MedStar Heart Institute

Cleveland Clinic
Heart and Vascular Institute

SYMPLICITY Obviate Imprudent New Devices

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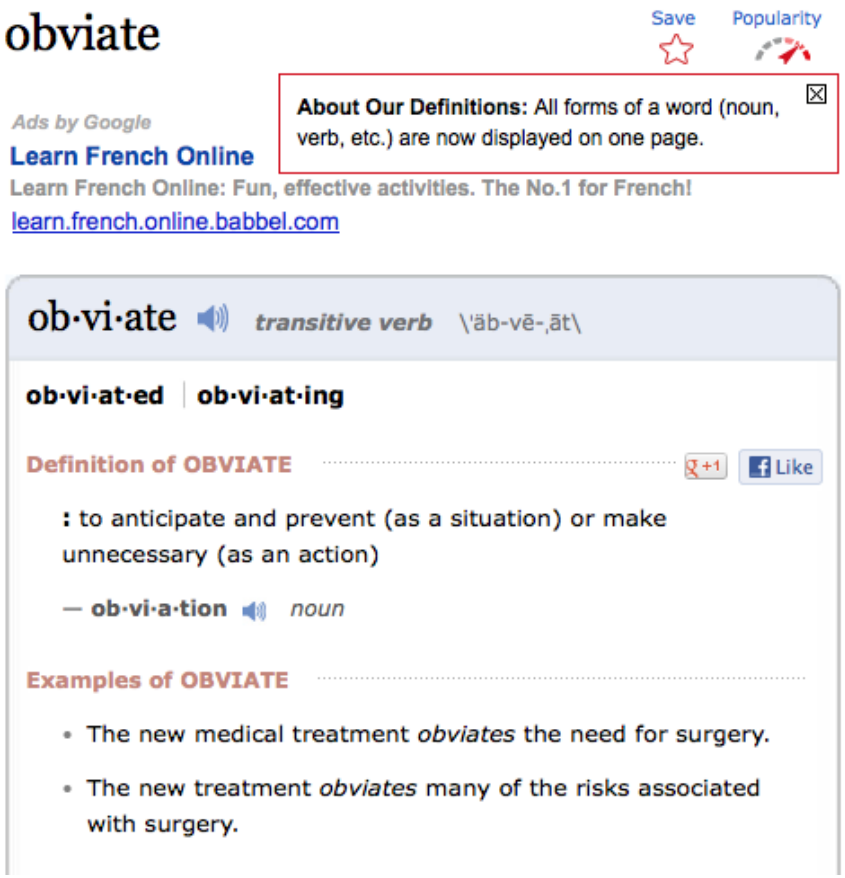
Disclosure Statement of Financial Interest

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	• Volcano • Medtronic Vascular • Abbott Vascular • Boston Scientific
• Consulting Fees/Honoraria	• Biotronik • Medtronic • Abbott Vascular • Boston Scientific • Lilly Daiichi • Astra Zeneca

Obviate Imprudent New Devices

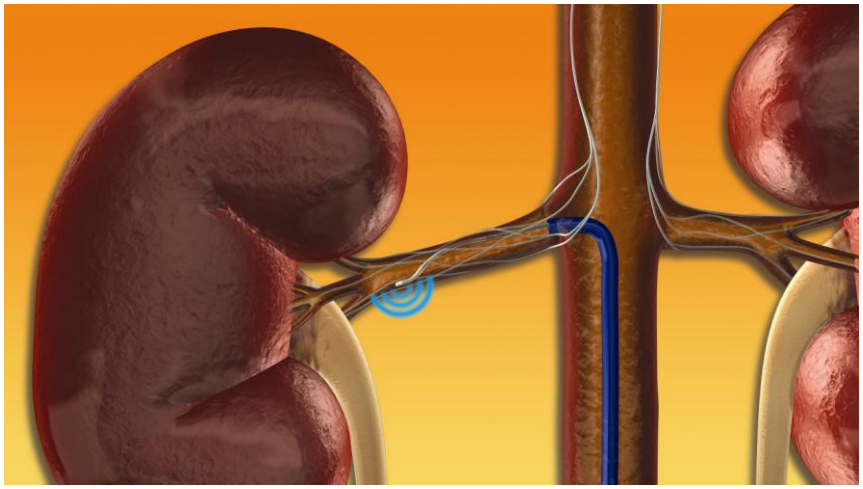


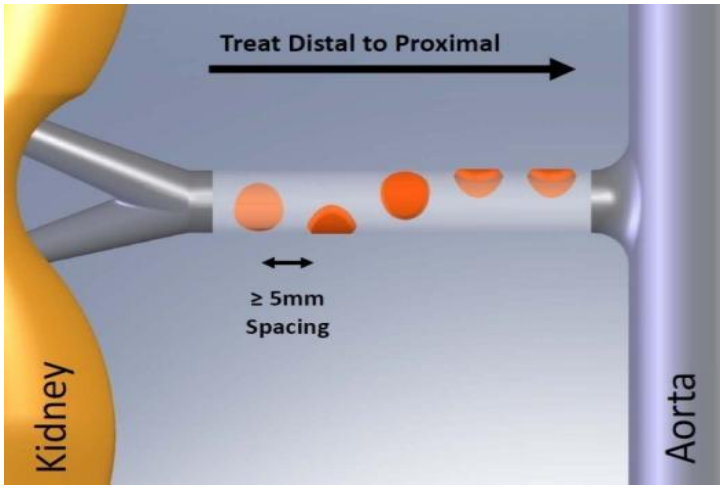
Examples of IMPRUDENT

It's politically imprudent to stir up such controversy during an election year.

<a very sweet girl, but so imprudent that no one trusts her with a secret>

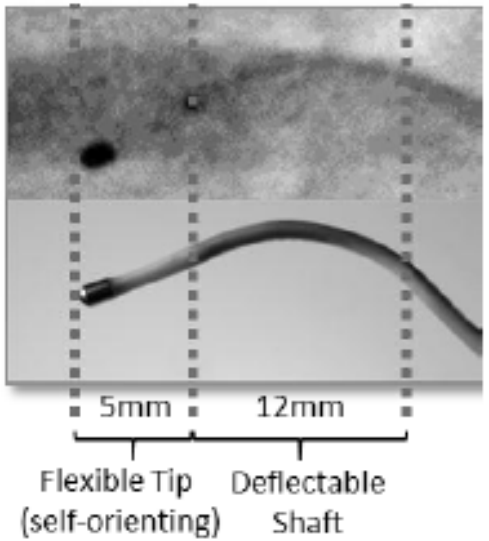
Renal Nerve Anatomy Allows a Catheter-Based Approach 2010





- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms

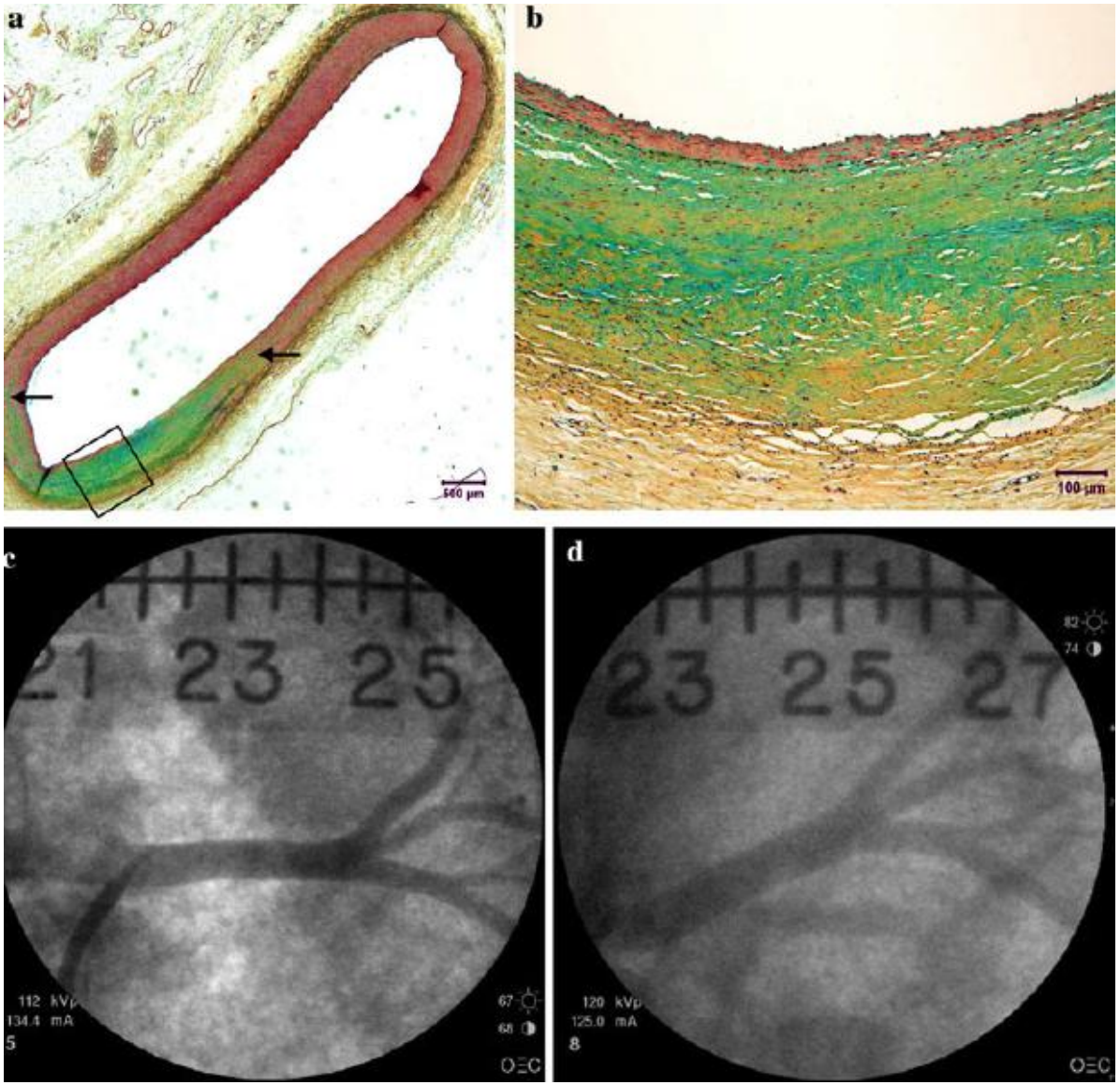
→ Current Symplicity™ Renal Denervation System

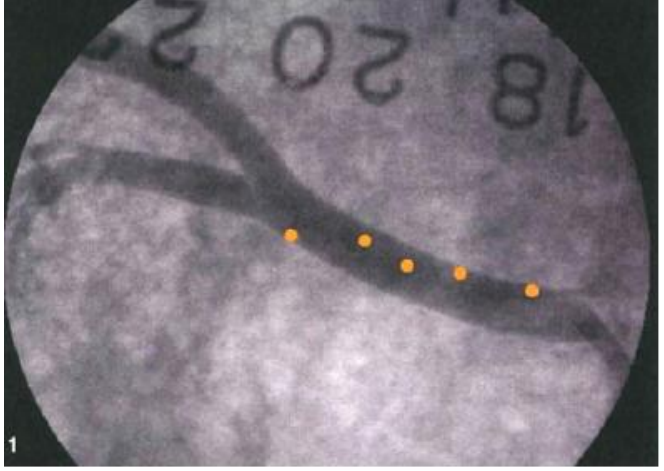


- Flexibility and maneuverability
- Responsiveness
- Handle controls
- 6F guide catheter compatible
- Designed for renal anatomy

- Fully automated generator
- Built-in safety algorithms
- Low-power (8W)
- Straightforward user interface

