SPYRAL HTN ON and OFF MEDS Trials Evolution of Evidence and Future Directions

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support	Biotronik, Boston Scientific, Medtronic CardioVascular, Medinol, Orbus Neich
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Intellectual Property Rights	None
Other Financial Benefit	None



ADVANCES OF SPYRAL HTN COMPARED TO SYMPLICITY HTN-3

EVOLUTION OF CLINICAL TRIAL DESIGN, CONDUCT, INDICATION AND METHODS





IVY Pre Clinical Trial: Combined Treatment in Main Artery and Branch Vessels in Porcine Model



Pre-clinical porcine data show significantly greater reductions in renal sympathetic activity with combined proximal and distal therapy application.









SPYRAL HTN – OFF MED RANDOMIZED, SHAM-CONTROLLED TRIAL



¹Only for patients discontinuing anti-hypertensive medications. ²According to scheduling.³Phone follow-up is required at 6 and 10 week visits. ⁴Drug testing. ⁵Med titration every 2 weeks until OSBP < 140 Kandzari D, et al. Am Heart J. 2016;171:82-91



RDN ASSOCIATED WITH SIGNIFICANT REDUCTION IN ALL BP MEASURES AT 3-MONTHS SPYRAL HTN-OFF MED BLOOD PRESSURE CHANGE FROM BASELINE





SPYRAL HTN ON MEDS STUDY DESIGN

- Randomized, sham-controlled, (patient and assessor) blinded, proof-of-concept trial
- 25 sites in Germany, UK, Austria, Greece, Japan, Australia and USA



¹According to scheduling Clinicaltrials.gov NCT02439775 Kandzari D, et al. *Am Heart J*. 2016;171:82-91



SPYRAL HTN ON MEDS BASELINE BLOOD PRESSURE

Mean ± SD	RDN (N = 38)	Sham Control (N = 42)
Office measurements		
Office SBP (mm Hg)	164.6 ± 7.1	163.5 ± 7.5
Office DBP (mm Hg)	99.6 ± 6.9	102.7 ± 8.0
Office heart rate (bpm)	75.6 ± 11.8	73.5 ± 10.4
24-hour measurements		
Mean 24-hour SBP (mm Hg)	152.1 ± 7.0	151.3 ± 6.8
Mean 24-hour DBP (mm Hg)	97.2 ± 6.9	97.9 ± 8.4
Mean 24-hour heart rate (bpm)	75.3 ± 11.3	75.6 ± 10.7

P = NS for differences in all baseline measurements



SPYRAL HTN ON MEDS BASELINE MEDICATIONS

	RDN (N = 38)	Sham Control (N = 42)
Number of anti-hypertensive medication classes		
Mean ± SD	2.2 ± 0.9	2.3 ± 0.8
Prescribed medication classes		
1	28.9 (11)	21.4 (9)
2	18.4 (7)	26.2 (11)
3	52.6 (20)	52.4 (22)
Medication class		
Thiazide diuretic	57.9 (22)	59.5 (25)
Calcium channel blocker	71.1 (27)	73.8 (31)
ACE-I/ARB	81.6 (31)	83.3 (35)
Beta blocker	10.5 (4)	14.3 (6)

P = NS for differences in all baseline medications

Kandzari et al. Lancet 2018



SPYRAL HTN ON MEDS 24 HR AND OFFICE BASELINE TO 6 MONTH BLOOD PRESSURE CHANGE





RISK REDUCTION FOR A 10 MM HG FALL IN OFFICE SYSTOLIC BLOOD PRESSURE

Meta-analysis ¹ : 123 HTN tri	ials, N=613,815		RR (95% CI)
	← Favors Intervention	Favors Control →	
Major CV events	 -		0.80 (0.77, 0.83)
Coronary heart disease			0.83 (0.78, 0.88)
Stroke			0.73 (0.68, 0.77)
Heart failure			0.72 (0.67, 0.78)
Renal failure	·•		0.95 (0.84, 1.07)
All-cause mortality	⊷		0.87 (0.84, 0.91)
Bol	0.5 0.7 0.9 lative Risk Per 10 mm Hg Bed	1.1 1.3 1.5 Justion in Systelic Blood Press	Irrespective of baseline BP or pre-existing conditions
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SPYRAL HTN ON MEDS 24 Hr ABPM Progressive Decline from Baseline to 6 Months



