 6 months post-procedure, as adjudicated by a Clinical Events Committee (CEC). The primary efficacy objective was the reduction of office systolic BP at 6 months post-procedure as compared to baseline. Study patients will continue follow-up at 1, 3, 6, 12, 18, and 24 months post-denervation procedure. The study was approved by each institution's Research Ethics Committee and is registered with Clinical Trials Registry (Registration No. NCT01836146). The trial is sponsored by St. Jude Medical, St. Paul, Minnesota, USA.

2.3. Baseline study procedures

Following written informed consent, medical history and physical examination including office BP were completed. The office BP was collected according to the Standard Joint National Committee VII Guidelines and ESC/ESH Guidelines [14,15]. Each center and each enrolled patient was provided with an Automatic BP Monitor (Omron Healthcare, Inc. Bannockburn, Illinois, USA) for collection of office and home BP values. All patients recorded home BP values for seven days (three readings in the morning and three readings in the evening), anti-hypertensive medication regimen daily for a minimum of 14 days and completed a 24-h Ambulatory BP assessment. The 24-h Ambulatory BP was obtained by using an Ambulatory Blood Pressure System (Spacelabs Healthcare, Inc. Issaquah, Washington, USA).

After the 14 day screening period, all patients returned to their respective study center to complete the baseline assessment. Blood and urine were collected for Complete Blood Count, Basic Metabolic Profile, Serum Creatinine, Estimated Glomerular Filtration Rate (eGFR), Cystatin C, and Urine Albumin to Creatinine ratio. An Office BP assessment using the BP monitor, office heart rate, quality of life questionnaire, a renal artery CT scan, and a review of medication logs were also performed. Qualifying patients were scheduled for the renal denervation procedure within the following 30 days.

2.4. The next generation EnligHTN renal denervation system

The St. Jude Medical EnligHTN™ renal denervation system used in this study consists of the next generation EnligHTN radiofrequency generator, the EnligHTN renal artery ablation catheter, and the EnligHTN renal artery guide catheter (Fig. 1). The generator utilizes a novel algorithm for the delivery of 60 s of radiofrequency energy, optimized for simultaneous delivery of therapy through all 4 electrodes. There is a two-stage rate of temperature rise with an initial rate of 4 °C/s, reducing to 1 °C/s between 65 and 70 °C. Preclinical studies show that the next generation generator with the updated algorithm delivers reproducible lesions consistent with preclinical data from the first generation system. The next generation generator also uses a proprietary algorithm described as Adaptive Control. Adaptive Control modulates the power and temperature to minimize interrupted ablation errors that may have caused electrode shut-offs with the first generation system. If the generator senses rapid impedance or temperature change indicating instability, it will respond by modulating the power. This is sometimes caused by patient discomfort/movement or heavy breathing and can be managed with the Adaptive Control modulation. The maximum temperature is now 70 °C and is administered for 60 s. Once again, these are based on extensive preclinical testing showing that the created lesions are consistent with the first generation system.

Importantly, this system utilizes a diagnostic mode, in order to ensure good electrode contact and thus provides a predictor of adequate lesion creation. In brief, approximately 0.5 W of radiofrequency energy is delivered to all electrodes simultaneously which should induce a 2 °C or greater temperature rise in each electrode. If this is not achieved, then

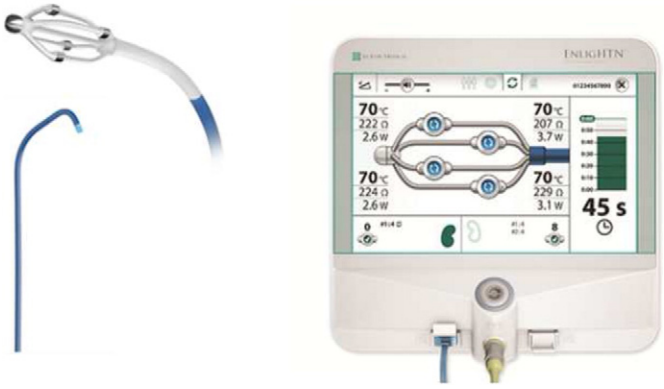

Fig. 1. The EnligHTN generation 2 renal denervation system, consisting of the EnligHTN renal artery guide catheter, EnligHTN renal artery ablation catheter, and next generation EnligHTN RF ablation generator.