Preclinical Evaluation



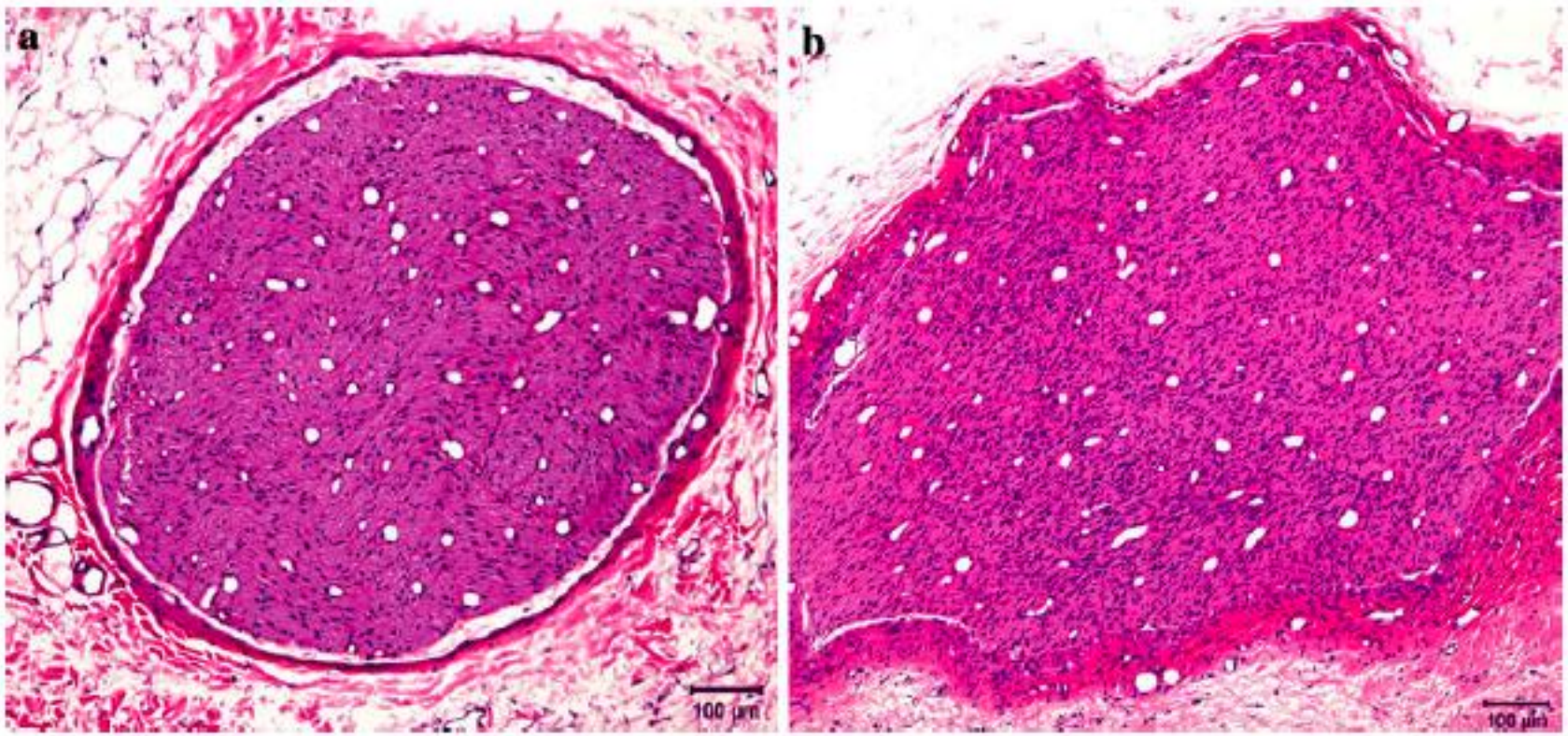


Treated Renal artery

Rippy et al
Clin Res Cardiol 2011

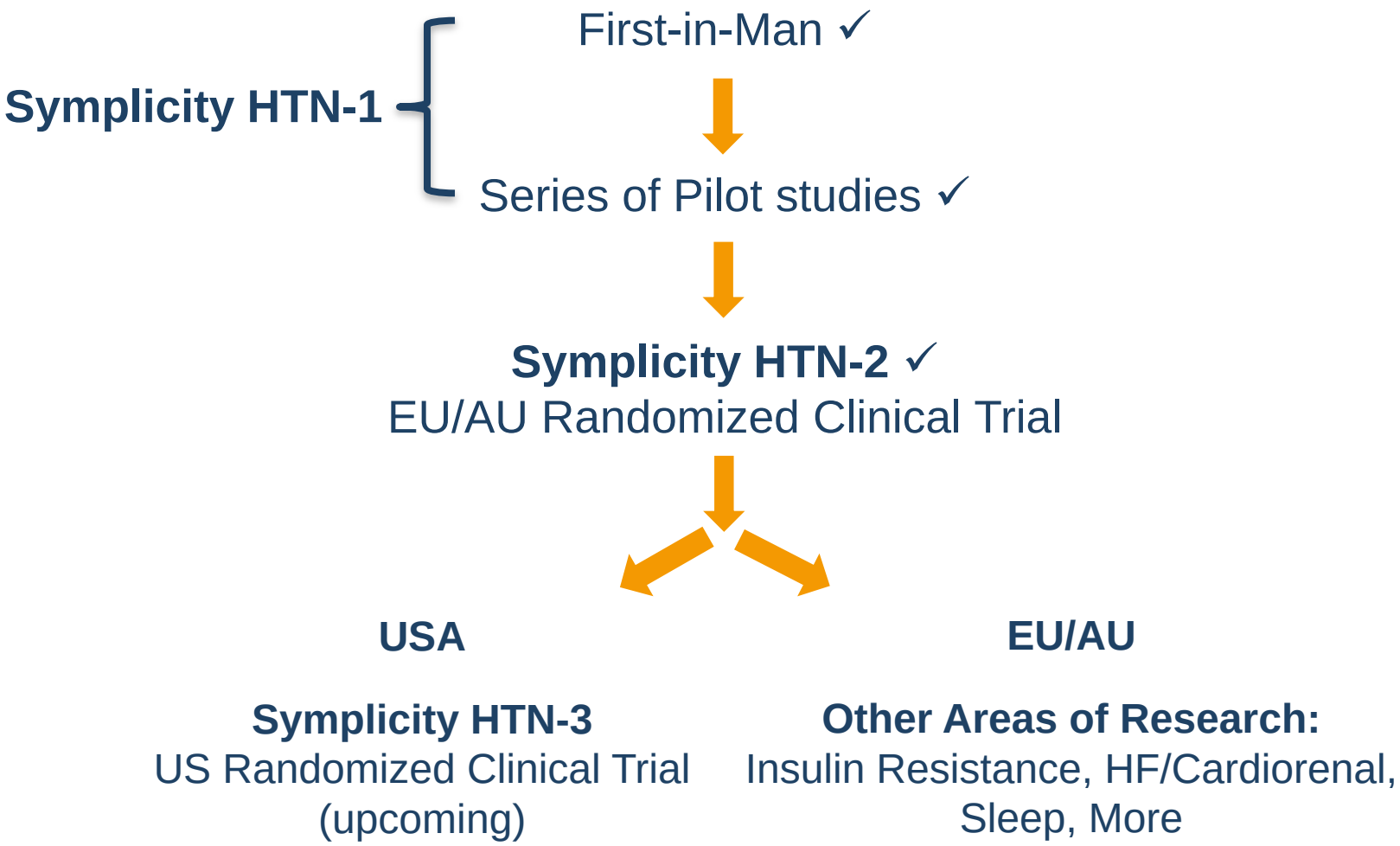
6 months most treatment up to 25% of media is affected

Histology H&E of a nerve untreated versus treated



Rippy et al Clin Res Cardio 2011

Staged Clinical Evaluation



Reduction of Renal Contribution to Central Sympathetic Drive: MSNA in Resistant Hypertension Patient

** 59 year old male on 7 HTN meds*

		MSNA (burst/min)		BP (mmHg)
Baseline		**56**	→	**161/107**
1 mo		**41** (-27%)	→	**141/90** (-20/-17)
12 mo		**19** (-66%)	→	**127/81** (-34/-26)

*** Improvement in cardiac baroreflex sensitivity after renal denervation (7.8 →11.7 msec/mmHg)**

Schlaich et al. NEJM. 2009; 36(9): 932-934.

Proof of Principle:
Related Changes in Underlying Physiology

		Baseline	1 mo	Δ
Office BP	*(mmHg)*	161/107	141/90	
Renal NE spillover	*(ng/min)*			
- left kidney		72	37	-48%
- right kidney		79	20	-75%
Total body NE spillover	*(ng/min)*	600	348	-42%
Plasma Renin	*(µg/l/hr)*	0.3	0.15	-50%
Renal Plasma flow	*(ml/min)*	719	1126	57%

LV Mass (cMRI) dropped 7% (from 78.8 to 73.1 g/m^2) from baseline to 12 months

Schlaich et al. NEJM. 2009; 36(9): 932-934.

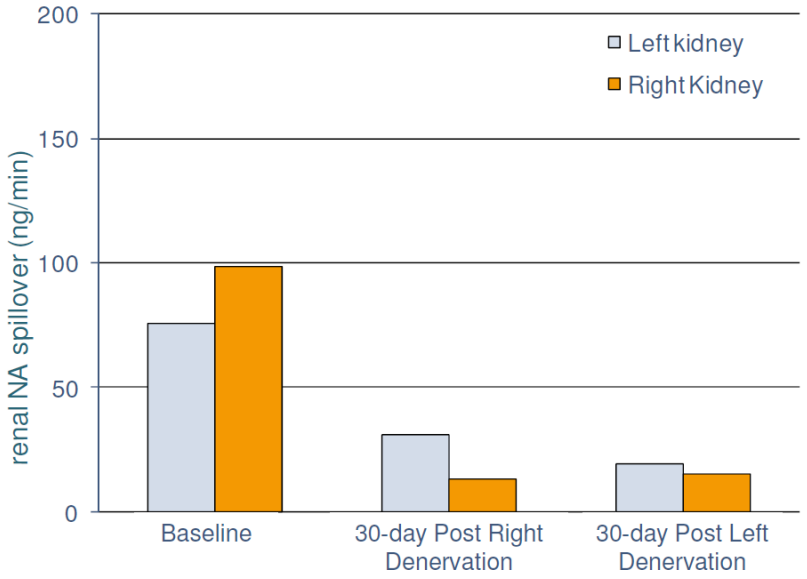
Renal Norepinephrine Spillover: 10 cases

- Mean total renal norepinephrine spillover ↓ 47%, p=0.023 (95% CI: 28–65%)
- Mean total body NE spillover ↓ 28%, p=0.043 (95% CI: 4–52%)

Example Case:

Left: 75 % reduction

Right: 85 % reduction

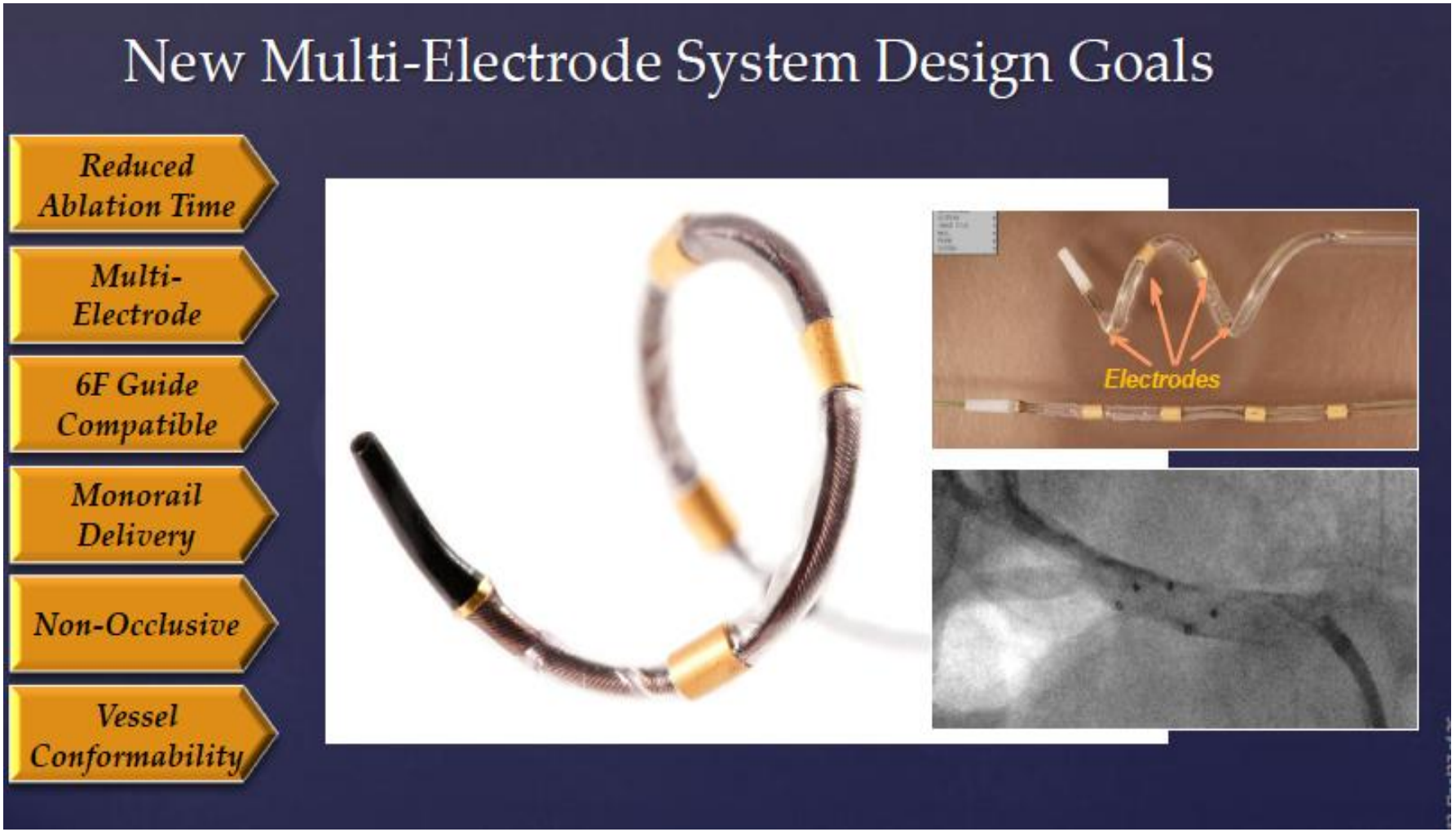


Esler et al. J Htn. 2009;27(suppl 4):s167.
Schlaich et al. J Htn. 2009;27(suppl 4):s154.

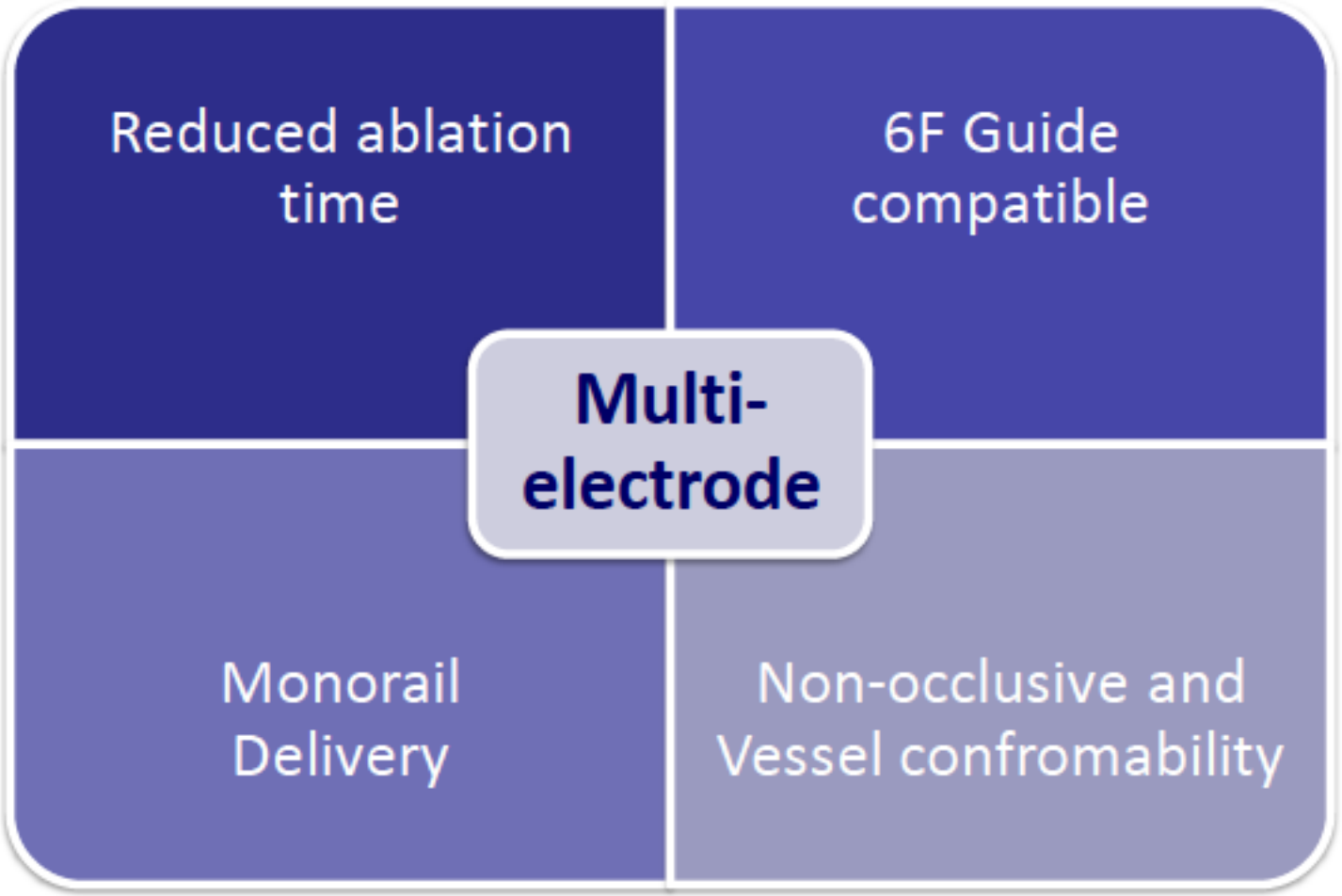
Technology Limitations: Room for Improvement

- The Preclinical model for efficacy is complex
- There is limited knowledge on the route of the sympathetic nerve.
- The procedure make take 40-60 minutes and limited to tthe anatomy of the renal arteries
- It is painful to the patient
- There are other sympathetic targets in the body
- Up to 10% of patients did not respond
- Patients still need to take their medications

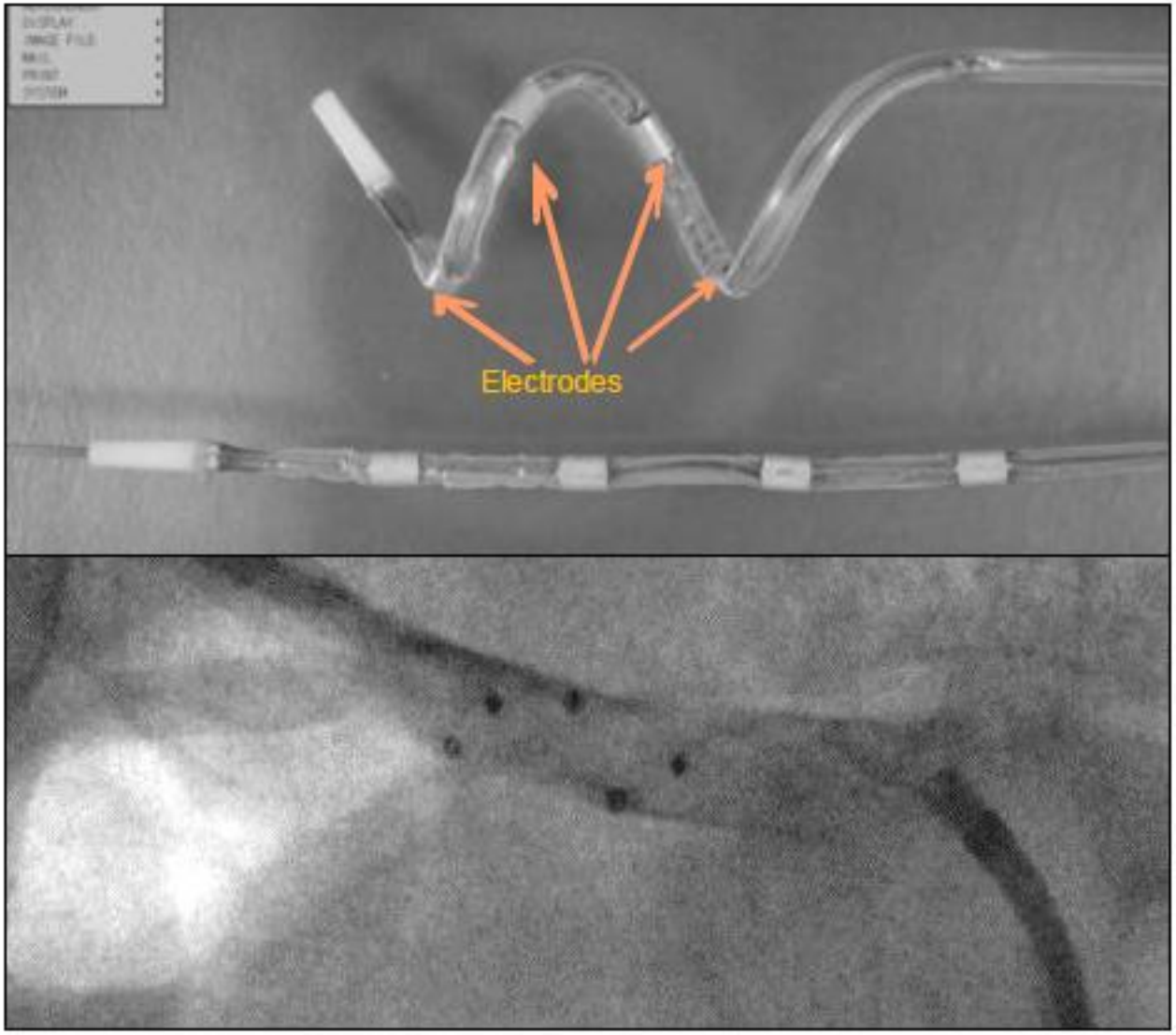
Medtronic introduced New Spiral Catheter to replace Symplicity



