INSTITUT CARDIOVASCULAIRE PARIS SUD

INSTITUT CARDIO-VASCULAIRE
LA ROSERAIE

Dénervation Rénale Technique et Résultats Cliniques

Hakim Benamer

ICPS Massy, ICGallien Quincy
ICV-GVM la Roseraie

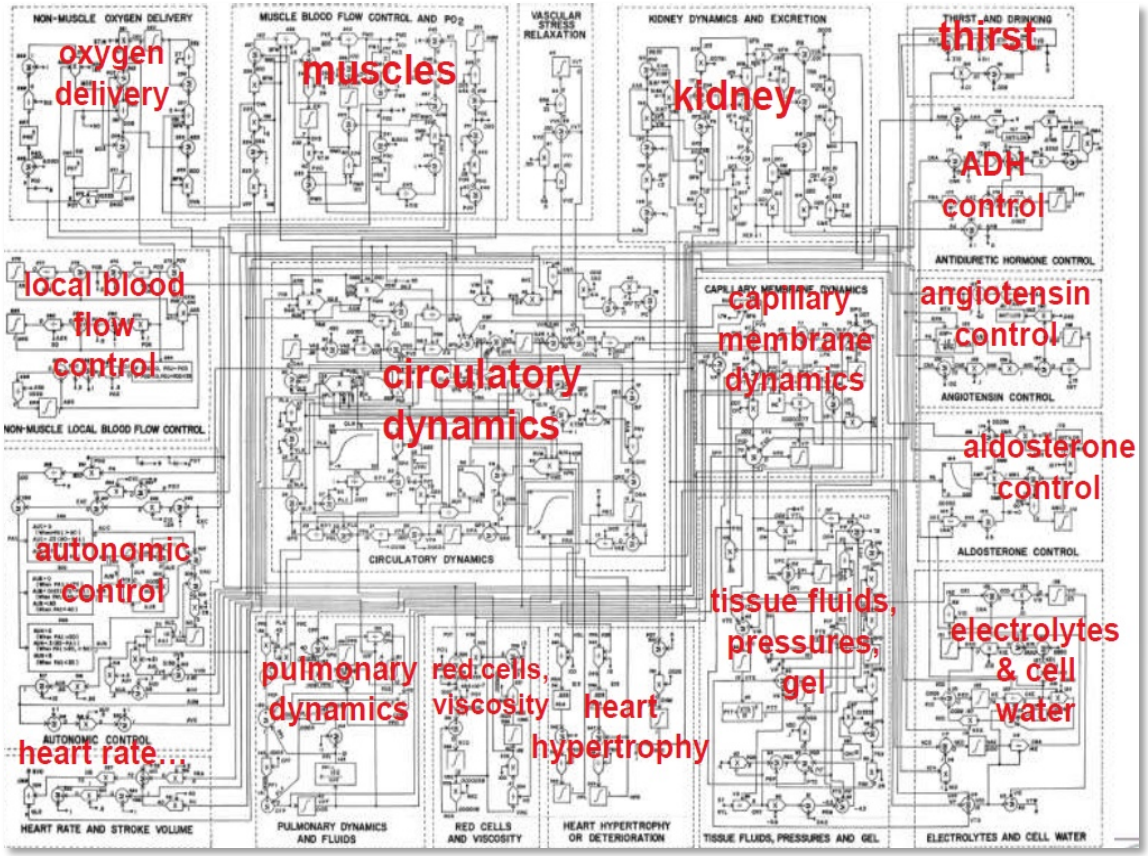
www.icps.com.fr

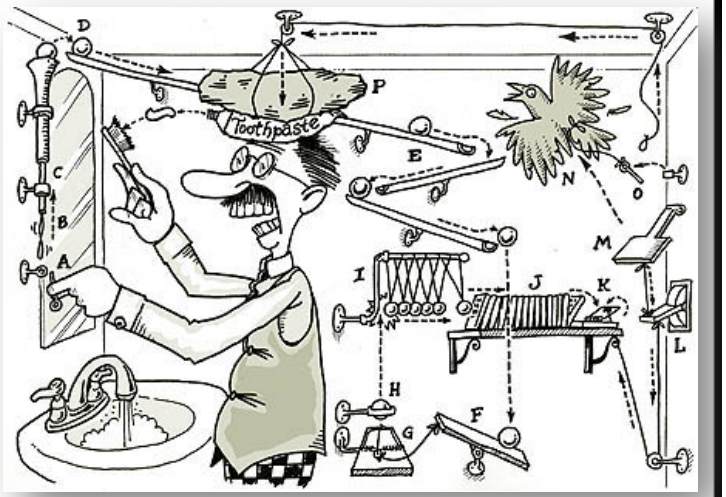
GRUPPO VILLA MARIA

GÉNÉRALE DE SANTÉ

SAPHIR:

"a Systems Approach for Physiological Integration of Renal, Cardiac, and Respiratory Functions"

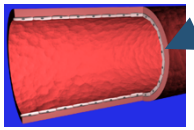




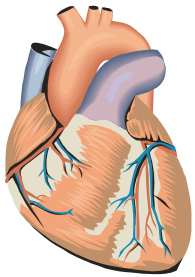
Guyton, Coleman, Granger (1972) *Ann. Rev. Physiol.*

Renal Sympathetic Nerve Activity:

Kidney as Origin & Recipient of Central Sympathetic Drive



- Vasoconstriction
- Atherosclerosis



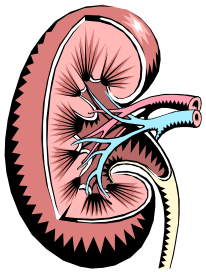
- ↑ Contractility
- ↑ Heart rate
- Hypertrophy
- Arrhythmia
- Heart Failure

Efferent Nerves

Afferent Nerves

Blood Pressure

+ Increase co-morbidities



↑ Renin Release → RAAS activation

↑ Sodium Retention

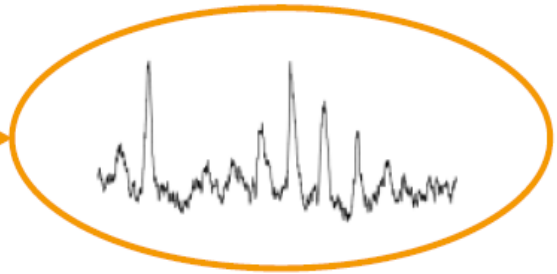
↓ Renal Blood Flow

↓ Kidney function

Schlaich et al. Hypertension. 2009;54(6):1195-1201

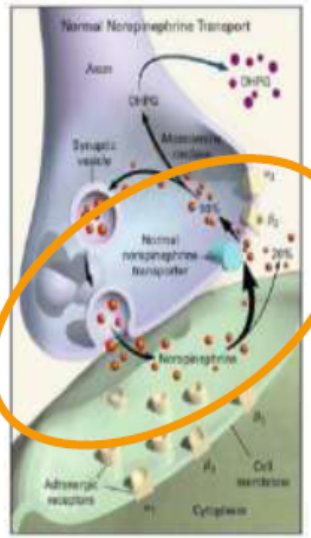
Measuring Central Sympathetic Drive

Central Sympathetic Nerve Activity



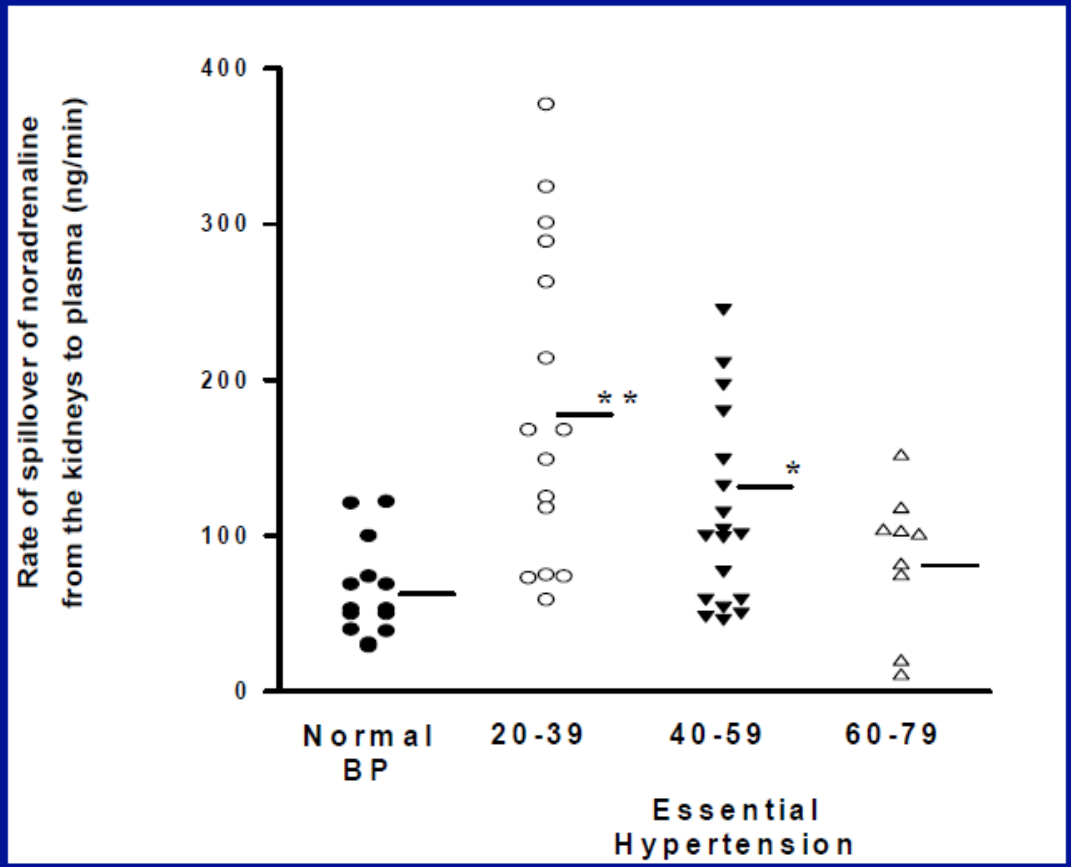
Muscle Sympathetic Nerve Activity (MSNA)

Renal Sympathetic Nerve Activity



Norepinephrine Spillover

"Activation of the Renal Sympathetic Nerves in Patients with Essential Hypertension"



M Esler, G Lambert, G Jennings
J Hypertension **1990; 8: S53-S57 (Updated)**

Concept Validated by Surgical History

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

THE BRITISH JOURNAL OF SURGERY

1952

SYMPATHECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT HYPERTENSION*

A REVIEW OF 76 PATIENTS

By C. J. LONGLAND and W. E. GIBB

THE JOURNAL

of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 152, NO. 16 — CHICAGO, ILLINOIS — AUGUST 15, 1953

SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

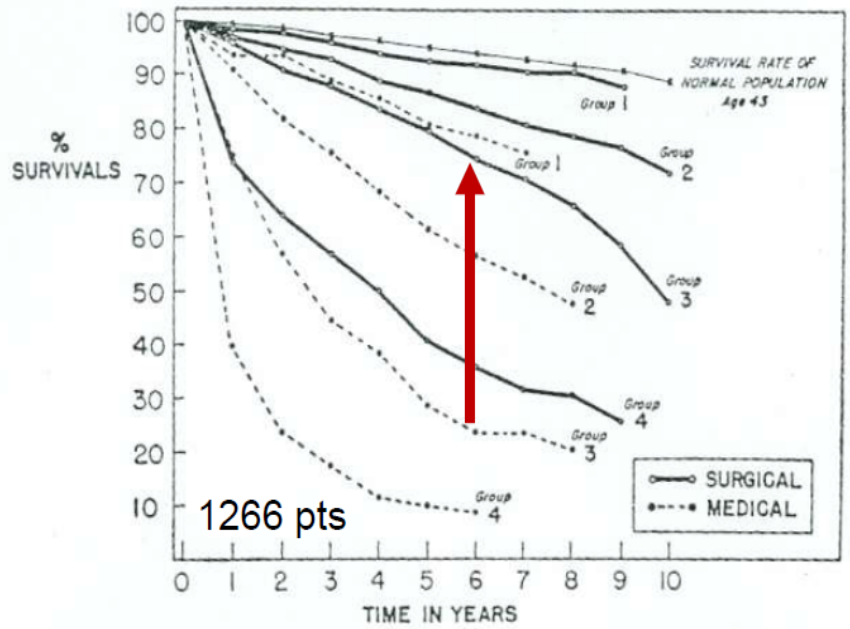
RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

Dr. Reginald H. Smithwick

Effective, but significant morbidity

Sympathectomy in Hypertension:
Effects on Survival, but Morbidity

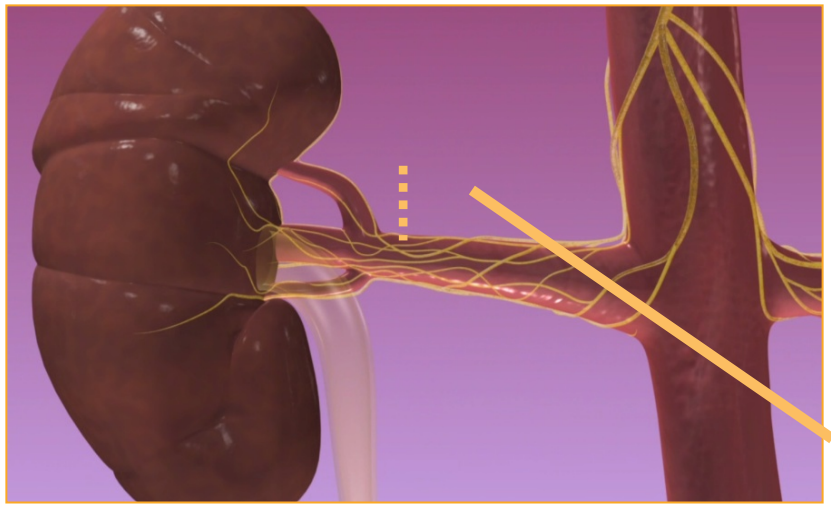


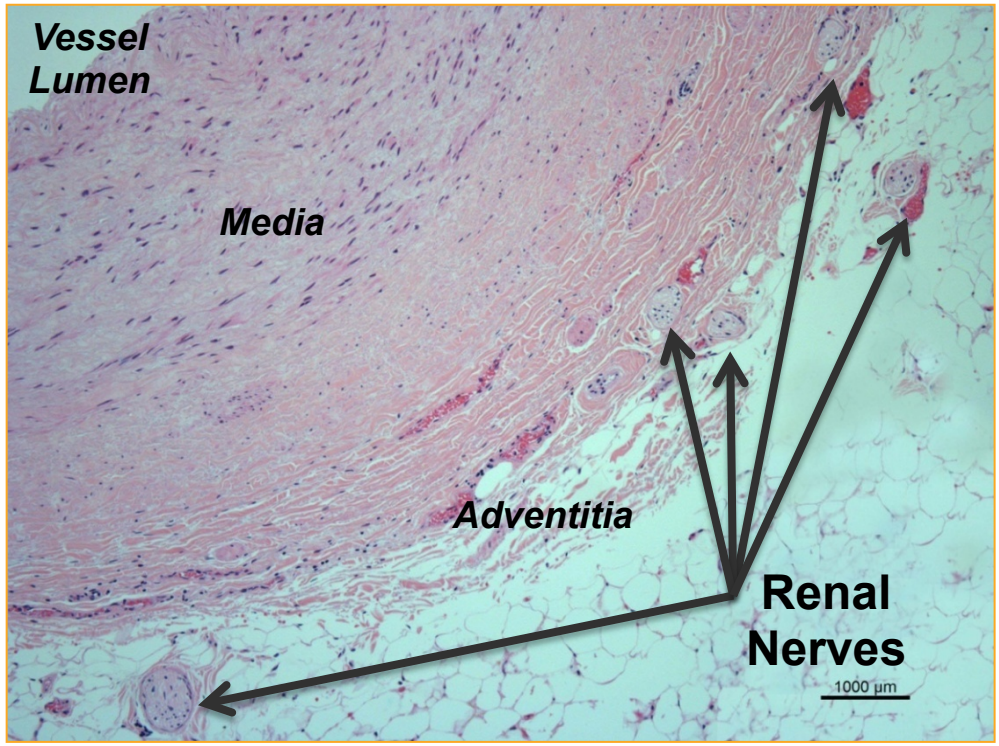
Denervating lower half of the body produced:

- **Mortality benefit**
- **Inconsistent BP results**
- **Significant morbidity including orthostatic hypotension, bowel & bladder dysfunction**

Smithwick RH, *J Am Med Assoc.* 1953;152:1501-1504

Renal Anatomy Allows a Catheter-Based Approach

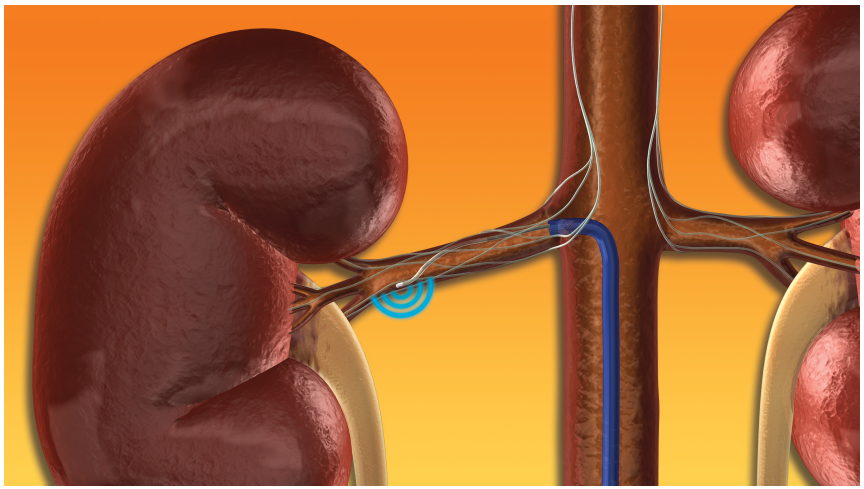


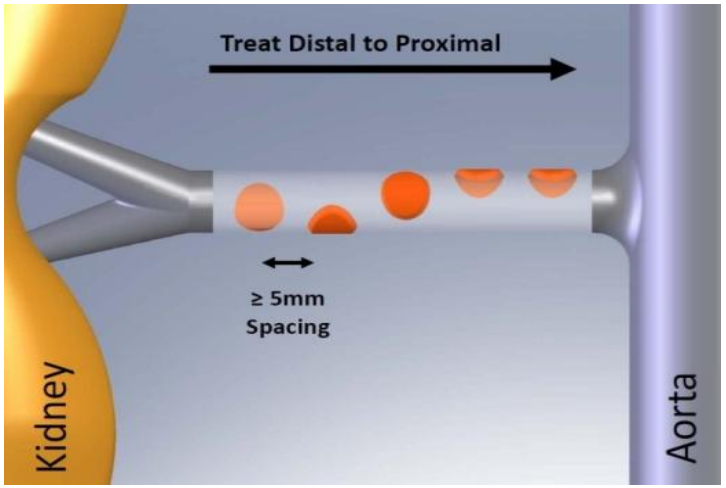


Renal Nerves

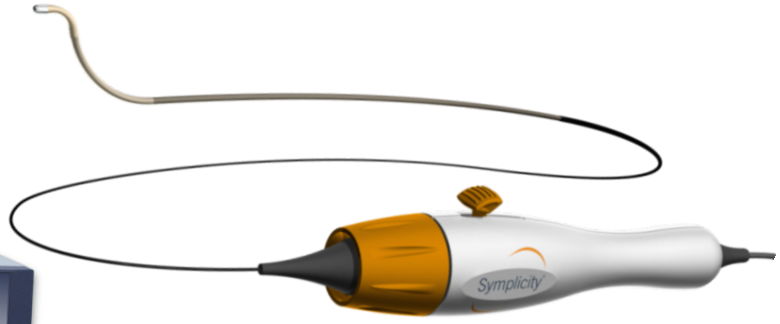
- Arise from D10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
- The only location that renal efferent & afferent nerves travel together

Symplicity Catheter System

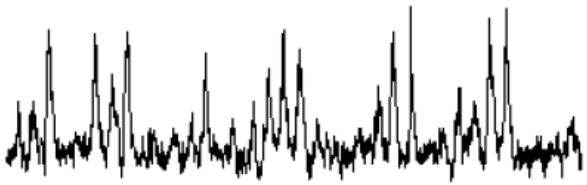




- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms



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.