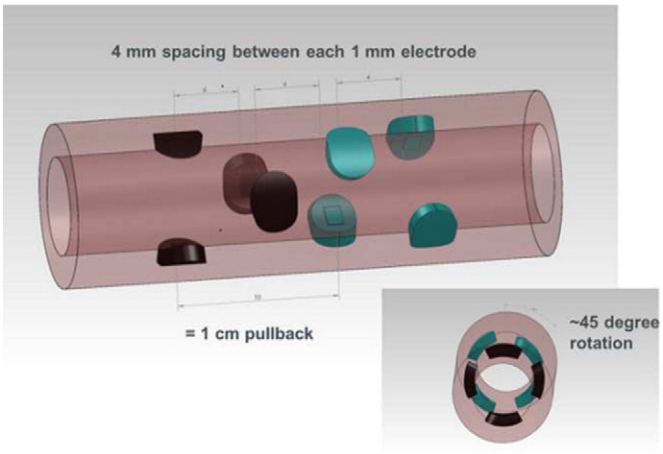

Fig. 2. Diagram demonstrating predictable, circumferential renal artery lesion pattern creation from the EnligHTN renal denervation system.

it is recommended to adjust the catheter position in order to better oppose the electrode to the vessel wall and re-test. The generator allows for up to 5 min of continuous delivery of 0.5 W of radiofrequency energy, which has failed to induce any vascular injury in preclinical models, attesting to the safety of this diagnostic mode.

The generator with this system comes with an interactive, intuitive user interface which simultaneously displays temperature, impedance and power for all four electrodes. Thus the results of temperature rise, impedance change and power modulation can be monitored continuously throughout both the diagnostic phase, as well as during therapy delivery. Furthermore, should adequate temperature rise to create an appropriate lesion not occur, as defined by the inability to achieve a temperature of at least 50 °C by 20 s, then the electrode can be deactivated by a simple touch screen command. Then, that electrode's position can be slightly manipulated and re-application of therapy at that single location can be performed. This is done by simple touch screen activation and deactivation of electrodes prior to therapy delivery (Fig. 2).

2.5. Renal denervation procedure

Patients were taken to the Catheterization Laboratory to undergo the renal denervation procedure, as previously published, using conscious sedation. Images of the left and right main renal arteries were recorded using non-ionic contrast and the diameter and length of each of the main renal arteries measured. The renal denervation basket size was determined from the renal artery diameter (small basket 4.0–5.5 mm diameter/large basket 5.5–8.0 mm diameter) and the renal denervation catheter was inserted such that the catheter's tip was proximal to the bifurcation of one of the main renal arteries. The basket on the catheter was then opened with the impedance of each electrode on the basket monitored in diagnostic mode.

Renal artery denervation was commenced and performed simultaneously by all four electrodes with the impedance, temperature and RF energy delivery monitored, as explained earlier. The basket was then collapsed and pulled back proximally approximately 1 cm to avoid lesion overlap. The basket was rotated approximately 45° and then expanded. Placement was confirmed under fluoroscopy and the ablation procedure was repeated. In general, 8 ablations were delivered per renal artery to achieve circumferential ablation. Images of the renal artery were taken using non-ionic contrast and checked for signs of renal artery irregularities (i.e., vasospasm, stenosis or dissection). The renal artery ablation procedure was then repeated for the other renal artery and the catheter was withdrawn. Finally, the sheath was removed and hemostasis achieved according to each center's standard of care. Procedural data were recorded for each patient, including procedure duration and number of ablations delivered.

2.6. Post-procedure and pre-discharge

Upon completion of the renal denervation procedure, the patient was moved to a recovery area and vital signs were monitored continuously. BP was measured every 15 min during the first 2 h post-procedure and then in 4-h intervals when the subject was awake until discharge. Patients were discharged from the hospital on the following day if medically stable.

2.7. Follow-up

Patients underwent the following during the post-discharge visits: office BP assessment, review of medications, blood and urine collection, 24-h Ambulatory BP assessment, home BP monitoring and physical assessment. Patients were scheduled for follow-up visits at 1, 3, and 6 months (Primary Objective) post-procedure and will continue being followed per study protocol at 12, 18, and 24 months post-procedure. Renal artery imaging by CT or duplex ultrasound was completed at the 6-month follow-up visit. Renal artery evaluation during other follow-up visits was performed if clinically indicated.