→ New Multi-Electrode System Design Goals



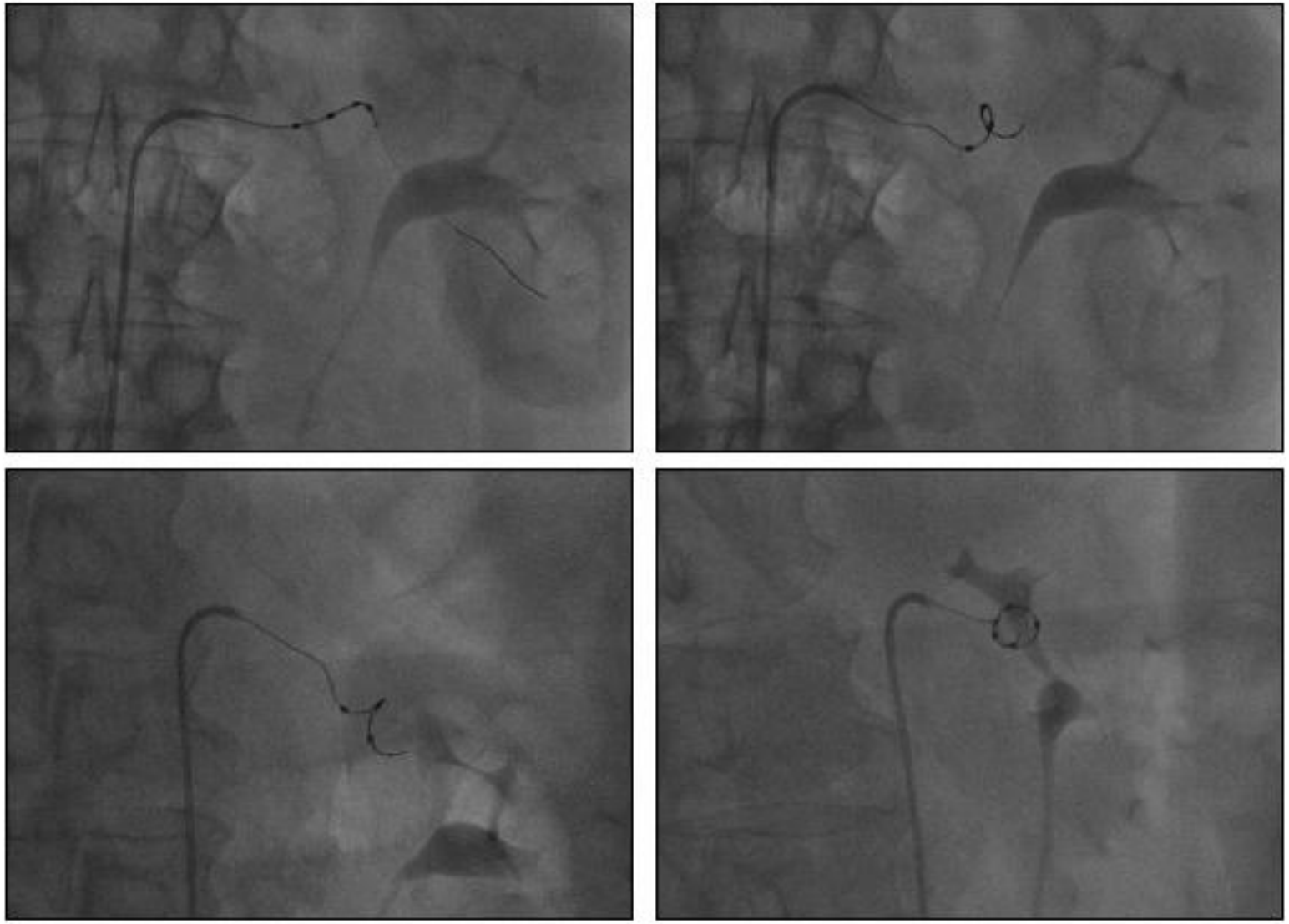
→ New Multi-Electrode System



Technology Comparison

Technology	Single Electrode	Multi-Electrode
Delivery Access	Direct	Monorail
Guide Catheter Compatability	6F	6F
No. of Electrodes	1	4
Electrode Selectability	1	4/ 3/ 2/ 1
No. of Placements/Artery	4-6	1
Energy Delivery Time per Placement	2 mins	1 min
Total Energy Delivery Time	16-24 mins	2 mins

→ Multi-Electrode System FIM

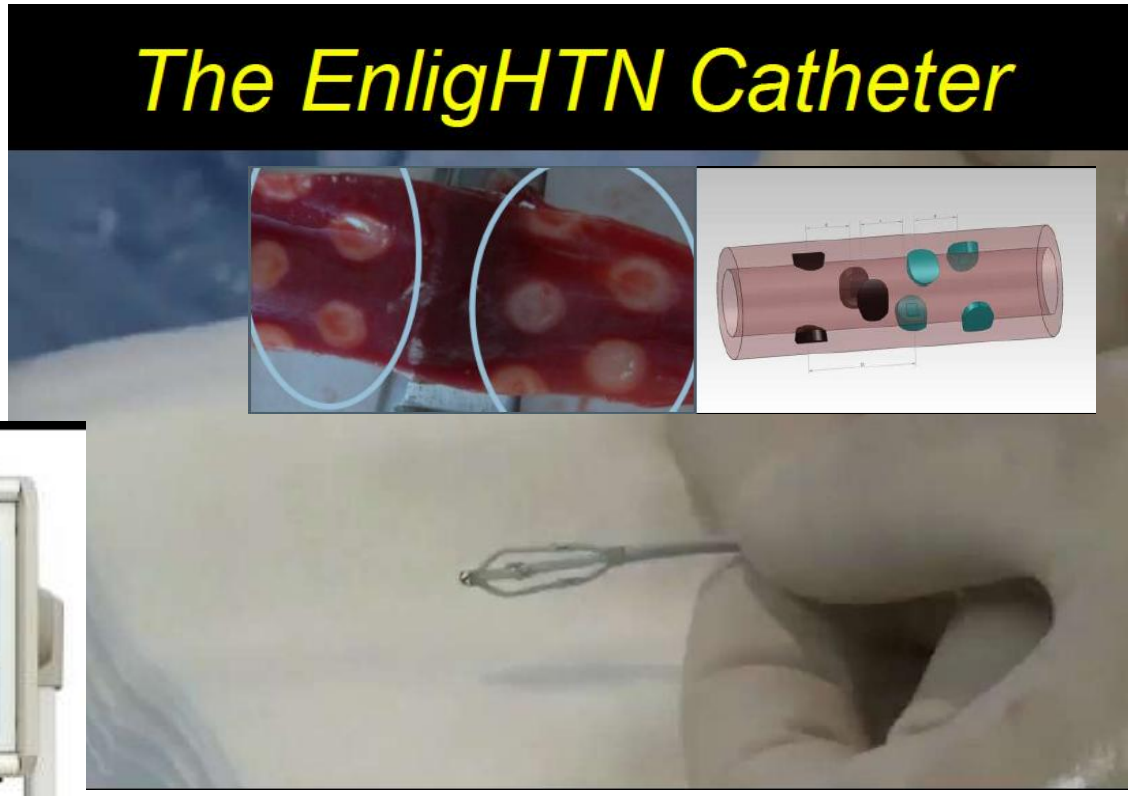


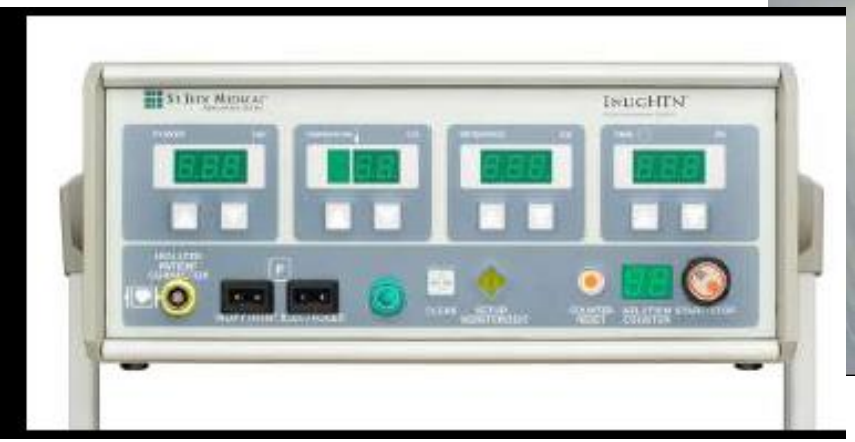
Me too Device or Real Innovation?

- RF based technologies Vessix One Shot , EnligHTN
- Local Delivery, guanetidine, Vincristine, Alcohol
- Ultrasound Energy
- Vascular Brachytherapy
- Baroreceptors stimulation
- Extenral high intensity ultrasound

The EnligHTN system St Jude

Basket-like structure with four “arms” each with built-in electrode which allow performance of the RND from a single position in the renal artery, an 8-fr renal double curve (RDC)-1 guiding catheter and a radiofrequency ablation generator available in two sizes to accommodate renal artery sizes of 4-6 mm (small basket) or 5.5-8 mm (large basket) delivered through an 8-fr system with the basket in a closed position



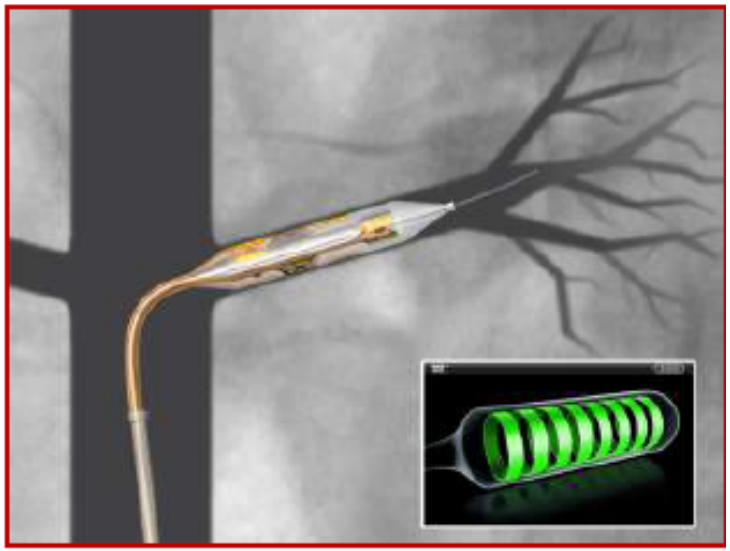


V^2 Renal Denervation System

Vessix Vascular (Laguna Hills, CA)

Over-the-wire inflatable balloon catheter

→ suitable for interventionalist with standard angioplasty skills



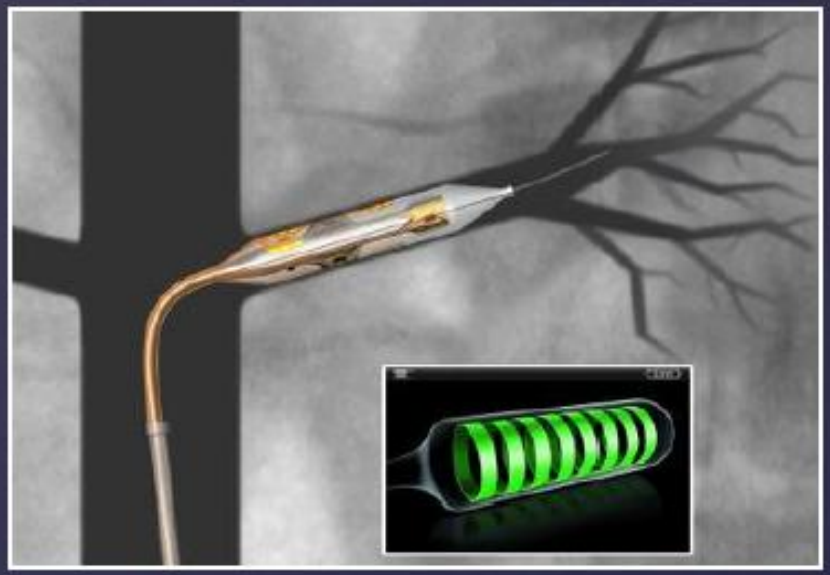
Balloon with mounted electrodes occludes artery