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Initial Cohort – Reported in the *Lancet*, 2009:

- First-in-man, non-randomized
- Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)
- 12-month data

Expanded Cohort – This Report (Symplicity HTN-1):

- Expanded cohort of patients (n=153)
- 24-month follow-up

Lancet. 2009;373:1275-1281

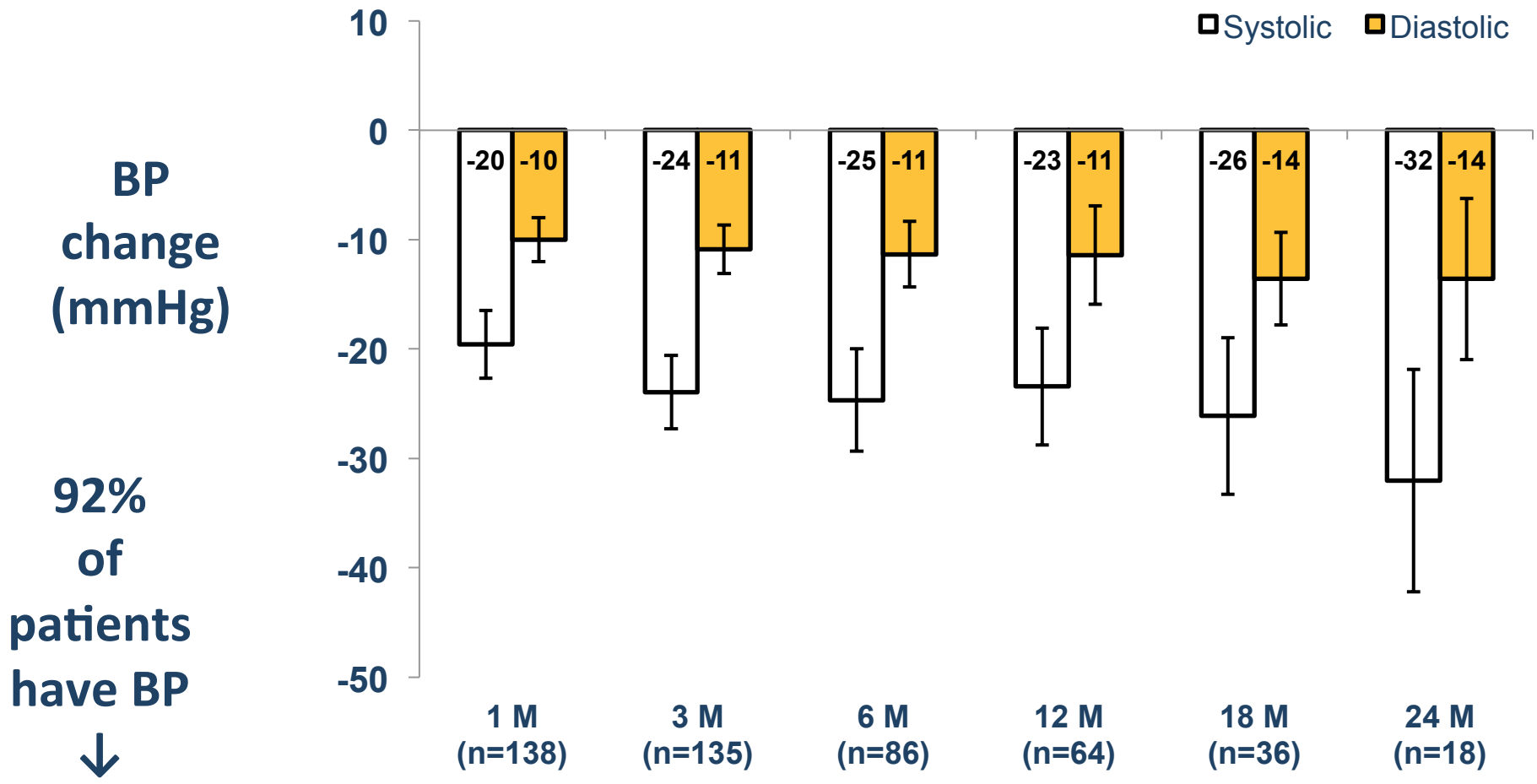
Baseline Patient Characteristics

Demographics	Age (years)	57 ± 11
	Gender (% female)	39%
	Race (% non-Caucasian)	5%
Co-morbidities	Diabetes Mellitus II (%)	31%
	CAD (%)	22%
	Hyperlipidemia (%)	68%
	eGFR (mL/min/1.73m^2)	83 ± 20
Blood Pressure	**Baseline BP (mmHg)**	**176/98 ± 17/15**
	Number of anti-HTN meds (mean)	**5.0 ± 1.4**
	ACE/ARB (%)	90%
	Beta-blocker (%)	82%
	Calcium channel blocker (%)	75%
	Vasodilator (%)	19%
	Diuretic (%)	95%
	Spironolactone (%)	21%

