Worthley, Stephen Grant; Tsioufis, Costas P.; Worthley, Matthew Ian; Sinhal, Ajay; Chew, Derek P.; Meredith, Ian Thomas; Malaiapan, Yuvaraj; Papademetriou, Vasilios
Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: The EnligHTN I trial, European Heart Journal, 2013; 34(28):2132-2140.

European Heart Journal (2013) **34**, 2132–2140
doi:10.1093/eurheartj/eht197

FASTTRACK CLINICAL RESEARCH

Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial

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Received 26 February 2013; revised 15 May 2013; accepted 16 May 2013; online publish-ahead-of-print 19 June 2013

Aims Catheter-based renal artery sympathetic denervation has emerged as a novel therapy for treatment of patients with drug-resistant hypertension. Initial studies were performed using a single electrode radiofrequency catheter, but recent advances in catheter design have allowed the development of multi-electrode systems that can deliver lesions with a pre-determined pattern. This study was designed to evaluate the safety and efficacy of the EnligHTN™ multi-electrode system.

Methods and results We conducted the first-in-human, prospective, multi-centre, non-randomized study in 46 patients (67% male, mean age 60 years, and mean baseline office blood pressure 176/96 mmHg) with drug-resistant hypertension. The primary efficacy objective was change in office blood pressure from baseline to 6 months. Safety measures included all adverse events with a focus on the renal artery and other vascular complications and changes in renal function. Renal artery denervation, using the EnligHTN™ system significantly reduced the office blood pressure from baseline to 1, 3, and 6 months by −28/10, −27/10 and −26/10 mmHg, respectively ($P < 0.0001$). No acute renal artery injury or other serious vascular complications occurred. Small, non-clinically relevant, changes in average estimated glomerular filtration rate were reported from baseline (87 ± 19 mL/min/1.73 m^2) to 6 months post-procedure (82 ± 20 mL/min/1.73 m^2).

Conclusion Renal sympathetic denervation, using the EnligHTN™ multi-electrode catheter results in a rapid and significant office blood pressure reduction that was sustained through 6 months. The EnligHTN™ system delivers a promising therapy for the treatment of drug-resistant hypertension.

Keywords Hypertension • Renal denervation • Blood pressure • Percutaneous

Introduction

Hypertension (HTN) remains the leading treatable cardiovascular risk factor throughout the world.[1–3] Approximately 1 billion people worldwide have HTN, and it is projected that this will increase to 1.5 billion by 2025.[4] Treatment of HTN in the USA consumes >$55 billion healthcare dollars a year and HTN-related costs account for ∼10% of the world's total healthcare expenditures.[5,6] Despite availability of multiple pharmacological agents from different classes to treat HTN, most patients (>50%) do not achieve goal blood pressure (BP).[7,8] In fact one out of every eight patients with HTN will not achieve appropriate BP targets despite the use of three or more agents.[9] Resistant HTN has a more than three-fold increase in cardiovascular risk when compared with treated and controlled patients with HTN.[10] Thus, there remains an unmet clinical need in improving BP control beyond current pharmacological management strategies.[11–13]

The renal sympathetic nervous system is thought to be important in the onset and maintenance of HTN.[13,14] Disruption of the renal sympathetic fibres using catheter-based radiofrequency (RF) ablation has been shown to be safe and efficacious in patients with resistant HTN.[15–17] However, the single electrode RF catheter system that

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has been widely used for this technique has the disadvantage of requiring the operator to manipulate the catheter within the renal artery lumen multiple times to achieve a series of lesions.[18] A multi-electrode RF system, with electrodes geometrically arranged in pre-specified positions, reduces the amount of catheter manipulation required within the renal artery and thus potentially reduces the risk of procedure-related renal artery injury.

The aim of this first-in-human, prospective, multi-centre, non-randomized study was to evaluate the safety and efficacy of a multi-electrode RF ablation catheter to interrupt the renal sympathetic nerve fibres in patients with resistant HTN.

Methods

Study population

Adult patients (18–80 years of age), who had been referred for management of resistant HTN by a primary healthcare practitioner or specialist at four participating centres (three in Australia and one in Greece), were screened for participation. Enrolled patients had an office systolic BP that remained ≥160 mmHg (≥150 mmHg for patients with DM) despite the stable use of ≥ three anti-hypertensive medications concurrently at maximally tolerated doses. At least one of the anti-hypertensive medications was required to be a diuretic. In all participating patients, the anti-hypertensive drug regimen was to remain stable for a minimum of 14 days prior to enrolment and through the 6-month follow-up.

Patients were withdrawn from the study and the ablation procedure not performed if the renal artery anatomy met any of the exclusion criteria based on the renal angiogram performed on the day of the scheduled ablation procedure. A complete listing of the key eligibility criteria is provided in *Table 1*.