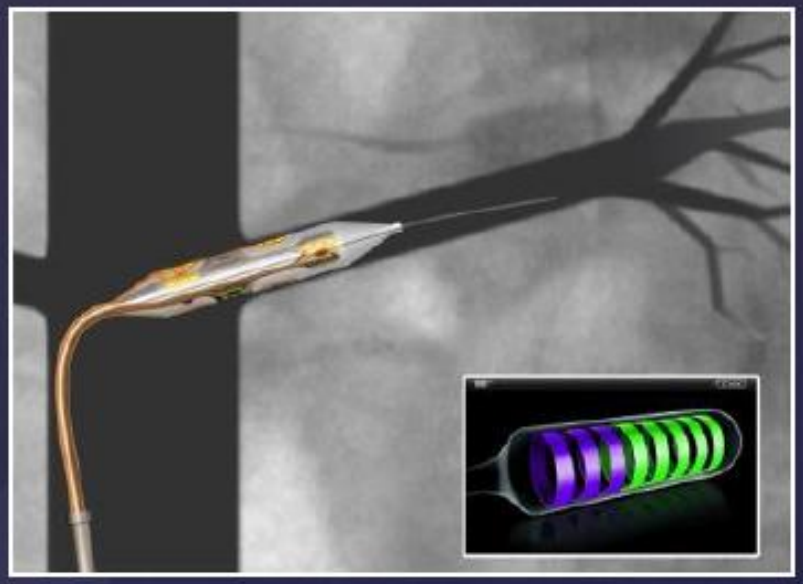
→ 1. no loss of heat energy into bloodstream
2. independent of blood flow / cooling

Short RF therapy time: 8 electrodes at the same time
only 30 seconds

→ 1. Short-lived/minimal pain for patient, less use of pain meds
2. Less exposure to radiation, contrast dye and lower renal toxicity

Vessix™ Occluding RF Balloon Catheter



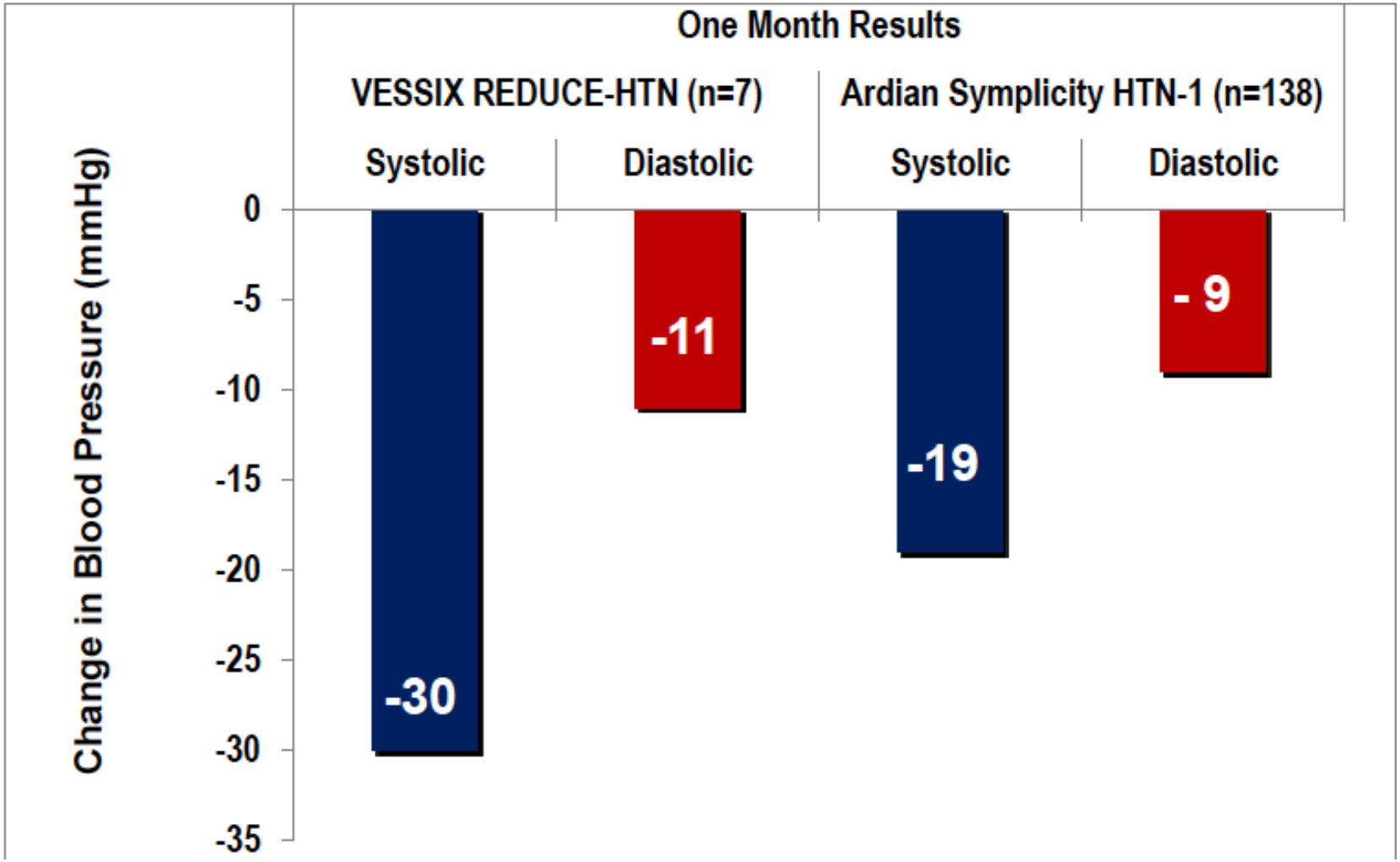


- RF treatment can be tailored to length of the artery landing zone
- Electrodes that are unapposed to vessel wall are automatically deactivated. For more moderate length arteries, 1.5 treatments can be applied
- For longer length renal arteries, 2 treatments (one distal, one proximal) can be applied

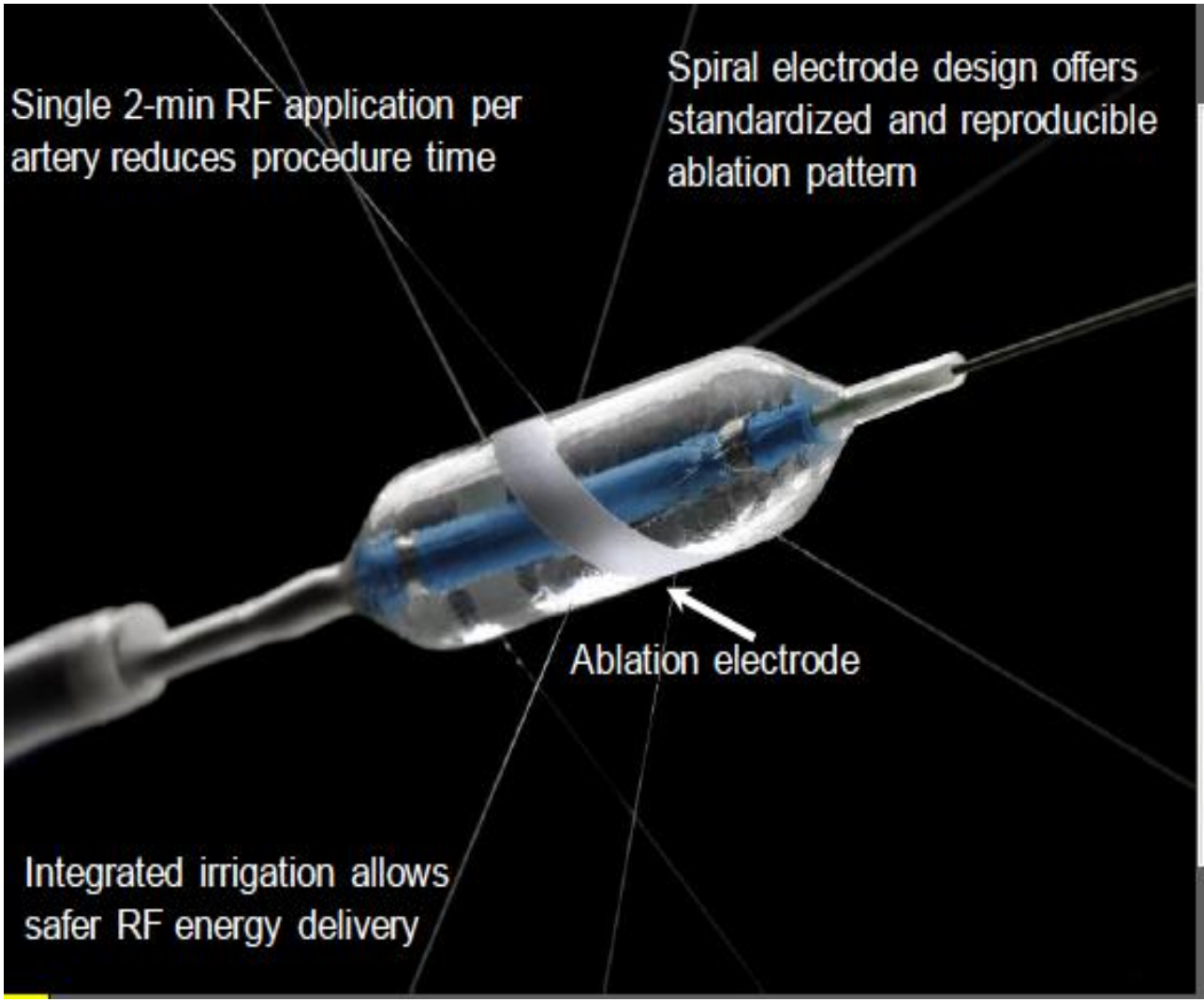
*The Vessix™ Renal Denervation System is not available for sale in the US.

RF=Radiofrequency

Comparison to Adrian at 1 Month



Covidien One Shot Balloon

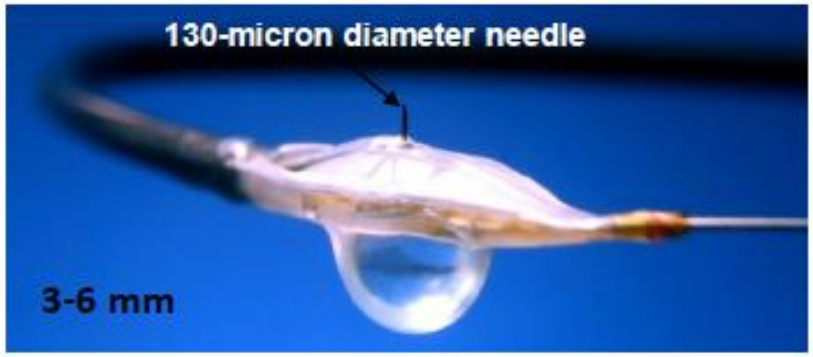


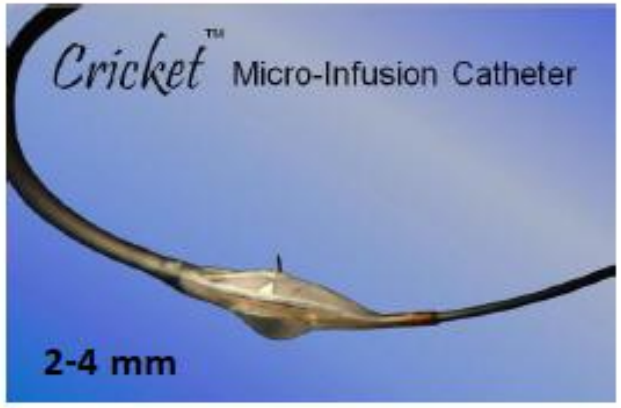

•6 Fr. Balloon Catheter
•One Size Fits All
•Non-compliant
•Low pressure
•Water-cooled