2.8. Study objectives

The primary efficacy objective was reduction of office BP from baseline to 6 months, which was measured according to guidelines at all follow-up visits. Additional efficacy data collection included changes in anti-hypertensive medication, home BP monitoring and 24-h Ambulatory BP. The primary safety objective was to characterize the rate of serious procedural and device related adverse events through 6 months post-procedure, as adjudicated by a Clinical Events Committee (CEC).

Additional objectives that will be assessed and reported include but are not limited to characterization of: the change in Ambulatory Blood Pressure parameters over time as compared to baseline, renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation over time as compared to baseline, and renal function change based on eGFR over time as compared to baseline.

2.9. Study oversight

An independent Clinical Events Committee (CEC) adjudicated all adverse events for relatedness and severity. The corresponding author and Steering Committee members had full access to the study data.

2.10. Statistical analyses

All continuous variables were summarized using mean, median, standard deviation (SD) and range. Normality of data was verified with the use of box plots and Kolmogorov–Smirnov normality test. For normally distributed data, comparisons of primary and secondary outcomes between time points were analyzed using paired t tests. In cases where the data was not normally distributed the non-parametric Wilcoxon Signed-Rank test was used to analyze the data. All categorical variables were summarized using frequencies and percentages. Statistical analyses were performed using SAS 9.3 (by SAS Institute Inc., Cary, NC, USA). Statistical significance was achieved if a two-sided test obtained a p value < 0.05.

3. Results

The study enrollment was conducted from April 2013 until August 2013. A total of 65 patients were consented for enrollment and underwent screening, of which 26 patients were excluded, mainly due to failure to continue to meet the BP enrollment criteria, the presence

of renal artery anomalies, or the presence of significant renal artery atherosclerosis as defined in the protocol. Thereafter, 39 patients completed baseline evaluation and were scheduled for the renal denervation procedure.

Baseline demographic, clinical condition, and medication data for the 39 patients are presented in Table 1. All 39 patients successfully underwent renal denervation. The median procedure time from initiation to completion of RF energy delivery was 13 min and the mean ± SD number of ablations delivered was 7.85 ± 0.49 for the right and 8.00 ± 0.69 for the left renal arteries. Thus, the total number of ablations was 15.85 ± 1.01 and this was delivered with a mean of 4.33 ± 0.62 sets of treatments.

3.1. Safety results

All adverse events were collected in the study. A CEC adjudicated the events for seriousness and relatedness to the procedure and device. A complete listing of serious and non-serious procedure and/or device related adverse events as adjudicated by the CEC is presented in Tables 2 and 3. There were no deaths or unanticipated adverse device effects reported in the trial.

Through six months of follow-up, there were no serious device related adverse events during the procedure, including no renal artery damage (i.e. no renal artery dissections, aneurysms, flow limiting renal artery vasospasms, or renal artery stenosis). There was one reported serious vascular access site complication (pseudoaneurysm of the femoral artery) which resolved after manual compression and thrombin injection. This event extended hospitalization by 24 h but has resolved without further sequelae. A number of minor peri-procedural events were noted without further clinical sequelae (Table 3).

Furthermore, there were no serious device related adverse events as independently adjudicated throughout the 6 month follow-up.

Renal artery evaluation was conducted on all patients at 6 months by CT imaging, or by ultrasound if contraindicated for a CT. No patients developed a new hemodynamically significant renal artery stenosis.

Renal function was evaluated by repeated measurements of eGFR, Serum Creatinine, and Cystatin C from baseline through 6 months of follow-up. No patient experienced a reduction in eGFR >50%, a two-fold increase in Serum Creatinine, or progressed to end stage renal disease. There were no statistically or clinically significant changes in eGFR or Creatinine at 6 months post-procedure versus baseline, attesting to the renal safety of the procedure. The eGFR (mL/min/1.73 m^2) values were baseline 74.0 ± 16.8 (n = 38), 1-month 75.9 ± 15.7 (n = 39), 3-months 73.7 ± 16.4 (n = 38) and 6-months 73.8 ± 17.4 (n = 37) (6-months p = 0.7075). The Serum Creatinine (μmol/L) values were baseline 88.9 ± 19.4 (n = 39), 1-month 86.7 ± 21.2 (n = 39), 3-months 88.2 ± 24.4 (n = 38) and 6-months 88.3 ± 26.2 (n = 37) (6-months p = 0.7062). Furthermore, there were no clinically significant changes in Cystatin C levels (mg/L, a renal injury marker): baseline 1.03 ± 0.30 (n = 37), 1-month 1.01 ± 0.28 (n = 39), 3-months 1.04 ± 0.28 (n = 35) and 6-months 1.09 ± 0.30 (n = 37) (6-months p = 0.0393).

