Hypertension Therapies Including Renal Denervation
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TCT-402
Renal Norepinephrine Reduction Following Radiofrequency Renal Denervation Correlates with Extent of Nerve Ablation: Roles of Ablation Areas, Anatomy, and Number of Treatments
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Background: Renal denervation is a treatment option for resistant hypertension. Preclinical models that explain the dependence of efficacy on treatment parameters can help differentiate and optimize device efficacy.

Methods: A total of 150 porcine renal arteries were treated with an irrigated multi-electrode helical catheter (Biosense Webster, CA). Between 2-5 electrodes were activated for 30-60 sec with power set points ranging from 6-20 W. Renal norepinephrine (NEPI) was measured 7 days post treatment and correlated with morphologic and morphometric assessments of treated sections. Measured nerve distributions and ablation areas informed a computational model for predicting the percentage of affected nerves (AN).

Results: NEPI across the range of treatment parameters exhibited a threshold-like, dependence on %AN, remaining in the range of control levels (>360 ng/g) up to AN=35% and dropping by 50% and 75% as AN increased to 52% and 70%, respectively. For 15W/30sec treatments, both NEPI and nerve effects tracked with number of activated electrodes (statistically significant for 5 vs 2 electrodes). Threshold (>50%) nerve and NEPI effects were only attained when >4 electrodes were powered. Average %AN increased with total ablation area as predicted by the computational model when accounting for the (average) measured non-uniform radial nerve distribution, but assuming that electrode-induced ablation areas achieved are mutually independent and predictable. Deviations from model-predicted %AN correlated variable nerve locations and sizes and/or deviant ablation areas. In particular, aberrantly low ablation areas were observed when electrode treatments were directed at neighboring blood vessels.

Conclusions: Variable ablation effects can be explained by the confluence of variable nerve locations and sizes and variable ablation shapes. The additive biomarker effects seen with angularly staggered treatments can be leveraged to optimize device design (e.g. electrode number and spacing) and treatment protocols (e.g. catheter rotation between two consecutive treatments) in the face of unknown variable micro-anatomy.

TCT-403
Peripheral Endothelial Function and Sympathetic Influence on Dermal Microcirculation Correlate with Long-Term Blood Pressure Response in Renal Denervation Patients
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Background: Renal denervation (RDN) has emerged as an interventional treatment option for treatment-resistant hypertension. Hypertensive patients are often characterized by an increased sympathetic tone as well as impaired endothelial function. However, there is a paucity of diagnostic tools to identify those hypertensive patients that will benefit from RDN (responders), and to prove successful RDN application. We therefore aimed to investigate the effects of RDN on vascular reactivity and sympathetic vascular response, with the ultimate goal to establish potential markers of therapeutic success.

Methods: 23 patients (mean age 64 years, 13 men, mean ambulatory blood pressure monitoring (ABPM) 148/83 mmHg; >3 (mean 4.78) antihypertensive drugs in adequate dosage and combination) underwent RDN (Medtronic Symplicity® (n=16), St. Jude Medical Enlight® (n=7)), flow-mediated dilation (FMD) and low flow-mediated constriction (L-FMC) as non-invasive measures of endothelial function were assessed. Sympathetic component to vasoconstrictor function in dermal microcirculation was determined by laser Doppler flowmetry.

Results: 13/23 (57%) of the patients showed an ABPM reduction ≥5mmHg at 6 months and hence were considered RDN-responders. Responders had a mean ABPM reduction of -21.6/6 mmHg as compared to baseline (p ≤ 0.003). In these patients, L-FMC was found to be significantly reduced (-2.54 to -4.02, p ≤ 0.017), and sympathetic influence on vascular tone was reduced from 54 to 50% (p ≤ 0.037), while non-responders did not show any significant differences.

Conclusions: Non-invasive endothelial and sympathetic functional assessment parameters correlate with successful blood pressure reduction responses to renal denervation in patients with treatment-resistant hypertension. Further and larger scale studies are necessary to analyze the potential predictive utility of these parameters in the clinical RDN setting, in particular with regard to optimized patient selection for the procedure.

TCT-404
First Clinical Experience with Neurotropic Agents for Treatment of Symptomatic Hypertension
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Background: New device-based solutions to treat hypertension are focused on the overactive sympathetic nervous system as the therapeutic target. Early results from the clinical simulation of carotid baroreceptors and energy-based (radiofrequency, ultrasound) ablation of renal nerves have shown the ability to reduce blood pressure.