Mercator MedSystems

The Bullfrog and Cricket Microinfusion-Catheters

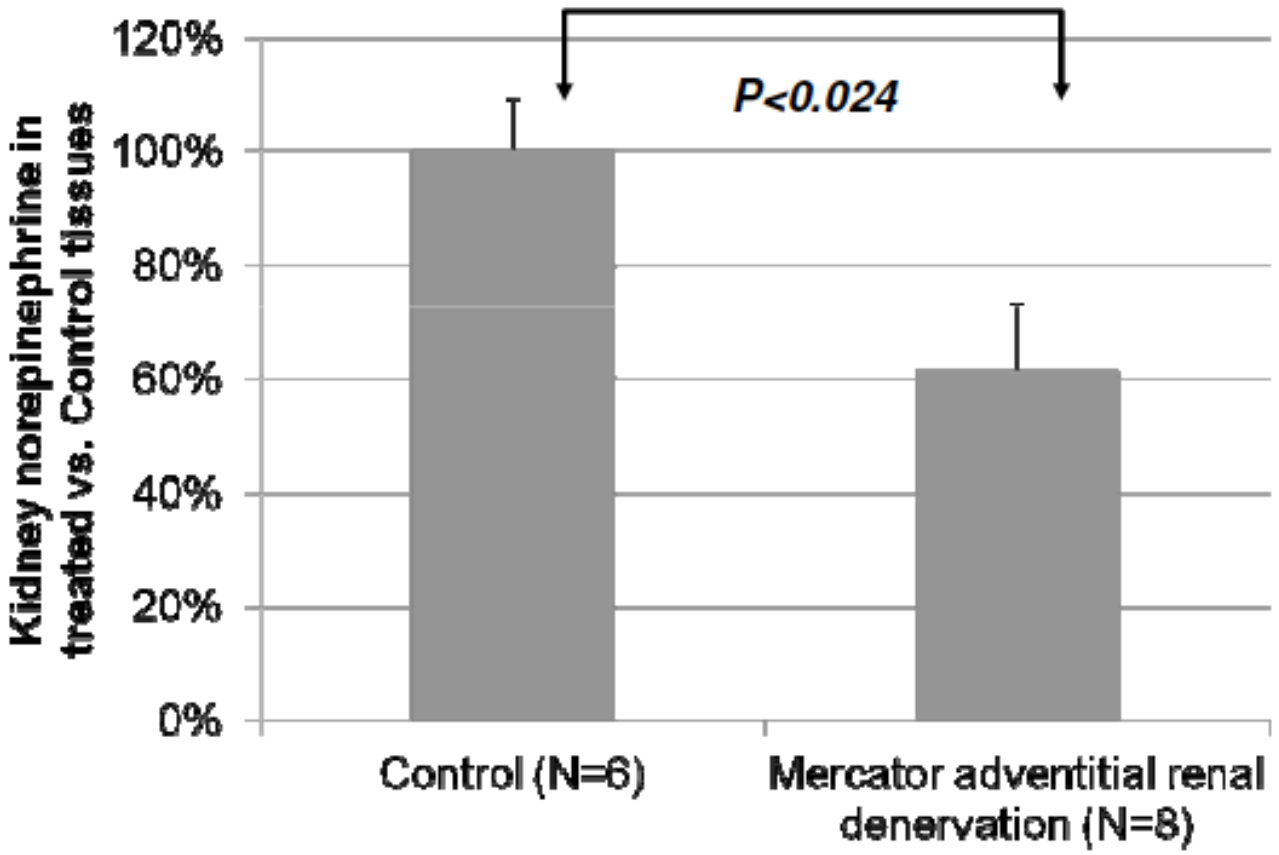
- No radiofrequency or ultrasound ablation
- Allows drug delivery to renal sympathetic nerve sheath
- Low pressure balloon (2 atm)
- Deploys a microneedle into the adventitia
- Catheters available for >2 mm arteries





Kirk P. Seward, Mercator MedSystems, TRenD 2011

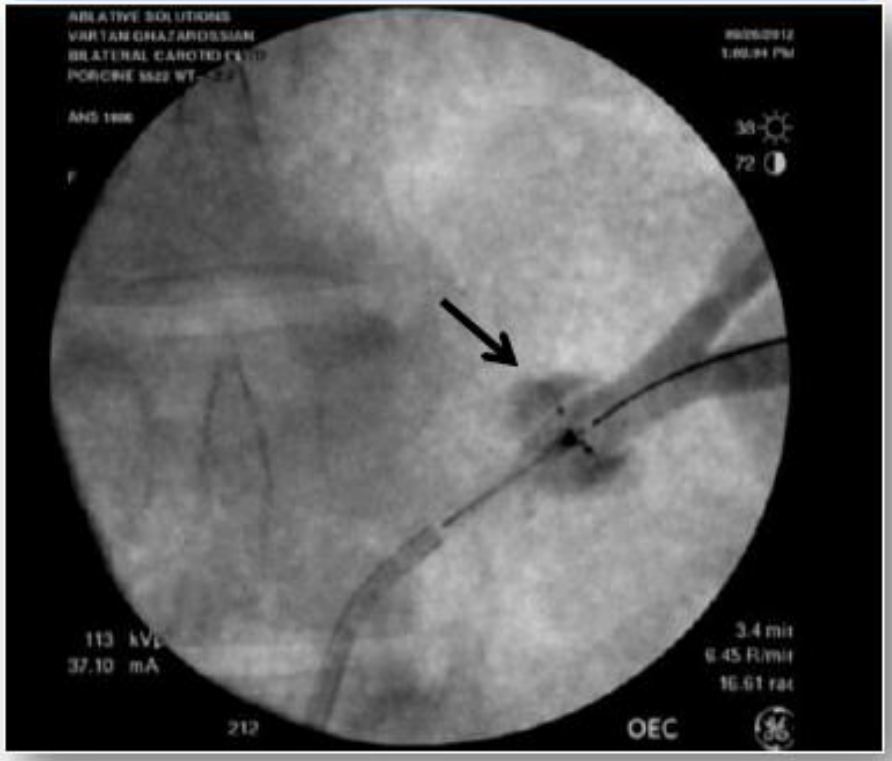
Guanethidine Preclinical Results
Norepinephrine reduction = denervation