Study design

The EnligHTN™ I study is a first-in-human, prospective, multi-centre, non-randomized study to evaluate safety and efficacy of a multi-electrode system for renal artery sympathetic denervation in patients with drug-resistant hypertensive. The primary safety objective was all adverse events (AEs) during the study. The primary efficacy objective was the reduction of office BP compared with baseline at 6 months. Study patients will continue follow-up at 12, 18, and 24 months post-denervation procedure. The study was designed with an enrolment target of 60 patients to achieve a minimum of 30 subjects eligible for the renal denervation procedure. The study was approved by each institution's Research Ethics Committee and is registered with Clinical Trials Registry (Registration No. NCT01438229). The trial is sponsored by St Jude Medical, St Paul, Minnesota, USA.

Table 1 Key eligibility criteria

Inclusion criteria
Patient has an office systolic blood pressure that remains ≥160 mmHg (≥150 mmHg for patient with type 2 diabetes) despite the stable use of ≥3 anti-hypertensive medications concurrently at maximally tolerated doses, of which one is a diuretic or patient was on diuretic previously but documented to be diuretic intolerant, for a minimum of 14 days prior to Enrolment and with an expectation to maintain for a minimum of 180 days
Patient is ≥18 and ≤80 years old
Exclusion criteria
Patient has evidence of renal artery stenosis (defined as a stenotic severity of >30%) in either renal artery
Patient has multiple main renal arteries in either kidney
Patient's main renal arteries are <4 mm in diameter or <20 mm in length
Patient has an eGFR of <45 mL/min per 1.73 m using the MDRD formula
Patient has type 1 diabetes
Patient has an identified secondary cause of hypertension
Patient is in chronic atrial fibrillation/atrial flutter

Study procedure

Baseline

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.[19,20] Each centre and each enrolled patient were provided with an Automatic BP Monitor (Omron Healthcare, Inc., Bannockburn, IL, USA) for collection of office and home BP values. All the patients recorded home BP values (three readings in the morning and three readings in the evening) and 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, WA, USA).

After the 14-day-screening period, all the patients returned to their respective study centre 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, a 12-Lead ECG and a review of medication logs were also performed. Patients who did not meet all the inclusion criteria or met one of the exclusion criteria were excluded from the study (screen failures) and did not undergo the denervation procedure. In total, 62 patients were consented for participation. Of those, 16 patients were screen failures (*Figure 1*). Patients were scheduled for the renal denervation procedure within the following 30 days. Patients were admitted to the hospital on the day of the procedure.

Renal denervation procedure

Patients were taken to the catheterization laboratory to undergo the renal denervation procedure. After administering conscious sedation as described and local anaesthesia, using fluoroscopic guidance, an 8 French guiding catheter sheath [e.g. Cordis Vista Brite Tip Guiding Catheter (New Jersey, USA) with renal double curve 1 or another appropriate guiding catheter sheath] was inserted to engage each main renal artery sequentially. Nitroglycerine was injected directly into the renal artery if needed. I.v. heparin was administered as per an institutional protocol (~3000–7000 U) although ACT monitoring was not mandated in the protocol. 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. Patients with small (<4 mm in diameter or <20 mm in length), multiple main, or highly tortuous renal arteries were excluded and did not undergo renal denervation. These patients were followed for safety events and asked to return for a follow-up visit at 6 months. An appropriate basket size was subsequently chosen (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 is 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.