Methods: We investigated a simple, catheter-based approach of delivering neurotropic agents near renal nerves, specifically targeting nerve axons, to interfere with sympathetic nerve function. A small volume of NW2013 (proprietary formulation developed by Northwind Medical, San Jose, CA), was injected into renal artery walls using an endovascular catheter with microcatheters.

Results: Seven (7) patients were technically successfully treated through local administration of NW2013 near renal nerves. There were no serious procedure-related, device-related or agent-related complications. Injury to the renal artery wall was minimal with no spasms, dissections or vessel perforations. Mild to moderate pain was reported during agent injection, which was managed by 5mg of morphine, and was significantly less compared to energy-based therapies. Five (5) patients completed their 1-month and 3-month follow ups and were included in the analysis. Mean systolic/diastolic office blood pressure (OBP) and 24-hour ambulatory blood pressure (ABP) at baseline were 181/92 and 164/105 mm of Hg, respectively. At 1 and 3 months after treatment, the average OBP reduction was 33% and 45% of Hg, respectively; equivalent ABP decrease was 12/13 and 22/16 mm of Hg. These results are very promising and demonstrate that treatment of sympathetic hypertension patients using local delivery of neurotropic agents is safe and feasible. In addition, the therapy offers advantages over energy-based methods in terms of nerve specificity, less pain and cost effectiveness.

Conclusions: Local administration of selective neurotropic agents surrounding renal arteries seems to be a safe and feasible procedure to treat sympathetic hypertension. Long-term data from randomized clinical studies are needed to further evaluate efficacy and durability of this procedure.

TCT-405
SYMPLECTY HTN-3: Outcomes in the African-American and non-African American Populations
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Background: SYMPLECTY HTN-3 was a randomized, blinded, sham-controlled trial of renal denervation (RDN) in patients with resistant hypertension that demonstrated safety but not efficacy of RDN. Results for the prespecified African-American (AA) and non-African American (non-AA) subgroups are presented.

Methods: All patients were required to have an office systolic blood pressure (SBP) of ≥160 mm Hg and an ambulatory 24-hour SBP ≥135 mm Hg while taking ≥3 anti-hypertensive drugs at maximally-tolerated dose, including a diuretic. Baseline clinical and procedural characteristics, baseline and 6-month antihypertensive medication use and changes in office and ambulatory blood pressure were compared between groups.

Results: AA patients comprised (26.2%) of the cohort in this trial. AA were younger, included more females, had a lower incidence of coronary artery disease and had a higher percentage of asthma, stroke and heart failure than non-AA patients. Changes in office and ambulatory BP measurements are shown in the table. Differences in Office SBP reduction at 6 months were not apparent at earlier time points. The use of vasodilators (majority hydralazine) was greater in the AA than the non-AA subgroup (47% vs 34%, p=0.03 for RDN patients and 56% vs 41%, p=0.09 for sham patients). The SBP decrease in the AA sham group on vasodilators was -21.9 mm Hg and -12.7 mm Hg in the RDN cohort not on vasodilators (p=0.276; p for interaction =0.185).

Conclusions: Non-invasive endothelial and sympathetic functional assessment parameters correlate with successful blood pressure reduction responses to renal denervation in patients with treatment-resistant hypertension. Further and larger scale studies are necessary to analyze the potential predictive utility of these parameters in the clinical RDN setting, in particular with regard to optimized patient selection for the procedure.
Conclusions: The difference in blood pressure changes in the AA vs. the non-AA subgroup may be due to greater BP reductions in the AA sham control group. This greater than expected drop in BP in the sham control group suggests a post-randomization interaction with an exposure that impacted BP lowering. Further investigation of factors that may impact sham response is warranted.

Methods: Swine underwent bilateral RDN and followed for 7, 30, and 180 days. A representative section of each time point was selected for H&E and immunohistochemical (IHC) analysis. IHC consisted on S100 (Schwann cell), Tyrosine hydroxylase (TH; efferent motor nerves), calcinonin gene-related peptide (CGRP) and substance P (SP); (CGRP and SP afferent sensory nerves).