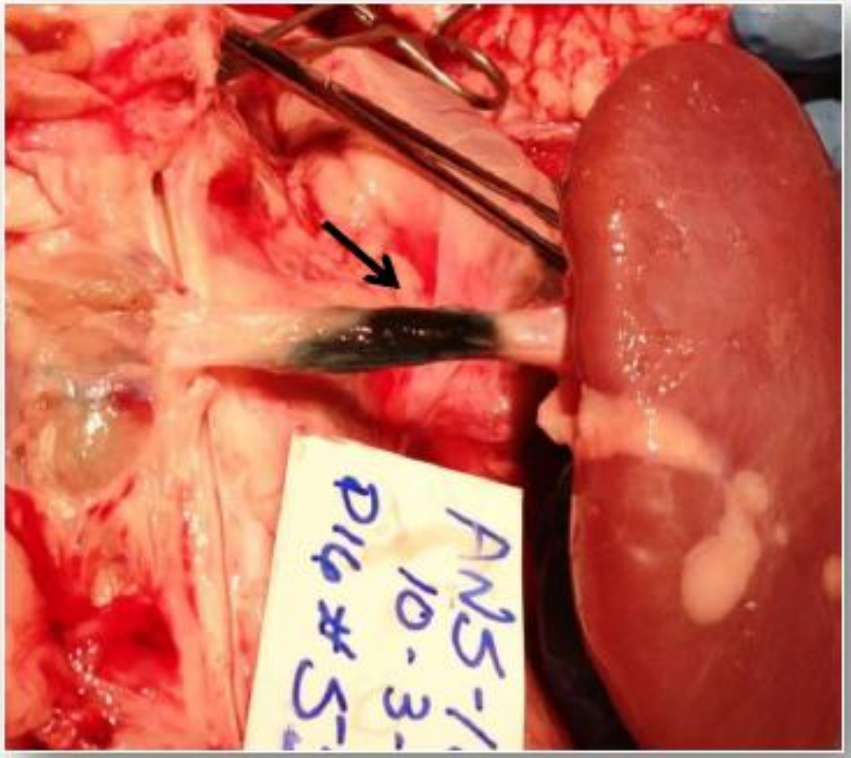
TCT 2010

Successful Perivascular and Circumferential Fluid Delivery

Contrast Delivery



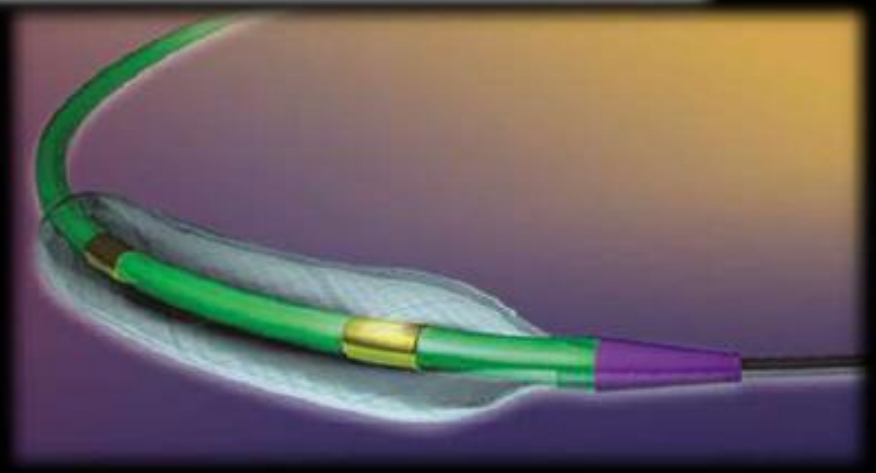
EtOH (+ Methylene Blue) Delivery



Results

Reproducible catheter centering, and perivascular, circumferential delivery

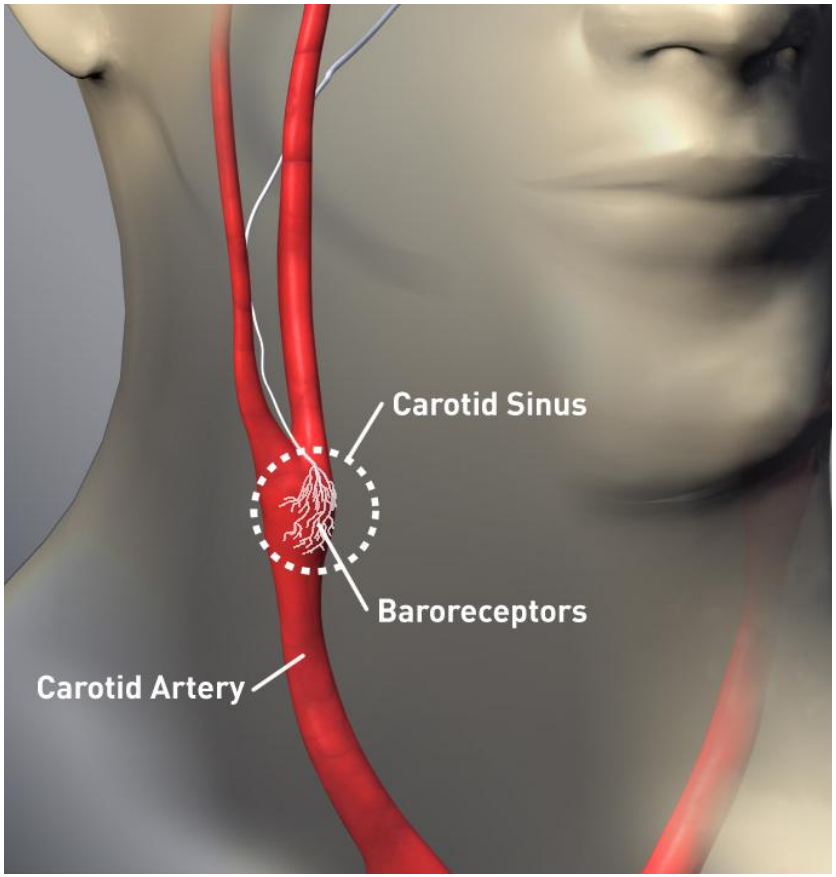
Vincristine via perfusion catheter

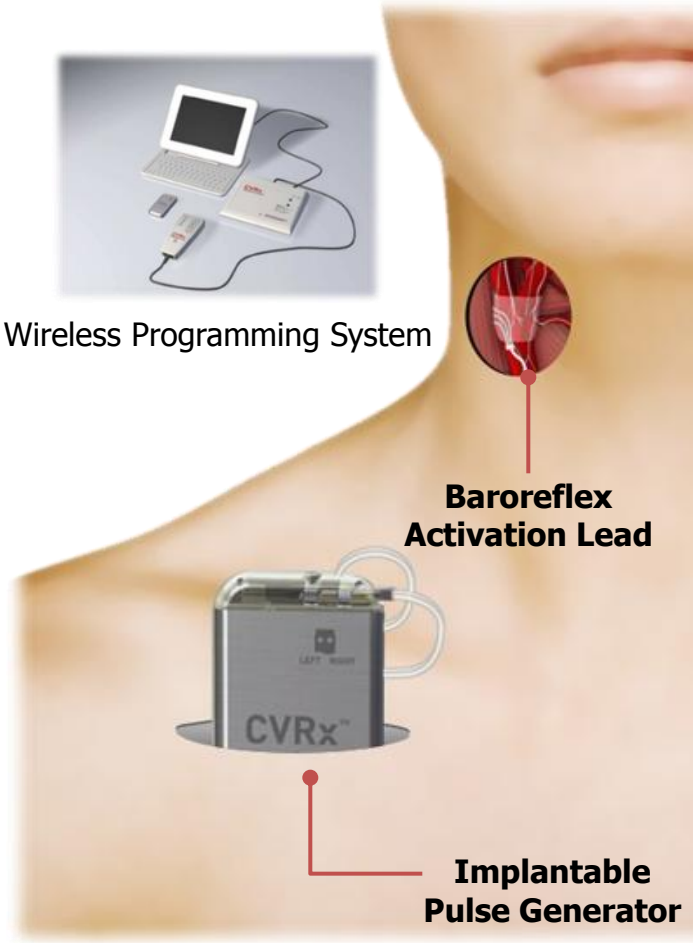


The catheter is a conventional balloon angioplasty catheter with ***6 side holes*** through which the drug is injected to the arterial wall under pressure.

C Stefanadis et al, Int J Cardiol. 2012 Jan 20. [Epub ahead of print]

Resistant Hypertension Treated with Baroreflex Activation

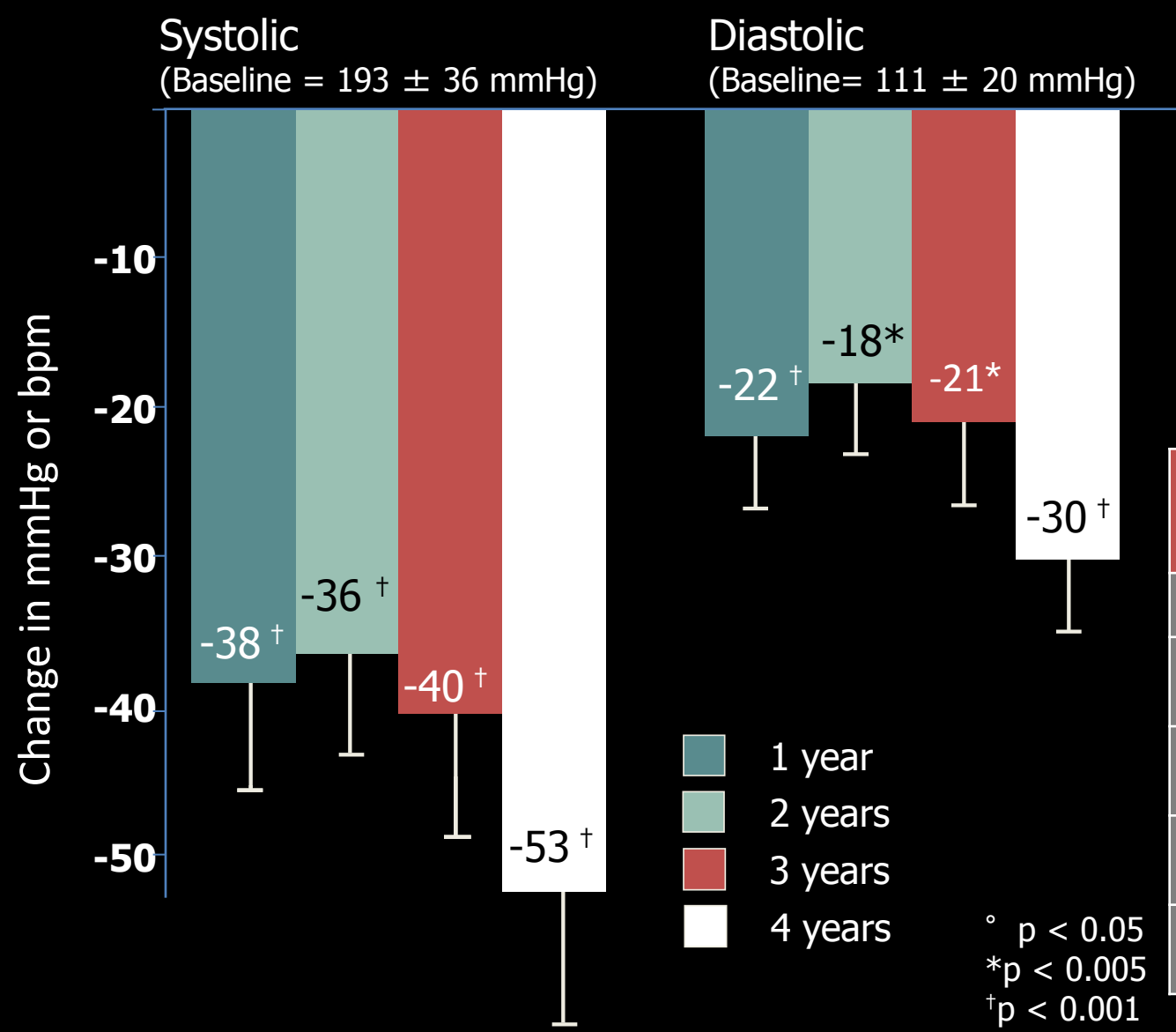




>400 patients treated worldwide, +5 years

CE Marked for the treatment of resistant hypertension

DEBuT 4-year Blood Pressure Reduction



Anti-hypertensive Medications	
Baseline	5.0 ± 1.3
1 year	-0.2 ± 0.3 *(p=0.51)*
2 years	-0.7 ± 0.4 *(p=0.14)*
3 years	-0.8 ± 0.4 *(p=0.06)*
4 years	-1.6 ± 0.5 *(p=0.02)*

(N=18)

Kroon et al, *Journal of Hypertension* 2010;28(e-suppl A):278

Vascular Dynamics

The Mobius

- Stent-like device for placement in the carotid sinus to enhance the baroreceptor reflex

Blood pressure rises

↓

Carotid arterial wall stretches

↓

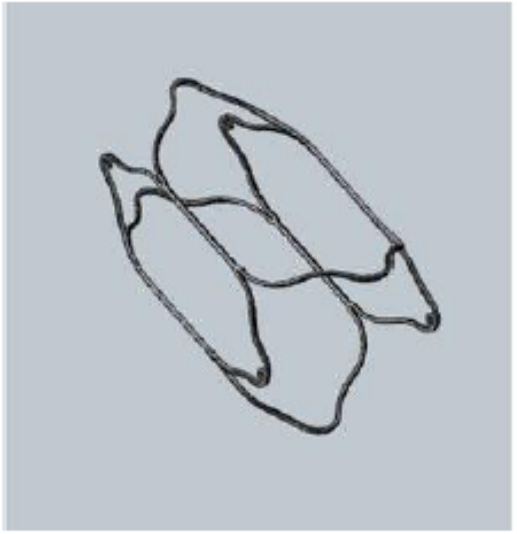
Baroreceptor cells activated

↓

Downregulation of the sympathetic drive

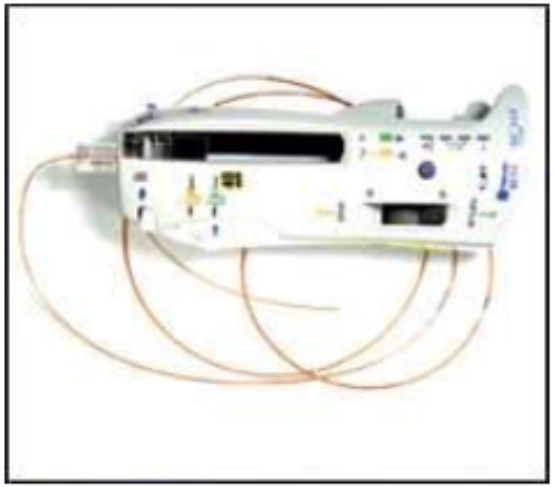
↓

Drop in blood pressure



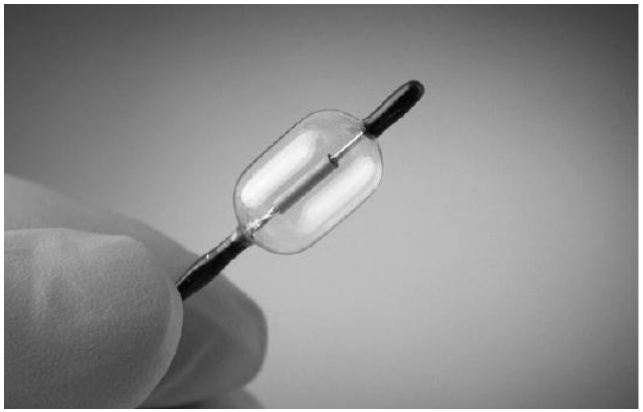
A novel approach for renal denervation by β-radiation using Beta-Cath™ 3.5F System (*Novoste*)

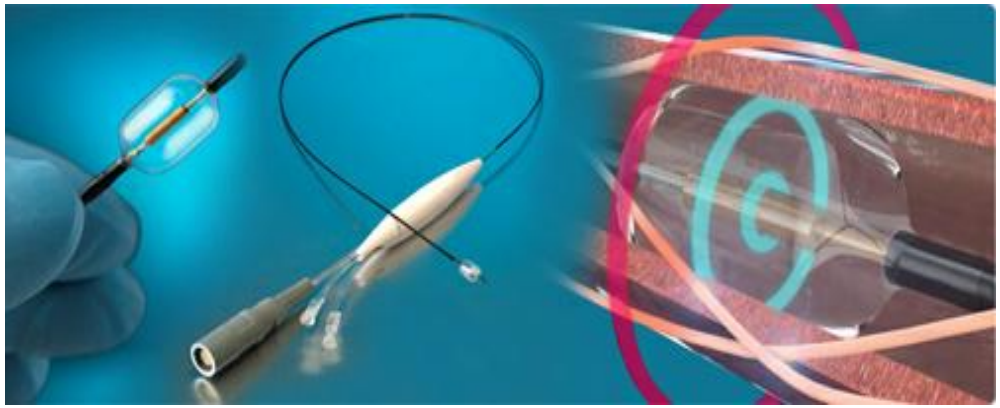
- Potential "sparing" of endothelial injury
- Localized effect
- Small sheath size
- Short procedure time
- 5-8 minutes per artery