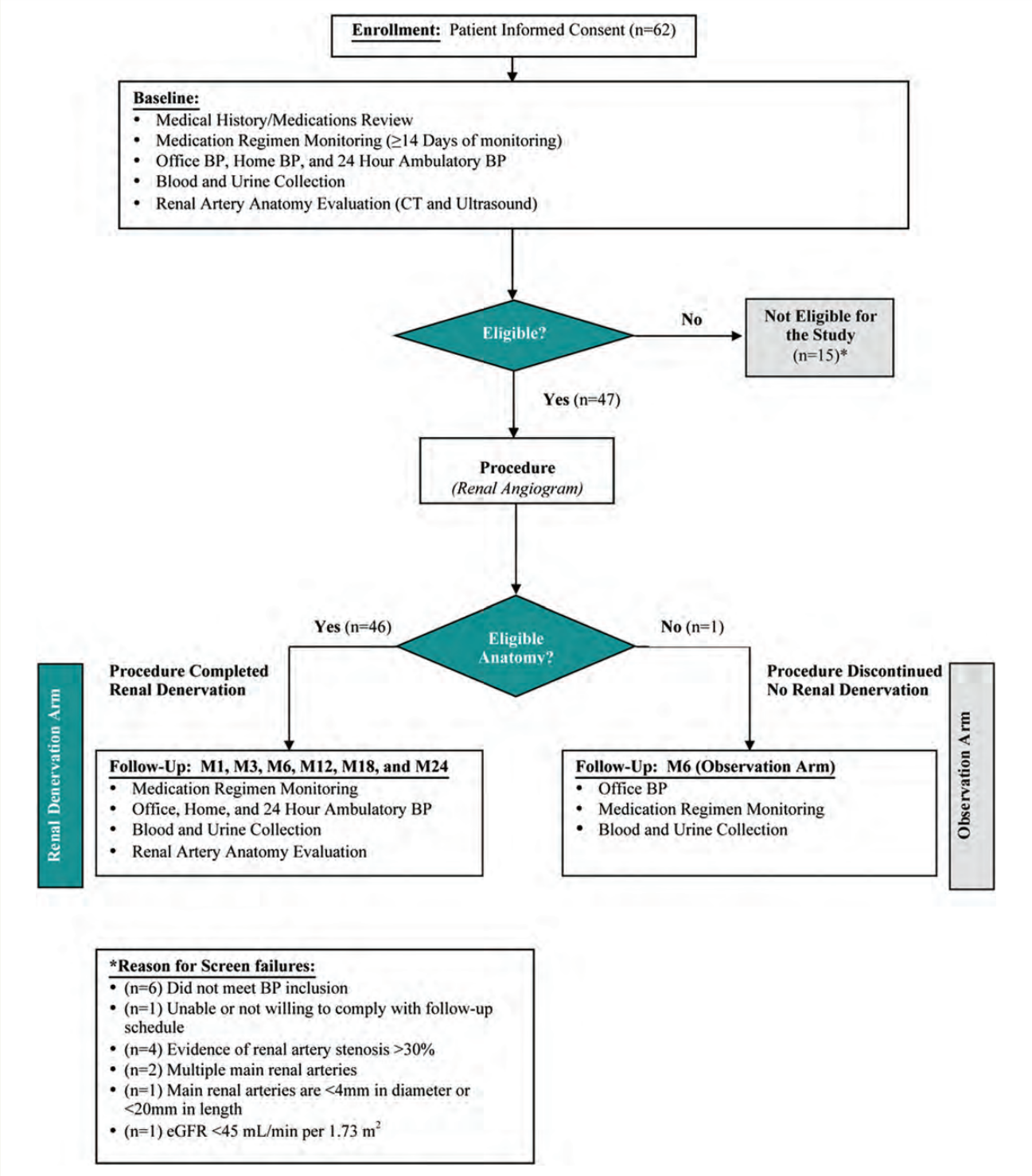

Figure 1 Study flowchart.

EnligHTN renal denervation system

The St Jude Medical EnligHTN™ renal denervation system used in this study consists of the following main components: the EnligHTN™ Ablation Catheter and EnligHTN™ Generator (Model 1500 T11.5 with Software 3.011).

The EnligHTN™ Ablation Catheter (St Jude Medical, St Paul, MN, USA) was designed with an expandable electrode basket with four Platinum–Iridium (Pt–Ir) ablation electrodes. The electrodes deliver low-level RF energy to the renal arterial wall. The distal segment of the ablation catheter is deflectable to assist in proper basket positioning.

The expandable feature of the basket and the deflectable distal catheter section establish good apposition between the ablation electrodes and the target ablation sites in the renal artery. Each electrode has a temperature sensor to monitor the temperature at the ablation site.

The EnligHTN™ RF Ablation Generator delivers RF energy to the EnligHTN™ Renal Artery Ablation Catheter using a proprietary algorithm. Each electrode on the ablation catheter has a corresponding display channel on the generator. The generator channels facilitate control and monitoring of the ablation process. It consists of four independent channels, which simultaneously monitor the temperature of each of the four ablation electrodes and adjusts the magnitude of the RF output power within the programmed maximum magnitude (6 W per electrode) to achieve and maintain the desired temperature (75°C) at each ablation site. The generator has built-in safety features, which include a self-test at power-up and automatic RF power shut-off if the measured tissue impedance is $<$50 Ohm or exceeds 400 Ohm or the temperature exceeds the setting by $>$5°C for $>$3 s or exceeds 80°C.

Renal artery ablation

There were two sizes of the EnligHTN™ Ablation Catheter available for use in the study. The small size basket is designed for renal artery diameters between 4 and 6 mm, and the large size basket is designed for renal artery diameters between 5.5 and 8 mm. After renal artery engagement and completion of a renal angiogram, the EnligHTN™ Ablation Catheter was inserted into the renal artery with the tip of the catheter positioned proximal to the bifurcation and the corresponding images recorded. The basket on the EnligHTN™ Ablation Catheter was then opened with the impedance of each electrode on the basket monitored. Renal artery denervation was commenced and performed sequentially by all four electrodes with the impedance, temperature, and RF energy delivery monitored. If further ablations were desired, the basket was collapsed and pulled back a sufficient distance (~1 cm) to avoid lesion overlap. The basket was rotated ~45° and then expanded. Placement was confirmed under fluoroscopy and the ablation procedure was repeated. A minimum of four to maximum of eight ablation sites were performed in each main renal artery, with each ablation lasting 90 s per electrode. In general, eight ablations were attempted per renal artery to achieve circumferential ablation. Only one patient received four ablations per artery with similar BP reductions as the entire cohort. 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 haemostasis achieved according to each centre's standard of care. Procedural data were recorded for each patient, including procedure duration and number of ablations delivered.