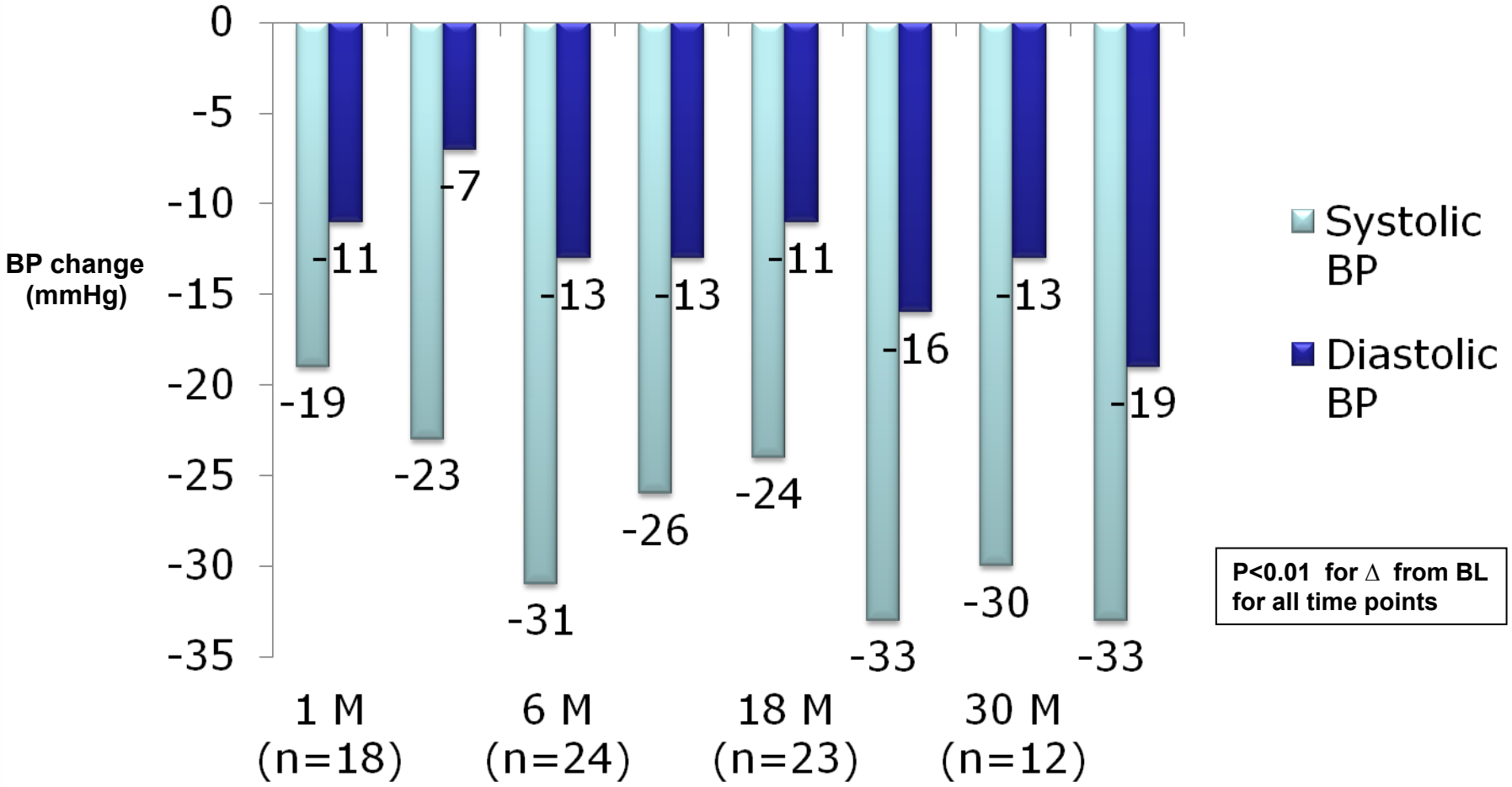
Procedure Detail & Safety

- Bilateral treatment; average of 4 ablations per artery
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- 38 minute median procedure time
- No device malfunctions
- No major complications
- Minor complications 4/153:
  - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  - 3 access site complications, treated without further sequelae

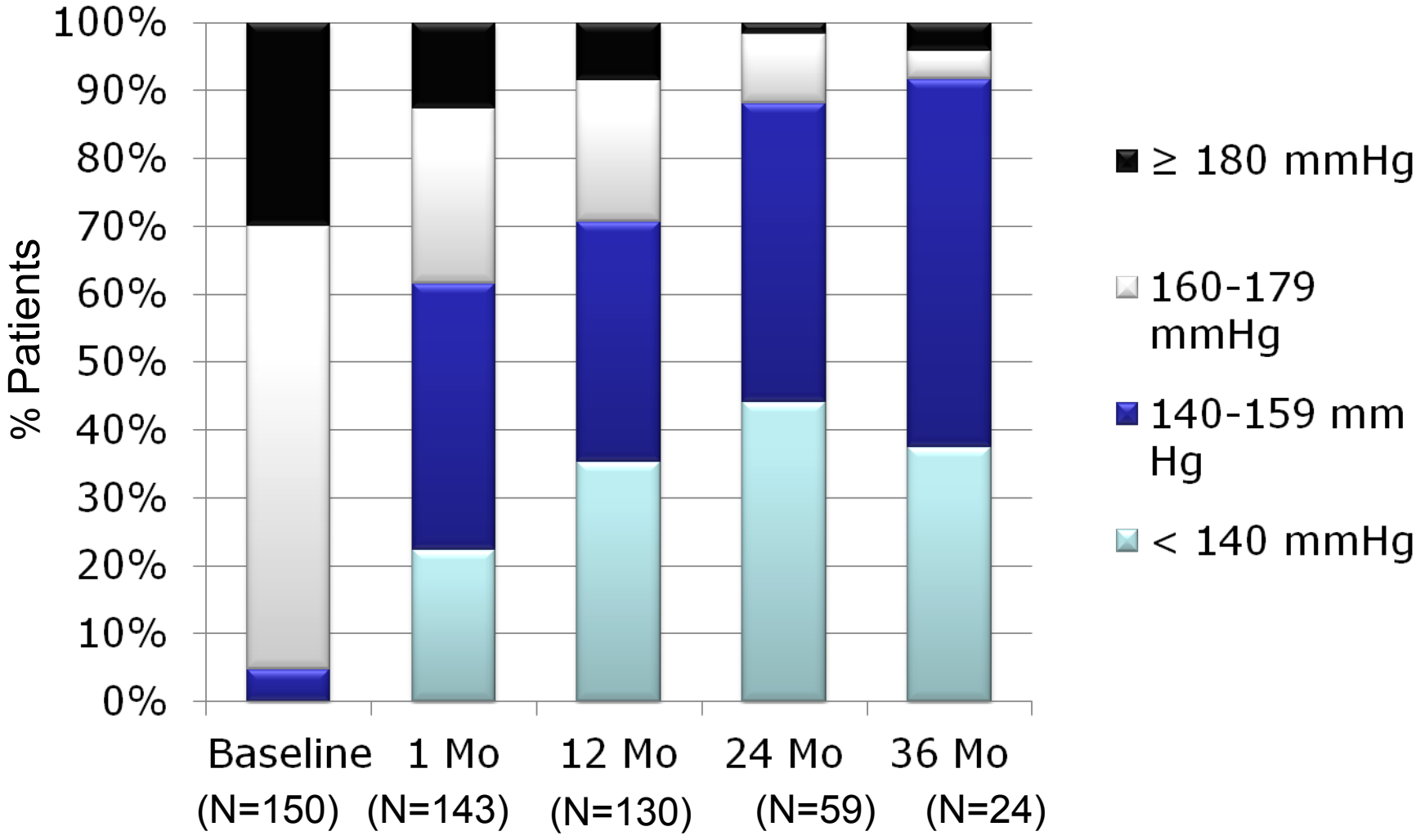
Treated Patients
Significant, Sustained BP Response