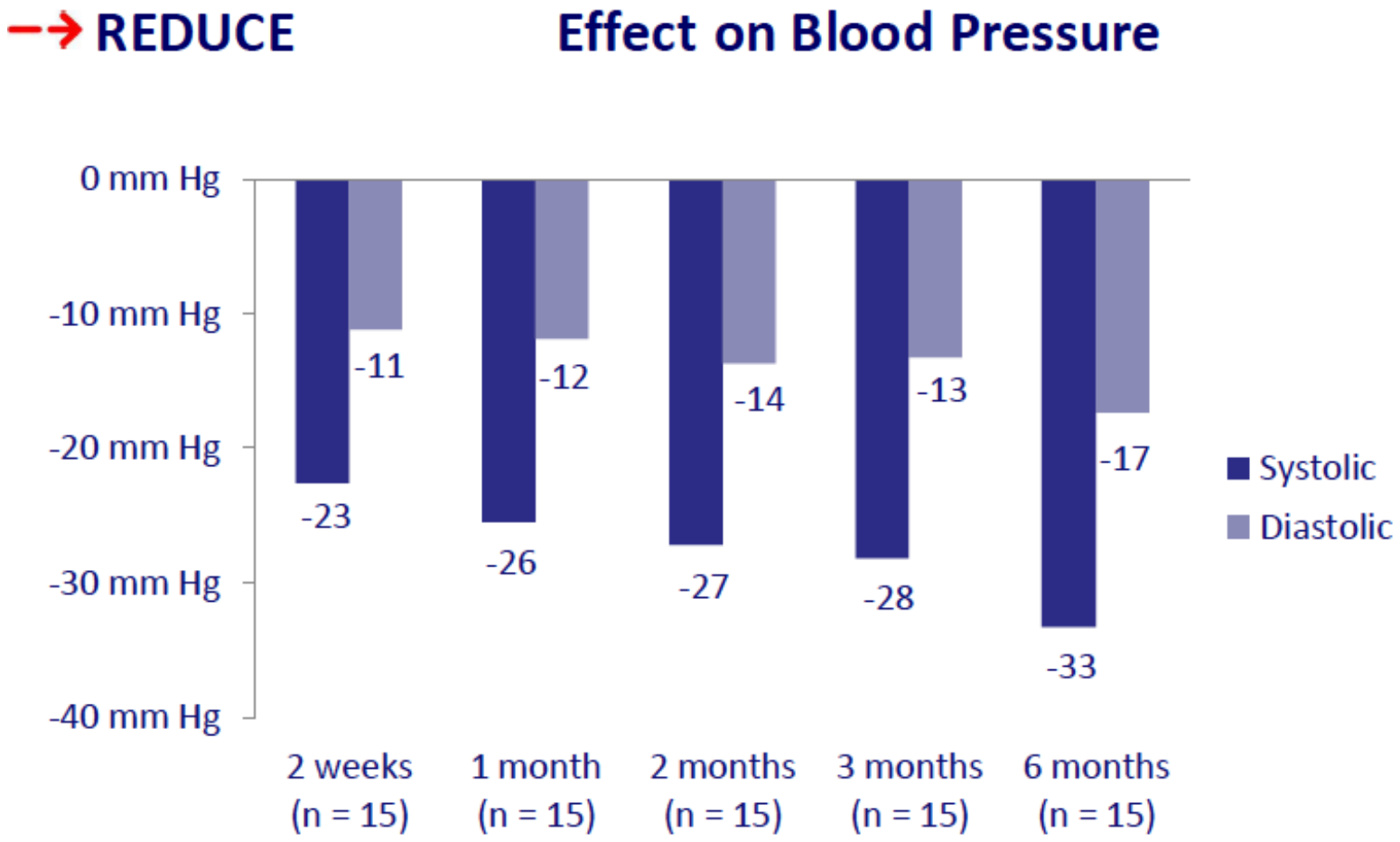
ReCor Medical Paradize

- ReCor Medical (Ronkonkoma, NY) Percutaneous Renal Denervation System (PARADISE™) is based on delivery of high ultrasonic energy to induce nerve tissue injury.
- The PARADISE system is composed of two components; a 6 French-compatible balloon catheter with a cylindrical ultrasound transducer that emits ultrasound energy circumferentially and a portable generator which controls automated balloon inflation and deflation and energy delivery





ReCor First in Man Trial



TIVUS™ System

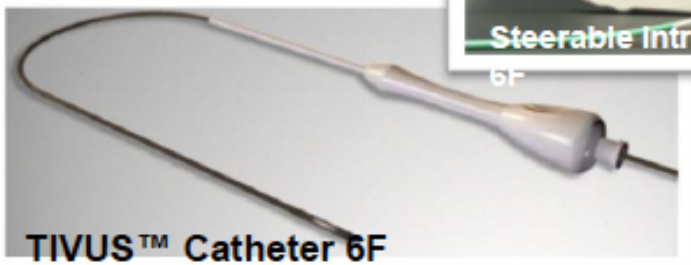
Technology

- High-intensity, ultrasonic catheter (0.014" OTW)
- Remote, localized, and controlled thermal renal denervation
- Real time ultrasonic feedback ensuring safety

Procedural Advantages

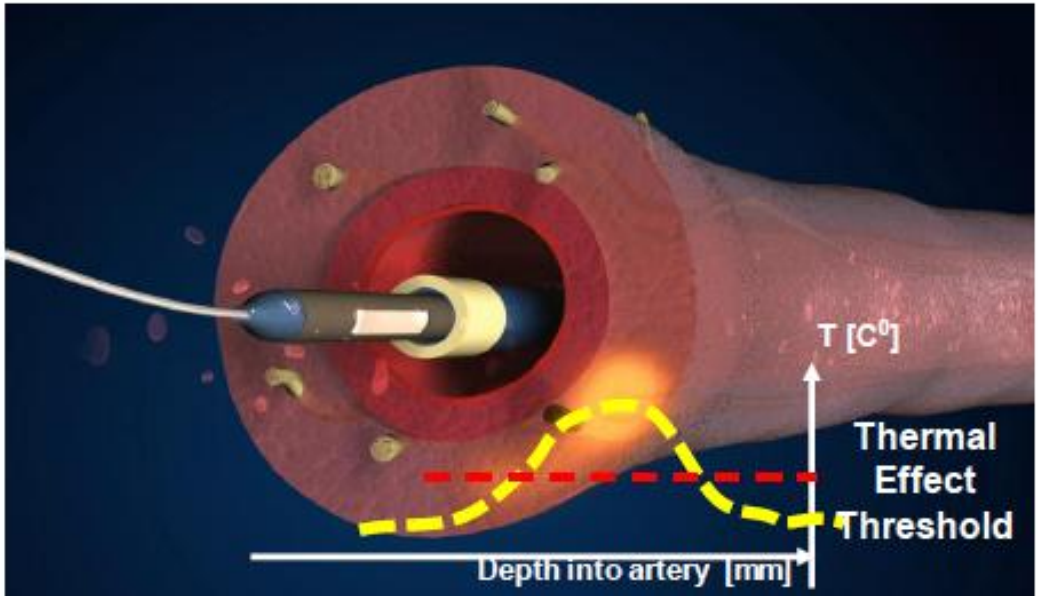
- Short excitation duration (30 seconds per treatment point)
- Simple positioning and navigation with online positioning safety feedback
- Allows treatment of short, small & narrow renal arteries
- Control of denervation level through treatment parameters
- Avoids vessel contact, no occlusion or flow reduction, endothelium sparing, 0.014" wire in place


Steerable TIVUS™ Catheter, 6F


TIVUS™ Catheter 6F

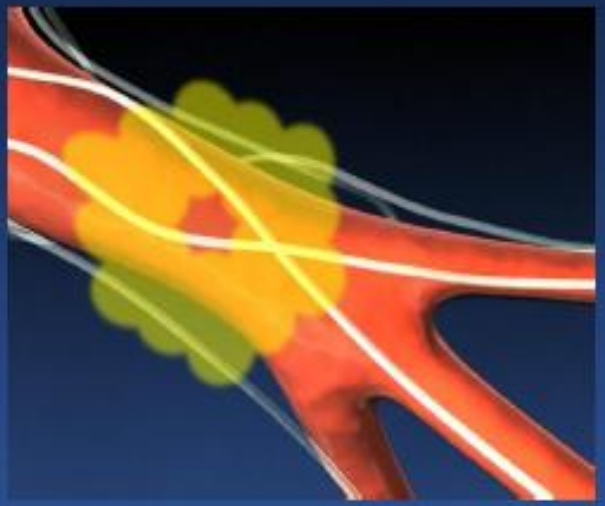

Steerable Introducer
6F

Core Technology:
Non-Focused High Intensity Ultrasonic Catheter

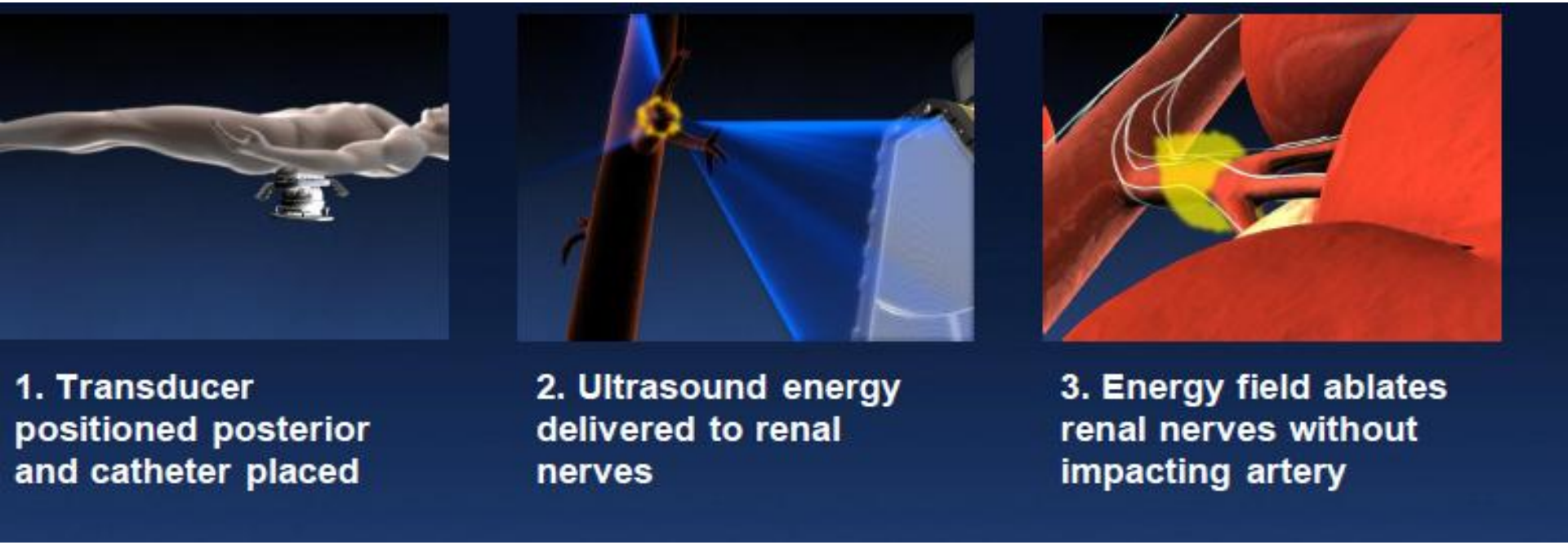


Surround Sound™ Ablative Field

- Shape of ultrasound energy field designed to provide coverage of renal nerves
- Safely ablates nerves without impacting artery or surrounding tissues


External Ultrasound



Innovation Never stops
But New is Not Necessarily Better