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 until discharge. Patients were discharged from the hospital on the following day if medically stable.

Follow-up

Patients underwent the following during the post-discharge visits: office BP assessment, review of medications for changes, 12-lead ECG, blood and urine collection, 24-h ambulatory BP assessment, home BP monitoring, and renal artery evaluation. Patients were scheduled for the follow-up visits at 1-, 3-, and 6-month (primary objective) post-procedure and continue being followed per study protocol at 12-, 18-, and 24-month post-procedure. Renal artery imaging by computed tomography (CT) and duplex ultrasound was completed at the 6-month follow-up visit. Renal artery evaluation during the 1-month and 3-month follow-up visits was performed if clinically indicated.

Study objectives

The primary efficacy objective was reduction of office BP from baseline to 6 months, which was measured according to guidelines[18,19] at baseline, pre-discharge, 1-, 3-, and 6-month post-procedure. Additional efficacy data collection included changes in anti-hypertensive medication, home BP monitoring, and 24-h ambulatory BP. The primary safety objective was the rate of AEs. Other data collection included blood analysis [complete blood count, basic metabolic profile, serum creatinine concentration, eGFR (using the modified diet in renal disease (MDRD) formula) and serum cystatin C], urine analysis (albumin-to-creatinine ratio), 12-lead ECG, and renal artery evaluation (using duplex ultrasonography and/or CT scan).

Study oversight

Various independent committees or labs provided study oversight for this trial. An independent Clinical Event Committee (CEC) adjudicated all AEs. In addition, an independent Duplex Ultrasound (VasCore, Boston, MA, USA) and CT scan core lab (Cornell University, New York, NY, USA) interpreted the study images. Monitoring and data analysis of the study was performed by St Jude Medical. The corresponding author and Steering Committee members had full access to the study data.

Statistical analysis

The minimum enrolment target for this study was 30 patients. No statistical calculation of the sample size was undertaken, as this study was a first-in-human study to evaluate safety and efficacy. All continuous parameters were summarized using mean, standard deviation, and range. Normality of data was verified with the use of box plots and the Kolmogorov–Smirnov normality test. For normally distributed data, comparisons of primary and secondary outcomes between time points were analysed using paired *t*-tests. Correlations between variables were performed using Pearson's correlation co-efficients. In cases where the data were not normally distributed, the non-parametric Wilcoxon signed-rank test was used to analyse the data. All categorical parameters were summarized using frequencies and percentages. Statistical analyses were performed using SAS 9.2 (by SAS Institute, Inc., Cary, NC, USA). Statistical significance was achieved if a two-sided test obtained a *P*-value $<$ 0.05.

Results

The study enrolment was conducted from October 2011 to March 2012. A total of 62 patients were consented for enrolment. Sixteen patients were excluded due to exclusion criteria during the screening process. One of the 16 patients was excluded from the study due to multiple renal arteries found on the screening renal angiogram. The procedure was discontinued per protocol (i.e. renal ablation not performed), and the patient was followed until 6-month post-procedure. Refer to *Figure 1* for further details of the excluded patients.

In total, 46 patients completed baseline evaluation and underwent the renal denervation procedure. Forty large baskets (71%) and sixteen small baskets (29%) EnligHTN catheters were used in total. Forty EnligHTN catheters of the same size were used for both the right and left renal arteries in patients (26 large and 14 small), and thus sixteen catheters of varying sizes were used in the remaining

patients. More than one EnligHTN catheter of course may have been used per case independent of size. Forty four of the 46 (96%) met all the inclusion and no exclusion criteria. There was one patient who did not meet the inclusion criterion for office systolic BP of >160 mm Hg, and a patient who did not have the baseline BP assessment completed per protocol. However, because these patients underwent the procedure, they are included in the analysis (the treated cohort). Baseline demographic, clinical condition, and medication data for the 46 patients are shown in *Table 2*. The procedure was generally performed with conscious sedation at the operators' discretion. This was not mandated in the protocol. It included, but was not limited to the combination of i.v. midazolam and fentanyl, titrated as appropriate. Most patients experienced back pain during the denervation procedure, which was generally well controlled with sedation and analgesia. Characteristics of the pain response were not captured in detail. The median procedure time (from initiation to completion of RF energy delivery) was 34.0 min and the mean (±SD) number of ablations delivered was 7.7 (±0.8) for the right and 7.4 (±1.4) for the left renal arteries. One patient had the renal denervation procedure performed on a single side only due to difficulty engaging the other renal artery. The mean fluoroscopic time was 11.0 (±7.1) min, and the mean contrast volume used was 139.5 (±93.2) mL.

Safety objective

All the AEs were collected in the study. A CEC adjudicated the events for seriousness and relatedness to the procedure and device. A complete list of reported procedure and/or device-related serious and non-serious AEs as adjudicated by the CEC is provided in *Table 3*.

