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Catheter-based renal denervation for resistant hypertension: Twenty-four month results of the EnligHTN™ I first-in-human study using a multi-electrode ablation system☆

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ABSTRACT

Background: Long term safety and efficacy data of multi-electrode ablation system for renal denervation (RDN) in patients with drug resistant hypertension (dRHT) are limited.
Methods and results: We studied 46 patients (age: 60 ± 10 years, 4.7 ± 1.0 antihypertensive drugs) with drug resistant hypertension (dRHT). Reduction in office BP at 24 months from baseline was −29/−13 mm Hg, while the reduction in 24-hour ambulatory BP and in home BP at 24 months were −13/−7 mm Hg and −11/−6 mm Hg respectively ($p < 0.05$ for all). A correlation analysis revealed that baseline office and ambulatory BP were related to the extent of office and ambulatory BP drop. Apart from higher body mass index (33.3 ± 4.7 vs 29.5 ± 6.2 kg/m^2, $p < 0.05$), there were no differences in patients that were RDN responders defined as ≥10 mm Hg decrease (74%, n = 34) compared to non-responders. Stepwise logistic regression analysis revealed no prognosticators of RDN response (p = NS for all). At 24 months there were no new serious device or procedure related adverse events.
Conclusions: The EnligHTN I study shows that the multi-electrode ablation system provides a safe method of RDN in dRHT accompanied by a clinically relevant and sustained BP reduction.

1. Introduction

Catheter-based renal denervation (RDN) for the treatment of drug-resistant hypertension (dRHT) has been shown to be safe in many studies [1–6], but the issue of effective blood pressure (BP) reduction has not yet been settled [6–9]. In contrast to previous mostly observational studies and registries [1–10], the randomized, blinded, sham-controlled Symplicity HTN-3 trial failed to show significant office and ambulatory BP reductions in patients with dRHT [5]. Apart from differences in patient phenotypes, technical issues such as ineffective or incomplete circumferential renal nerve ablation when using a single tip ablation electrode may provide potential explanations why Symplicity HTN-3 failed in its primary efficacy endpoint [8].

The 6 and 12 month data of the EnligHTN I, an unblinded and single-arm study, in patients with dRHT have previously been published [3,4]. In this article we report the complete set of data on 18 and 24 month office, ambulatory and home BP change, long term safety data and RDN responder analyses.

2. Methods

The EnligHTN I study was the first-in-human, prospective, multicenter, non-randomized study designed to address safety and efficacy endpoints of a multi-electrode system for RDN in patients with dRHT [3]. The primary safety objective was all adverse events (AEs) during the study. The primary efficacy objective was the reduction of office BP compared to baseline at 6 months. According to the study protocol, study patients would continue follow-up at 12, 18, and 24 months post RDN procedure.

The study protocol was approved by the Ethics Committee of each participating center and informed written consent was obtained by all patients. The study is registered with

Abbreviations: RDN, Renal denervation; dRHT, Drug resistant hypertension; BP, Blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; eGFR, Estimated glomerular filtration rate.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Subject demographics.

Variable	n = 46
Age (year)	60 ± 10
Body mass index (kg/m^2)	32 ± 5
Gender (male)	31 (67%)
Ethic origin (White)	45 (98%)
Coronary artery disease	9 (20%)
Hyperlipidemia	27 (59%)
Type II diabetes	15 (33%)
Sleep apnea	14 (30%)
eGFR	84.7 ± 18
Serum creatinine (μmol/L)	77.6 ± 17
Cystatin C (mg/L)	1.14 ± 0.29
Urine albumin-to-creatinine ratio (mg/g)	167.6 ± 493
Number of anti-hypertensive medications	4.7 ± 1.0
Office systolic BP (mm Hg)	176 ± 16
Office diastolic BP (mm Hg)	96 ± 14
Average 24 hour ambulatory systolic BP (mm Hg)	150 ± 14
Average 24 hour ambulatory diastolic BP (mm Hg)	83 ± 13
Heart rate (bpm)	71.0 (±11.7)

BP = blood pressure.
eGFR = estimated glomerular filtration rate.

Clinical Trials Registry (NCT01438229) and was sponsored by St. Jude Medical, St. Paul, Minnesota, USA. The sponsor provided funding and contributed in the study design, data analysis and manuscript review. The corresponding author had full access to all data and declares responsibility for the integrity of analyses and final version of the manuscript.

Details about the entire methodology and of BP measurements have been previously described in detail [3,4]. Office, ambulatory and home blood pressure measurements were taken using standardized techniques and validated equipment.

2.1. EnligHTN renal denervation system

The RDN was performed as previously described using the EnligHTN™ multi-electrode renal denervation system by St. Jude Medical [3,4]. The procedure was standardized and every attempt was made to place two sets of 4 lesions in each renal artery in circumferential pattern.