ANCOVA adjusted analysis



SPYRAL HTN ON MEDS 24 Hr ABPM



Dashed line represents the 24-hr mean at baseline (blue) and 6 months (red) W = Self reported wake time or 7:00 AM if not reported



Kandzari et al. Lancet 2018

RDN SAFETY: SPYRAL ON and OFF MEDS NO MAJOR ADVERSE EVENTS IN TWO PILOT TRIALS

	OFF MED PILOT STUDY 3M POST-PROCEDURE		ON MED PILOT STUDY 3M & 6M POST-PROCEDURE	
Major Adverse Events (%)	RDN (n = 38)	Sham Control (n = 42)	RDN (n = 38)	Sham Control (n = 42)
Death	0	0	0	0
New myocardial infarction	0	0	0	0
Major bleeding (TIMI ¹)	0	0	0	0
New onset end stage renal disease	0	0	0	0
Serum creatinine elevation >50%	0	0	0	0
Significant embolic event resulting in end- organ damage	0	0	0	0
Vascular complications	0	0	0	0
Hospitalization for hypertensive crisis/emergency	0	0	0	0
New stroke	0	0	0	0
New renal artery stenosis > 70%			0	0

1. Townsend R, et al. Lancet. 2017;390:2160-2170; 2. Kandzari D, et al. Lancet. 2018;391:2346-2355

3. TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of procedure.



No Difference in Renal Function Difference through 6 Months







"...there are also unknown unknowns—the ones we know we don't know. And if one looks throughout history...it is the latter category that tend to be the difficult ones."

- Donald Rumsfeld



SPYRAL HTN ON MEDS MEDICATION ADHERENCE



Drug testing of urine and serum by tandem HPLC and mass spectroscopy. Medication adherence defined as detectable levels of all prescribed antihypertensive medications at each follow-up visit and includes cases in which an extra antihypertensive medication was also detected.



Kandzari et al. Lancet 2018

TREATMENT RESISTANT OR RESISTANT TO TREATMENT? ~50% ARE PARTIALLY ADHERENT WITHIN FIRST YEAR OF TREATMENT

Even with combination pills, studies show patients become non-adherent





Patient Preference Study





SPYRAL HTN PIVOTAL RANDOMIZED, SHAM-CONTROLLED TRIAL



¹Only for patients discontinuing anti-hypertensive medications. ²According to scheduling. ³Drug testing to ensure no medications are present. ⁴Optional follow up at weeks 6 and/or 10 if the patient is not controlled. ⁵Only for patients with BP ≥140 mmHg at 3M. ⁶Drug testing to ensure prescribed medications are present (if on drug). ⁷6 and 12 month renal imaging.



SPYRAL HTN-ON MED RCT Study Design

	ON-MED Feasibility	ON-MED RCT
Geography Expansion	25 sites max. in US, Europe, Australia, Japan	55 sites in US, Europe, Australia, Japan and Canada
Sample Size	Up to 110 Randomized/700 enrolled	Up to 340 Randomized/1600 enrolled
Primary Endpoints	ABPM and secondary OBP efficacy endpoints	Powered for ABPM
Randomisation	1:1 Randomization	2:1 Randomization
Crossover	Unblinding @ 12 months	Unblinding and Crossover @ 6 months
Renal Imaging	Duplex ultrasound imaging (6 months)	Duplex Ultrasound imaging (6 months) renal artery CTA or MRA imaging (12 months) (min 50 and up to 340 subjects)



Next Steps in RDN Trials Is RDN Ready for Clinical Practice?

- New blood pressure guidelines motivated by increasing awareness of benefit with more intensive blood pressure control, abysmal levels of hypertension control, and epidemic non-adherence to antihypertensive medications identify the need for non-drug treatment options
- Renal denervation results in **statistically significant and clinically relevant blood pressure reductions** at 6 months
 - In **uncontrolled hypertensive** patients compared with sham control
 - In the **absence and presence** of commonly prescribed anti-hypertensive medications
- Blood pressure after renal denervation **continued to decrease** between 3 and 6 months
- Blood pressure reductions following renal denervation were present throughout the day and night ("always on" effect)
- No major safety events across studies despite a more complete denervation procedure that includes extension into renal artery branch vessels
- SPYRAL HTN PIVOTAL trial in an OFF MEDS population in addition to ON MEDS trial are underway
 - Trials will further inform the safety and effectiveness of RDN modalities for the treatment of uncontrolled hypertension
 - Future directions include patient reported health status and preference and continued real world surveillance