No serious vascular AEs occurred during the procedure, including no renal artery damage (i.e. no renal artery dissections, aneurysms, or flow limiting renal artery vasospasms) or serious vascular access site complications. Minor peri-procedural events which were attributed to either the device or procedure were reported and include: non-flow limiting vasospasms, vascular access site haematomas, hypotension, vasovagal episodes, bradycardia, transient haematuria, pain, and nausea (*Table 3*). Vasospasm was reported as an AE although no specific threshold was established for reporting the event. An independant CEC reviewed all vasospasms and determined

Table 2 Baseline characteristics

Variable at baseline	*n* = 46
Age at baseline (years)	59.9 ± 10.2 (32, 79)
Gender (male)	67.3% (31)
Ethnic origin (non-white)	2.2% (1)
Body mass index (kg/m^2)	32.4 ± 5.2
Diabetes mellitus type II	32.6% (15)
Coronary artery disease	19.6% (9)
Hyperlipidaemia	58.7% (27)
Sleep apnoea	30.4% (14)
Number of anti-hypertensive classes	4.1 ± 0.57
Drug classification (number of patients)	—
ACE inhibitors/ARBs/DRI	100% (46)
Beta-blockers	73.9% (34)
Calcium channel blockers	91.3% (42)
Diuretics	97.8% (45)
Aldosterone antagonists	13.0% (6)
Vasodilator	13.0% (6)
Sympatholytic agents[a]	50.0% (23)

Data presented as mean ± SD or % (*n*).
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; DRI, direct renin inhibitors.
[a]α, blockers, combined α- and β-blockers and centrally acting α_2 agonists.

Table 3 Device and/or procedure-related adverse events

Event	Number of events	Number of subjects (%)	Time of onset (average number of days from procedure)
Serious adverse events			
Hypertensive renal disease progression	1	1 (2)	93
Hypotension	1	1 (2)	137
Progression of pre-existing renal artery stenosis	1	1 (2)	169
Non-serious adverse events			
Vasospasm	12	7 (15)	0
Haematoma	8	8 (17)	1
Hypotension	3	3 (7)	21
Vasovagal response	3	2 (4)	0
Bradycardia	2	2 (4)	0
Transient haematuria/discoloured urine	2	2 (4)	2
Pain—due to ablation	1	1 (2)	0
Pain—back discomfort	1	1 (2)	0
Nausea/vomiting	1	1 (2)	0
Hypertensive renal disease progression	1	1 (2)	85
Progression of pre-existing renal artery stenosis	1	1 (2)	173

none were flow limiting (>50% reduction in vessel lumen diameter). All minor peri-procedural events were reported to have resolved without further clinical sequelae.

Serious AEs that were deemed possibly related to the procedure and/or device were reported in three (6.5%) patients over 6 months of follow-up. Events include hypotension, progression of pre-existing renal artery stenosis, and a progression of hypertensive renal disease with an increase in serum creatinine.

Renal artery evaluation was conducted on all patients by CT imaging at 6 months. No patients developed a new haemodynamically significant renal artery stenosis. Two patients with pre-existing renal artery stenosis at baseline experienced asymptomatic progression of their renal artery stenosis at 6 months. One was adjudicated as serious (>50% occlusion in artery diameter) and one was non-serious. Neither patient has required clinical intervention at 6 months and their renal function parameters (eGFR, serum creatinine, and cystatin C values) remain stable.

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. While the eGFR decreased (baseline mean of 87−82 mL/min/1.73 m^2 at 6 months, *P*-value = 0.004) and serum creatinine increased (baseline mean of 78−83 μmol/L at 6 months, *P*-value = 0.004), the mean cystatin C decreased (baseline mean of 1.14−1.00 mg/L at 6 months, *P*-value = 0.00013). To further evaluate changes in renal function, a more meaningful assessment of eGFR with a clinically relevant cut-off of <60 mL/min/1.73 m^2 was also undertaken. At baseline, three patients had an eGFR level of <60 mL/min/1.73 m^2. One of these patient's eGFR remained <60, while the other two improved to 60 or greater at 6 months. In contrast, two other patients with baseline eGFR values >60 (63 and 61) decreased to <60 at 6 months.

The urine albumin-to-creatinine ratio decreased significantly throughout the course of the study, with absolute results at baseline 169.4 mg/g, 1 month 142.9 mg/g, 3 months 141.2 mg/g, and 6 months 139.3 mg/g (*P* = 0.007).

Efficacy objectives

Compared with baseline, office and ambulatory systolic BP of the entire cohort significantly decreased at all-time points (*P*-value < 0.0001). The average office BP (mmHg) at baseline was 176/96 (mmHg). The resulting average office BP (mmHg) reductions from baseline at 1 month, 3 months, and 6 months were −28/−10, −27/−10, and −26/−10 (*Figure 2*). Over the follow-up period, as many as 80% of patients had a reduction in office systolic BP of at least 10 mmHg or greater and up to 41% had an office BP of < 140 mmHg (*Figure 3*). Baseline systolic BP (*P*-value < 0.0001) was a strong predictor of response.