2.2. Statistical analysis

Data are summarized using descriptive statistics, as appropriate. Continuous Parameters as mean, standard deviation, and minimum and/or maximum were presented. For categorical parameters frequencies and percentages are presented. Comparisons of primary and secondary outcomes between time points were analyzed using paired t-tests when data were normally distributed, or Wilcoxon signed-rank test when data were non-normal. Correlations between variables were performed using Pearson correlation coefficient. For analyses comparing the Responder vs. non-responder group, each variable identified was summarized separately using descriptive statistics along with P values using two sample t-test or Fisher's Exact test as appropriate. These variables were then used as possible predictors for the logistic regression modeling using stepwise selection process with significant level of 0.5 for variables staying in the model. Statistical analyses were performed using SAS 9.2 or higher (by SAS Institute, Inc., Cary, NC). Statistical significance was achieved if a 2-sided test obtained a p value of <0.05.

3. Results

Baseline characteristics of the 46 patients who underwent RDN are shown in Table 1. The average number of antihypertensive medications at baseline was 4.7 ± 1.0 and remained fairly stable during the 24-month follow-up period (Table 2).

The extent and representation of each of the major antihypertensive medication classes in the pharmacological treatment regimens remained mostly consistent during the 2-year follow-up period.

3.1. Safety

Serious device and/or procedure related adverse events are summarized in Table 3. Minor peri-procedural or device-related events have been reported previously and were resolved. Serious adverse events that were deemed possibly related to the procedure or device were reported in 3 (6.5%) patients through the 24 months of follow-up. These events included symptomatic hypotension (n = 1), progression of pre-existing renal artery stenosis (n = 2 events in 1 patient) and a progression of hypertensive renal disease with an increase in serum creatinine (n = 1).

Evaluation of renal arteries was performed in all patients by computed tomographic angiography at baseline and 6 months and by duplex ultrasound at 12 and 24 months. Two subjects with pre-existing renal artery stenosis at baseline (<30%) experienced a worsening of renal artery stenosis during the study. In one subject the worsening was adjudicated as non-serious (<50% change from baseline). In the second subject, the pre-existing non-significant renal artery stenosis in the proximal part of the left renal artery progressed to 75% approximately 10 months after the procedure while minor vascular irregularities were identified in the middle part of the artery. The stenosis in the proximal part was treated with stent implantation and the procedure was uneventful. The subject's BP was not improved and 18 months post RDN the new angiogram revealed a new stenotic lesion (70%) extending from the distal end of the previously implanted stent and including the area of the aforementioned irregularity in the middle part of the artery. The new lesion was also covered successfully with a stent.

From baseline to 24 months, serum creatinine, estimated glomerular filtration rate (eGFR) and cystatin C indicated a trend for decrease in renal function (Table 4). One patient had an asymptomatic worsening of renal function at the 24-month follow-up. A duplex ultrasound was performed to evaluate for stenosis with no findings and the subject was referred to a nephrologist for further evaluation. The adverse

Table 2
Anti-hypertensive medication summary.

Medication	Baseline (n = 46)	Month 1 (n = 46)	Month 3 (n = 46)	Month 6 (n = 45)	Month 12 (n = 45)	Month 18 (n = 44)	Month 24 (n = 44)
Angiotensin converting enzyme inhibitors	15 (32.6%)	14 (30.4%)	14 (30.4%)	14 (31.1%)	15 (33.3%)	15 (34.1%)	14 (31.8%)
Angiotensin receptor blockers	41 (89.1%)	41 (89.1%)	41 (89.1%)	40 (88.9%)	40 (88.9%)	39 (88.6%)	37 (84.1%)
Direct acting renin inhibitors	1 (2.2%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	1 (2.2%)	1 (2.3%)	1 (2.3%)
Diuretics	44 (95.7%)	44 (95.7%)	42 (91.3%)	41 (91.1%)	41 (91.1%)	40 (90.9%)	39 (88.6%)
Calcium channel blockers	41 (89.1%)	41 (89.1%)	40 (87.0%)	40 (88.9%)	40 (88.9%)	39 (88.6%)	38 (86.4%)
Beta blockers	34 (73.9%)	34 (73.9%)	33 (71.7%)	32 (71.1%)	31 (68.9%)	30 (68.2%)	30 (68.2%)
Alpha adrenergic blockers	9 (19.6%)	9 (19.6%)	8 (17.4%)	8 (17.8%)	9 (20.0%)	8 (18.2%)	9 (20.5%)
Centrally acting sympatholytics	17 (37.0%)	17 (37.0%)	17 (37.0%)	17 (37.8%)	17 (37.8%)	17 (38.6%)	16 (36.4%)
Aldosterone antagonists	8 (17.4%)	7 (15.2%)	7 (15.2%)	8 (17.8%)	10 (22.2%)	10 (22.7%)	13 (29.5%)
Direct acting vasodilators	1 (2.2%)	1 (2.2%)	1 (2.2%)	2 (4.4%)	3 (6.7%)	3 (6.8%)	3 (6.8%)
Total number of medications	4.7 ± 1.0 (3.0, 8.0)	4.7 ± 0.9 (3.0, 7.0)	4.6 ± 1.1 (1.0, 7.0)	4.7 ± 1.1 (1.0, 7.0)	4.8 ± 1.3 (1.0, 8.0)	4.9 ± 1.4 (1.0, 8.0)	4.8 ± 1.5 (0.0, 8.0)