The Urine Albumin-to-Creatinine ratio decreased at 6 months versus baseline although this did not reach statistical significance. The mean Urine Albumin-to-Creatinine ratio values were baseline 306.5 ± 841.9 with median 32.4 mg/g (n = 36), 1-month 230.2 ± 659.0 with median 27.0 mg/g (n = 36), 3-months 106.0 ± 234.2 with median 21.2 mg/g (n = 33) and 6-months 274.6 ± 613.2 with median 25.6 mg/g (n = 31) (6-months p = 0.4809).

3.2. Efficacy results

Compared to baseline, Office and Ambulatory Systolic BP of the cohort significantly decreased at all time points (p values ≤ 0.0030). The average Office BP (mm Hg) at baseline was 174/93 (mm Hg). The resulting average Office BP reductions from baseline were: 1-month −19/−7 mm Hg,

Table 1
Baseline characteristics (n = 39).

Variable	Mean ± SD (min, median, max) or n (%)
Age (year)	63.49 ± 8.75 (42.0, 65.0, 78.0)
BMI (kg/m^2)	31.92 ± 5.17 (20.7, 31.7, 48.1)
Gender (female)	15 (38.5%)
Coronary artery disease	6 (15.4%)
Hyperlipidemia	23 (59.0%)
Diabetes type II	13 (33.3%)
Obstructive sleep apnea	5 (12.8%)
eGFR (mL/min/1.73 m^2)	73.97 ± 16.78 (46.0, 76.0, 110.0)
Serum Creatinine (μmol/L)	88.90 ± 19.39 (51.0, 87.0, 142.0)
Cystatin C (mg/L)	1.03 ± 0.30 (0.6, 1.0, 1.9)
Urine Albumin-to-Creatinine ratio (mg/g)	306.53 ± 841.90 (2.7, 32.4, 3996)
Average office systolic blood pressure (mm Hg)	174.23 ± 12.71 (161.0, 170.0, 208.0)
Average office diastolic blood pressure (mm Hg)	92.90 ± 14.99 (56.0, 94.0, 125.0)
Average office heart rate (BPM)	67.67 ± 15.58 (43.0, 67.0, 107.0)
Average daytime systolic ABP (mm Hg)	158.72 ± 14.02 (138.0, 155.0, 200.0)
Average daytime diastolic ABP (mm Hg)	84.77 ± 12.46 (58.0, 86.0, 108.0)
Average daytime heart rate (BPM)	65.54 ± 14.19 (45.0, 63.0, 110.0)
Average night-time systolic ABP (mm Hg)	146.41 ± 16.16 (112.0, 148.0, 188.0)
Average night-time diastolic ABP (mm Hg)	75.92 ± 12.46 (54.0, 76.0, 102.0)
Average night-time heart rate (BPM)	61.79 ± 12.41 (39.0, 60.0, 92.0)
Average 24 h systolic ABP (mm Hg)	154.85 ± 15.63 (121.0, 152.0, 200.0)
Average 24 h diastolic ABP (mm Hg)	82.08 ± 12.25 (58.0, 83.0, 105.0)
Average 24 h heart rate (BPM)	64.74 ± 13.72 (44.0, 63.0, 110.0)
Number of anti-hypertensive medications	4.67 ± 1.11 (3.0, 5.0, 7.0)
Patients taking the following medications:	
Aldosterone antagonists	11 (28.2%)
Alpha adrenergic blockers	16 (41.0%)
Angiotensin converting enzyme inhibitors	20 (51.3%)
Angiotensin receptor blockers	26 (66.7%)
Beta blockers	26 (66.7%)
Calcium channel blockers	30 (76.9%)
Centrally acting sympatholytics	14 (35.9%)
Diuretics	33 (84.6%)
Nitrates	2 (5.1%)
Vasodilators	1 (2.6%)

Table 2
Summary of serious adverse events related to the procedure.