In addition, the in-office resting heart rate was collected at baseline (71 b.p.m.), 1 month (69 b.p.m.), 3 months (67 b.p.m.), and 6 months (66 b.p.m.) and demonstrated a decrease over time (*P* = 0.007 at 6 months). The baseline HR was a predictor of change in office systolic BP (*r* = −0.31, *P* = 0.039). In addition, the reduction in HR was correlated with reduction in office systolic BP (*r* = 0.33, *P* = 0.025).

The average 24-h ambulatory BP at baseline was 150/83 (mmHg). The average 24-h ambulatory BP (mmHg) reduction from baseline to 1 month, 3 months, and 6 months was 10/−5, −10/−5, and −10/−6, respectively (*Figure 4*). The change in average 24-h ambulatory BP correlated with both the change in office systolic BP (*r* = 0.56, *P* < 0.0001) and office diastolic BP (*r* = 0.55, *P* < 0.0001).

These reductions in office and ambulatory BPs were achieved with minimal modifications to the cohort's anti-hypertensive medical regimen during the follow-up period. Over the 6-month follow-up period, six (13.0%) patients had a decrease in their anti-hypertensive medications and four (8.7%) had an increase in anti-hypertensive

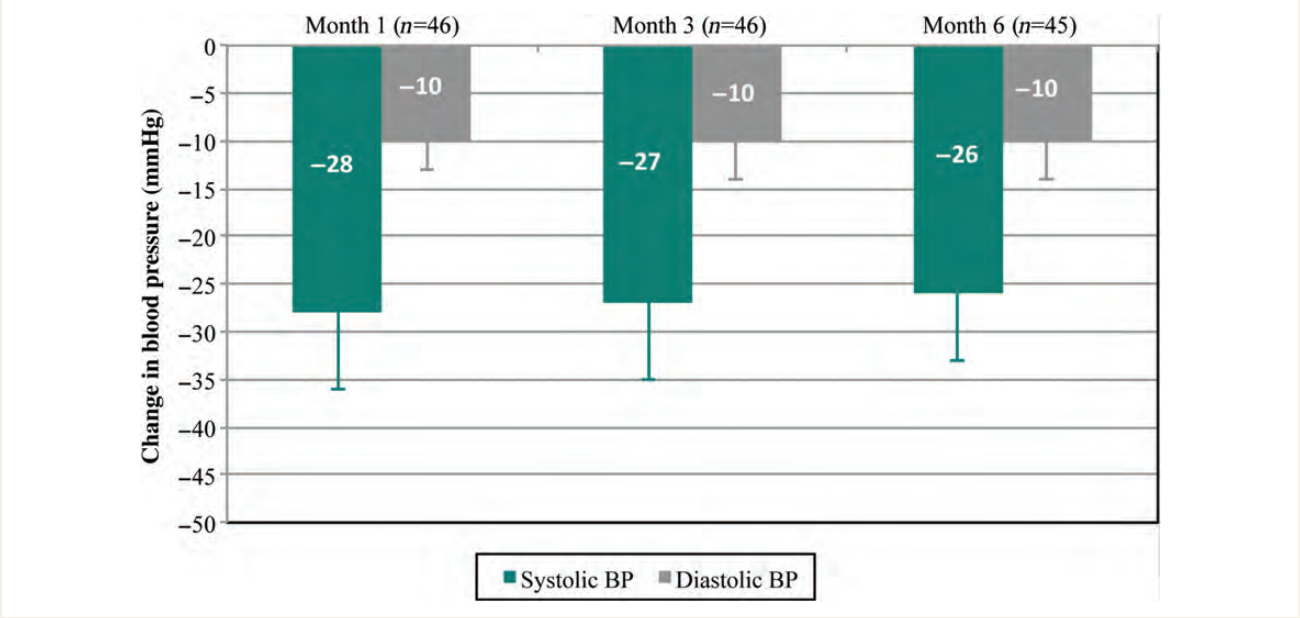

Figure 2 Mean office blood pressure reduction (*P*-value < 0.001).