Results: H&E displayed the typical acute (7 days: nerve necrosis, distal atrophy) and chronic (180 days: nerve fibrosis) nerve injury. At 180 days we could observe evidence of nerve remodeling and tentative regeneration, morphological recovery of S100, and TH staining and to variable degrees of CGRP and SP staining. However, there was evidence of TH and S100 staining spill over and expansion of neural bundles within and across the thickened perineurium, forming neurotubular tangles highly reminiscent of amputation neuromas (neuromatous regenerative). IHC revealed that the nerve displayed early signs of TH and S100 positive fibers within and beyond the fibrous perineurium as early as 7 days following RDN. This perineurial neuromatous proliferation becomes more evident at longer time points. At 180 days, the neuromatous tangles became very prominent with affected nerves completely remodeled into neuromatous proliferative bundles. Conclusions: It has been previously demonstrated in renal transplant models that sympathetic nerves have the ability to regenerate. Furthermore, there are evident signs of increased nerve count in swine model at longer time points following RDN. However this is the first evidence that this “regenerative nerve attempt” occurs as early as 7 days following RDN therapy and is progressively increasing over time, resulting in the formation of poorly organized tangles of nerve fibers, Schwann cells, and connective tissue. This is the first complete histological characterization of neuromatous nerve regrowth following RDN.

TCT-408
Renal Artery Denervation With A New Simultaneous Multielectrode Catheter For Treatment Of Resistant Hypertension: 12-Month Update From The SYMPLECTIC Spyral First-Man Study
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Background: The SYMPLECTIC Spyral first-in-man (FIM) study investigated the safety and effectiveness of the Spyrals™ multicatheter renal denervation catheter to lower blood pressure in patients with resistant hypertension. Methods: The prospective, open label Spyrals FIM study enrolled 50 subjects with resistant hypertension defined as an office systolic blood pressure of ≥160 mm Hg (≥150 mm Hg for type 2 diabetics) despite adherence to an antihypertensive regimen of ≥3 drug classes (ideally including a diuretic). Subjects with an estimated glomerular filtration rate of < 45 mL/min/1.73m2, type 1 diabetes mellitus, renal artery stenosis of >50%, renal artery aneurysm, and prior renal artery intervention were excluded. The protocol specified one denervation treatment per artery via delivery of 4 simultaneous 60 seconds ablations per artery. The safety endpoint is a composite of vascular complications, renal artery intervention, new onset end stage renal disease, death. The medical safety, significant device event resulting in end-organ damage, hypertensive crisis and new renal artery stenosis. Effectiveness is measured by change in office BP from baseline at 1, 3, 6, and 12 months and annually thereafter.
Results: The mean age of subjects was 63 years, 46% were men, 46% had type II diabetes mellitus, and baseline estimated glomerular filtration rate was 85.1 ± 15.0 mL/min/1.73m2. Baseline systolic and diastolic blood pressure was 181 ± 17 mm Hg and 95 ± 12 mm Hg, respectively, and the mean number of antihypertensive drug classes was 4.5 ± 1.1. The mean number of ablations per artery was 3.25. There were site-site pseudoaneurysms and 1 mycocardial occlusion during the months 6 months follow-up. No new renal artery stenosis or hypertensive emergencies occurred, and there was no clinically meaningful change in renal function. The change in office-based blood pressure was -19.9 ± 25.0 ±7.3 ± 11.5 mm Hg at 6 months, p<0.001.
Conclusions: Renal denervation using the Spyrals multielectrode catheter is safe and results in significant reduction of office blood pressure from baseline. 12-month follow-up results will be available for presentation in September.

TCT-409
Percutaneous and Early Clinical Experience of a Non-vascular Treatment for Resistant Hypertension
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Background: The Symplicity HTN-3 recently failed to meet its primary efficacy endpoint in blood pressure reduction. The device used in this study as well as all other denervation systems only ablate peri-arterial nerves. The Verve Medical system directs radiofrequency energy to the renal pelvic space where the preponderance of autonomic nerves originate and are closely accessible. We have previously demonstrated the feasibility of the Verve Medical NephroBlate to ablate these nerves.
Methods: We developed a protocol to treat a small number of patients (n=3, 4 kidney) undergoing elective nephrectomy. After submission to the hospital institutional review board and after patient informed consent we treated three patients with end