Adverse event	Number of events	Number of patients (%)
Access site pseudoaneurysm	1	1 (2.6%)

Table 3
Summary of non-serious adverse events related to procedure or device.

Adverse event	Number of events	Number of patients (%)
Access site bleeding	1	1 (2.6%)
Access site bruise	9	9 (23.1%)
Access site drainage	5	5 (12.8%)
Access site hematoma	11	10 (25.6%)
Access site pain	3	3 (7.7%)
Arterial hypertension/hypertension	1	1 (2.6%)
Back pain	4	4 (10.3%)
Emesis/vomiting	2	2 (5.1%)
Fever	1	1 (2.6%)
Headache	1	1 (2.6%)
Heartburn	1	1 (2.6%)
Hypotension	6	5 (12.8%)
Kidney pain/flank pain	3	3 (7.7%)
Low back pain	2	2 (5.1%)
Nausea	2	2 (5.1%)
Pain	2	2 (5.1%)
Vaso vagal response	1	1 (2.6%)
Vasospasm	4	4 (10.3%)
Total	59	30 (76.9%)

3-months −26/−9 mm Hg and 6-months −25/−7 mm Hg ($p \leq 0.0005$) (Fig. 3). With regards to responder rates using a definition of a reduction in office systolic BP of at least 10 mm Hg or greater, rates were as follows 1-month − 67% (n = 26/39), 3-months − 82% (n = 31/38) and 6-months − 81% (n = 30/37). In addition, by 6 months, over one-third of patients are now controlled (<140 mm Hg systolic) and the majority are <160 mm Hg (Fig. 4).

In addition, in-office resting heart rate was collected at baseline 67.7 ± 15.6 (n = 39) bpm, 1-month 65.0 ± 14.5 (n = 39), 3-months 65.5 ± 15.9 (n = 38), and 6-months 66.0 ± 14.8 (n = 37).

The average 24-h Ambulatory BP at baseline was 155/82 mm Hg. The average 24-h Ambulatory BP (mm Hg) reduction from baseline were, 1-month −7/−4 mm Hg, 3-months −10/−3 mm Hg and 6-months −8/−2 mm Hg ($p \leq 0.0030$ for systolic changes) (Fig. 5).

Fig. 6 shows average office BP, 24-h ABPM, and daytime ABPM measures at baseline and at 1, 3, and 6 months post-procedure. Both systolic and diastolic values measured in the office or by ambulatory monitoring were consistent, exhibiting reductions at 1-month and remaining stable through 6-months post-procedure.

Over the 6 month follow-up period, 15/37 subjects (41%) had changes to their anti-hypertension medications: nine patients had a decrease in their number of anti-hypertensive medications or doses and six had an increase in their number of anti-hypertensive medications or doses. For patients that did not have an increase or decrease in their number of anti-hypertensive medications or doses (n = 22) the 6 month office blood pressure reduction was similar to the entire cohort at −23/−6 mm Hg (p-values ≤ 0.0006) as well as 24-h ABPM reductions of −8/−3 mm Hg (p-values: 0.0025, 0.0738).

4. Conclusions

4.1. Discussion

This data demonstrates that the next generation EnligHTN renal denervation system is safe and effective in the treatment of patients with drug-resistant hypertension. This is evidenced by the absence of serious device or procedure related adverse events affecting the renal arteries or renal function throughout the primary endpoint of 6 months of follow-up and the presence of a statistically and clinically significant −25/−7 mm Hg reduction in office BP at 6 months.

The safety data from this study are excellent and add to the growing body of data regarding the safety of this technique. In the SYMPLICITY HTN-1 trial one patient had a renal artery dissection and this low frequency has been described in other datasets [8]. Furthermore, renal artery stenosis is a described phenomenon occurring in approximately 2% of patients after renal artery denervation in early trials [8,9]. The absence of any of these serious adverse events in this study warrants discussion. Although possible that it is simply chance given the sample size tested, it is worth noting that this study was performed by experienced operators all of whom had prior renal denervation experience with most having specific experience with the EnligHTN catheter and system. In addition, the EnligHTN catheter requires less manipulation which may reduce the risk of renal artery injury. Also, the fact that all patients enrolled were able to undergo renal denervation in both renal arteries is evidence of both the selection process and the procedural performance.