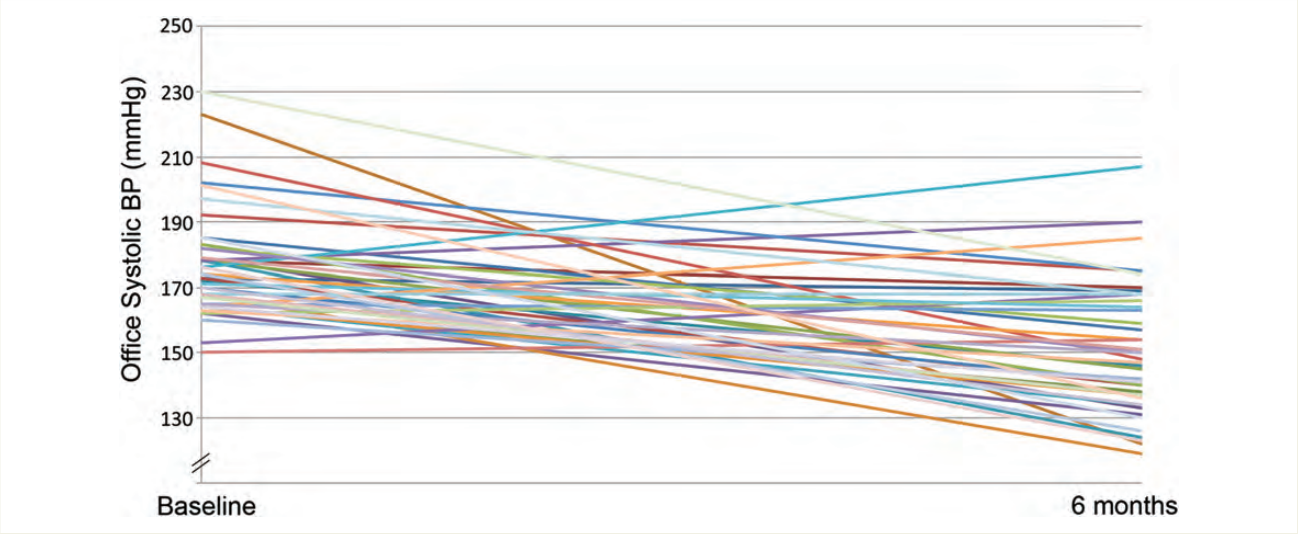

Figure 3 Graphic display of the office systolic BP results for each of the patients enrolled at baseline and 6 months.

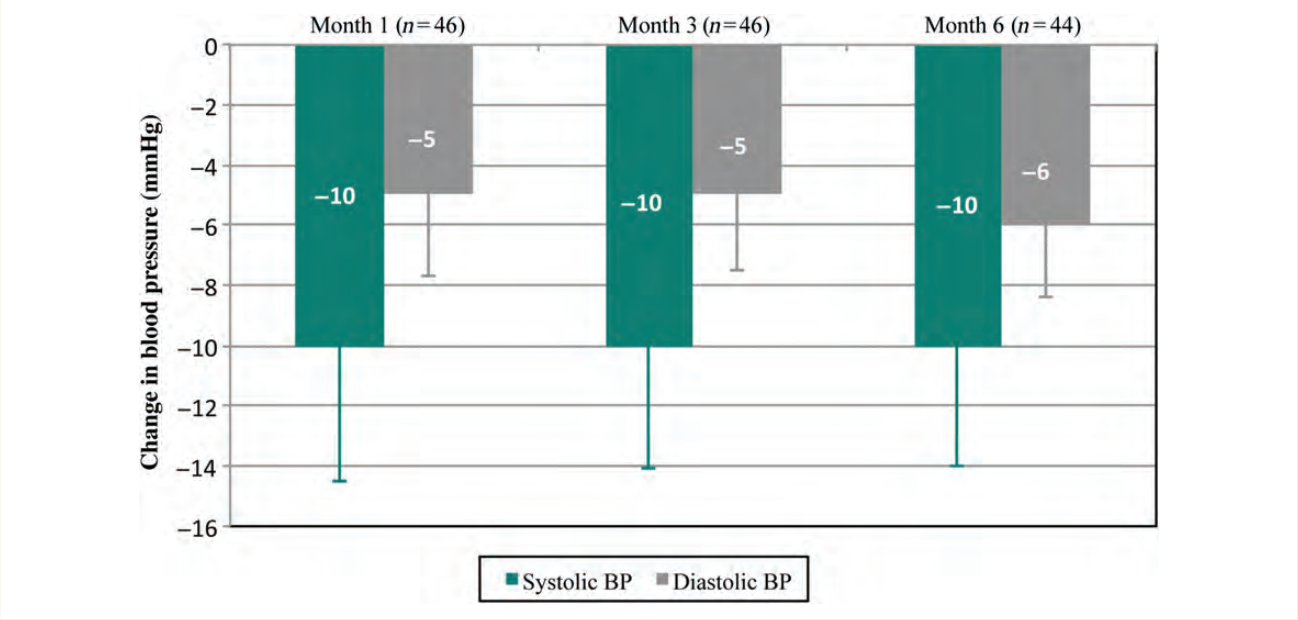

Figure 4 Mean ambulatory blood pressure reduction (*P*-value < 0.001).

medication(s). For patients that did not have an increase or decrease in their anti-hypertensive medication(s) the 6-month office BP reduction was similar to the entire cohort at −25/−10 mmHg, as well as mean ambulatory blood pressure (ABPM) reductions of −10/−5 mmHg.

Discussion

This is the first-in-human, multi-centre study to evaluate the safety and efficacy of a multi-electrode RF ablation catheter for renal artery sympathetic denervation in patients with drug-resistant HTN. A significant reduction in office and ambulatory BP was demonstrated at all follow-up time points through 6 months. No serious peri-procedural vascular events occurred and renal function remained within expected range for a hypertensive population following the procedure and up to 6-month post-renal denervation.