The efficacy seen in this study is commensurate with that seen in other published studies, including the EnligHTN I study, and confirms the consistency of this therapy in experienced hands [9,10]. The lesser reduction in office systolic BP at 1-month than was seen at 3- and 6-months is consistent with many other studies of renal denervation, although different than what was seen in the EnligHTN I study [8–10]. There is no clear explanation for this difference, however we should be careful to speculate too broadly given the small sample size. However, looking at the datasets of first-in-human trials of renal denervation to date, generally there is a lesser blood pressure reduction at 1-month that appears to be numerically greater at the 6-month time point [8,10].

The efficiency and speed of the next generation system can be directly compared with the first generation EnligHTN system, and indirectly with those of other systems. Indeed in this study, the time taken to perform the procedure, the time spent with the renal denervation catheter in situ in the renal arteries, were all less that for the first generation EnligHTN system. In particular, the median time from initiation to completion of RF energy delivery was reduced by more than half with the next generation system versus the first system (13 min versus 34 min). This provides evidence for potentially improved work-flows in the Cath lab and potentially would impact cost-effectiveness analyses for the technique. More than this, though, is the potential that the shorter procedural times played some role in the excellent safety seen in this study. The marked reduction in the time of renal artery instrumentation required to perform the entire renal denervation procedure may have been a factor in the absence of serious device related adverse events seen in this study.

Further issues remain about the best definition of responder and whether this is an office or ABP index and at what time point it should be considered. Datasets have shown increased responder rates at the 24-month time-point and beyond [13]. This may be more reflective of additional therapies or other changes, rather than the index renal denervation event however. Clearly further data and focused study is required to better understand patient and procedural predictors of response to renal denervation.

This is a single arm, observational first-in-human study. Although the efficacy signal seen is consistent with many other such trials, it is not a randomized placebo controlled trial. The SYMPLICITY HTN-3 trial

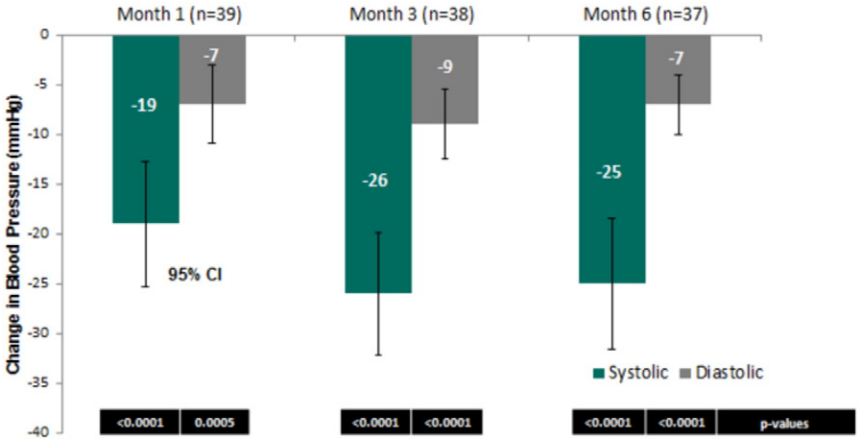

Fig. 3. Office blood pressure reduction from baseline.

Fig. 4. Office systolic blood pressure reduction rates.

was a rigorous, randomized sham-controlled trial of 535 patients that failed to show that renal denervation with the SYMPLICITY catheter was superior to sham control for the purpose of reducing office BP at 6 months [12]. Many factors may be suggested to explain this lack of benefit, including the limited number of lesions created, raising the question of the adequacy of the renal denervation procedure. For example, the mean number of lesions in HTN-3 was 9.2 versus 15.9 in this study. There are also some potential concerns around the geographic location of lesions with a single-electrode system that are solved with a geometrically pre-specified electrode array of the EnligHTN system. However, it remains for future studies to prove that next generation multielectrode renal denervation systems are superior to appropriate placebo based comparator arms. This study is therefore very important in this context as it sets the benchmark from a safety and efficacy perspective for the EnligHTN system with which to undertake such a study.