The EnligHTN I data set is the most complete of those published in the area of renal denervation with all patients remaining enrolled and followed through 6 months (no deaths, lost to follow-up, or exits for any reason). Only one visit was missed resulting in a 99.3% overall follow-up visit compliance rate. The overall reductions in office BP seen in the current study are comparable with those reported in two previous studies where single electrode RF catheters were

used.[15,16] Of interest, reductions in BP were recorded earlier in the current study (−28/10 by 1 month), whereas previous studies found that while BP was reduced at 1 month, a comparable reduction was not seen until 6 months.[16] Arguably, the more rapid response seen in the current study may reflect more complete renal denervation acutely due to the use of a multi-electrode RF catheter system compared with a single electrode system. This variance may simply reflect the limited sample sizes being addressed. The reduction in office systolic BP was greater than the reduction in 24 h ABPM and is similar to the difference in the two measures as seen in other studies. [15,16] One may argue this biases the endpoint however office systolic BP is the gold standard for the diagnosis, treatment, and monitoring of patients with HTN, therefore, the reduction in office systolic BP is clinically meaningful.

We found a reduction in HR over 6 months, which is consistent with previously published data,[16,21] and consistent with a reduction in sympathetic activity. We also identified baseline HR as a predictor of reduction in office systolic BP, and change in HR over 6 months was correlated with office systolic BP reduction. Although this seems intuitive and consistent with the hypothesis that the reduction in sympathetic activity also drives the reduction in systolic BP, this is different to a previous study.[21] Some reasons for this difference include the way heart rate was measured (in office HR assessment from the BP monitor vs. electrocardiogram), and the degree of baseline sympathetic activity as evidenced by the baseline HR (71 vs. 66 b.p.m.). Clearly, larger observational data sets will assist in clarifying such relationships.

The laboratory measures indicative of renal function vary slightly over time; however, there is no abrupt change in eGFR or serum creatinine immediately following the procedure. In addition, the cystatin C values improved over time, as did the urinary albumin-to-creatinine ratios, which suggest an improvement in renal function using these indices. Although changes in eGFR and serum creatinine reach statistical significance at 6 months, a shift of $<6\%$ is not considered clinically relevant, particularly in a population with normal renal function. These changes can be attributed to a number of reasons such as small sample size, excessive diuretic dosage including aldosterone antagonists, natural variability and progression over time, or contrast administration for the 6-month protocol specified CT angiogram. The protocol required a vascular image with contrast at 6 months, but it did not specify the timing in relation to renal function evaluation. It is possible that blood samples were collected after contrast administration when usually a small transient rise in serum creatinine may be noted. Nevertheless, renal function will be followed at 12 and 24 months and further assessment will be made. It is important to note that the total number of patients with an eGFR <60 was no different at baseline and 6 months ($n = 3$).

Additional studies with larger sample sizes and a randomized concurrent control group would be beneficial in further assessing benefits and risks of renal denervation therapy. A randomized trial comparing outcomes between single electrode and multi-electrode RF systems for renal denervation would allow more direct comparison of potential advantages/disadvantages of the two systems, in particular whether earlier reduction in BP is achieved with the use of a multi-electrode RF catheter. Current guidelines around clinical appropriateness and future directions with regard renal denervation have been very recently published.[22]

In conclusion, renal artery sympathetic denervation was performed safely in patients with drug-resistant HTN, using the EnligHTN™ multi-electrode catheter, and resulted in a rapid and significant reduction in office BP as well as ambulatory BP that was sustained through 6 months. Thus, the EnligHTN™ multi-electrode system delivers a promising therapy for the treatment of drug-resistant HTN.

Funding

This study was funded by St. Jude Medical Inc, St Paul, Minneapolis, USA.

Conflict of interest: S.G.W. received modest Research Grant and honoraria from St Jude Medical and Medtronic, Inc. C.T. received modest Research Grant and modest honoraria from St Jude Medical. M.W.: none. A.S.: none. D.C. received speaker fees from Astra Zeneca Australia, Eli Lilly Australia, Sanofi Aventis Australia, and travel assistance from Heart.org. I.M. received modest honoraria from Medtronic, Inc. and Boston Scientific. Y.M. none. V.P. received modest Research Grant and modest fees as a consultant/advisory board member from St Jude Medical and significant fees/honoraria from the lecture Bureau Astra Zeneca.

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INTERACTIVE CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/eht144
Online publish-ahead-of-print 2 May 2013

A jogger with tightness of the chest

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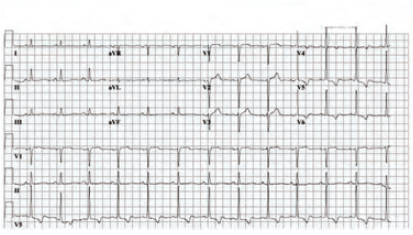

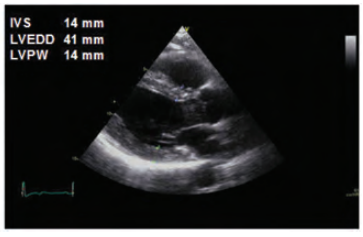

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