4.2. Summary

Primary results from the second generation EnligHTN system, which permits simultaneous delivery of all four electrodes, demonstrates the new system is both safe and effective in the treatment of patients with resistant hypertension. Future studies will need to address the utility of this system against an appropriate placebo based comparator.

Novelty and significance

What is new?

- This is the primary endpoint manuscript of the first in human experience with a novel multi-electrode renal artery denervation system.
- This new system allows simultaneous delivery of radiofrequency energy to all four electrodes.
- This next generation system with be studied in future randomized controlled trials

What is relevant?

- This novel renal denervation system in this trial specifically addresses patients with drug resistant hypertension.
- In light of the recent publication by Kandzari in Eur Heart J Jan. 2015 highlighting the relationship between number of ablations in the renal arteries and need for all four quadrants to receive ablations, this new system addresses many of the potential short comings of earlier single electrode renal artery denervation systems.

Summary

- The next generation EnligHTN renal; artery denervation system is safe and efficacious for the treatment of drug resistant hypertension in this first in human experience.
- Future randomized controlled trials with this system are warranted and planned.

Disclosures

SW has received honoraria and consulting fees from Medtronic and St. Jude Medical, and proctorship fees from St. Jude Medical. No other authors have any conflicts of interest to disclose.

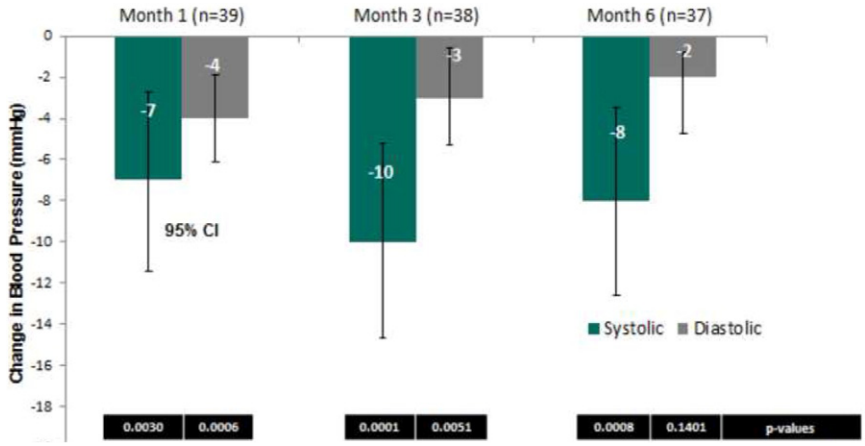

Fig. 5. 24 h ambulatory blood pressure reduction from baseline.

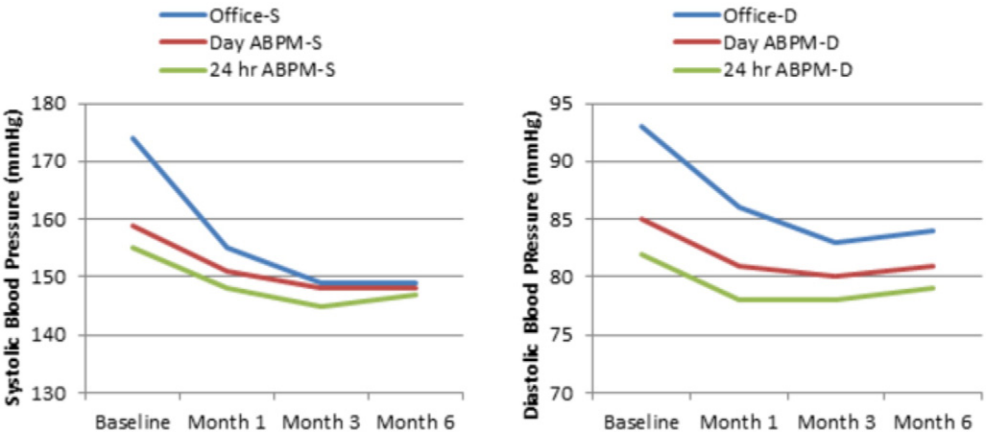

Fig. 6. Change in office, 24-h ambulatory, and daytime ambulatory measurements over time. ABPM indicates Ambulatory BP monitoring; D, diastolic; S, systolic.

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