Change in Office Blood Pressure for 24 Patients with 36 Month Follow-up



Distribution of SBP Change at BL, 1, 12, 24, and 36 Months



Chronic Safety

- 81 patients with 6-month renal CTA, MRA, or Duplex evaluation

- One progression of a pre-existing renal artery stenosis
  - » not at a site of RF delivery
  - » possibly related to catheter manipulation
  - » successfully stented

- No change in renal function (Δ eGFR)
  - 12 Months: -2.9 mL/min/1.73m^2 (n.s.)

- No orthostatic or electrolyte disturbances

- Two deaths within the follow-up period; both unrelated to the device or therapy

Symplicity HTN-2

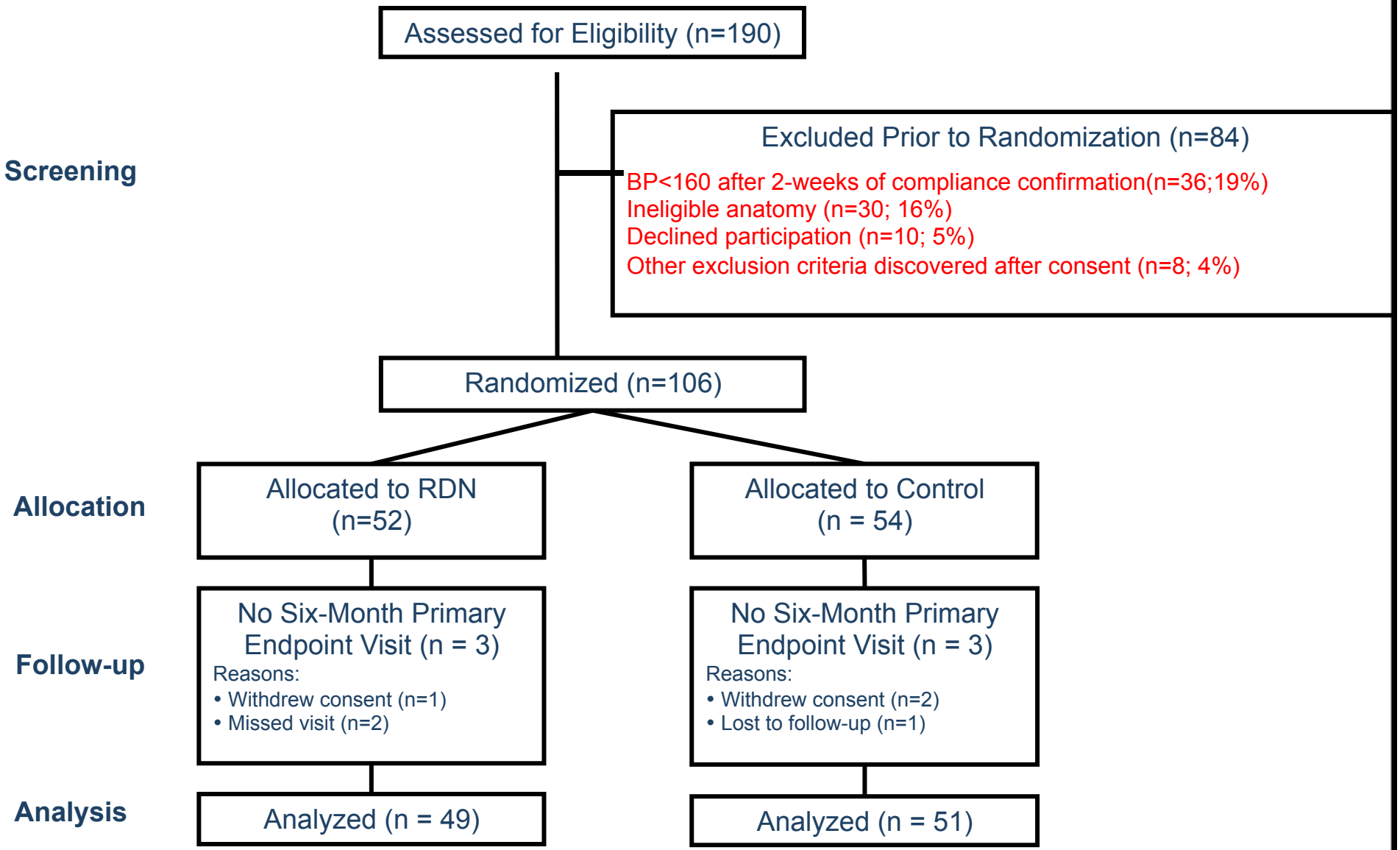
Inclusion Criteria:

- Office SBP ≥ 160 mmHg (≥ 150 mmHg with type II diabetes mellitus)
- Stable drug regimen of 3+ more anti-HTN medications
- Age 18-85 years

Exclusion Criteria:

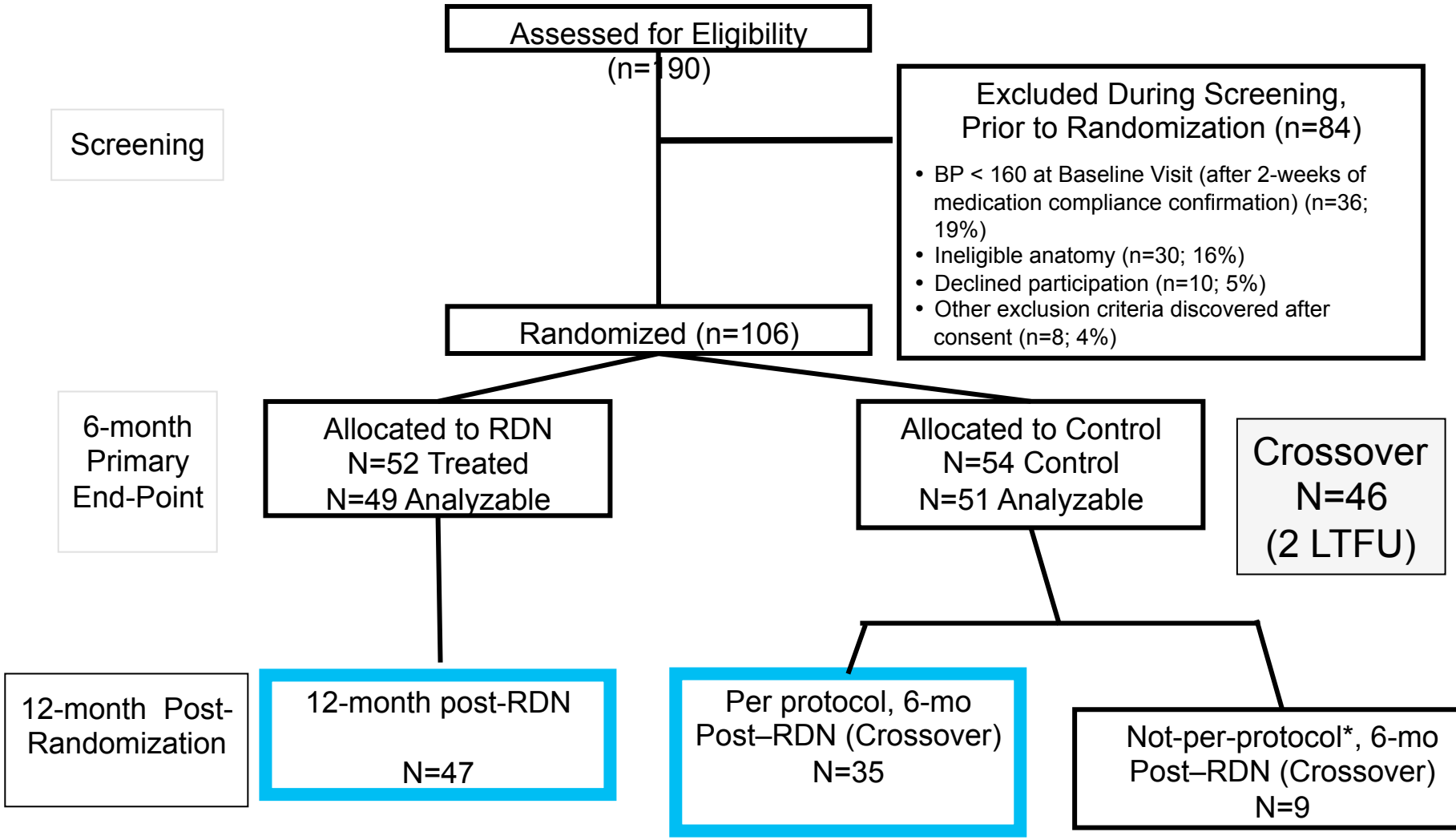
- Hemodynamically or anatomically significant renal artery abnormalities or prior renal artery intervention
- eGFR < 45 mL/min/1.73m^2 (MDRD formula)
- Type 1 diabetes mellitus
- Contraindication to MRI
- Stenotic valvular heart disease for which reduction of BP would be hazardous
- MI, unstable angina, or CVA in the prior 6 months

Symplicity HTN-2 Investigators. The Lancet. 2010.

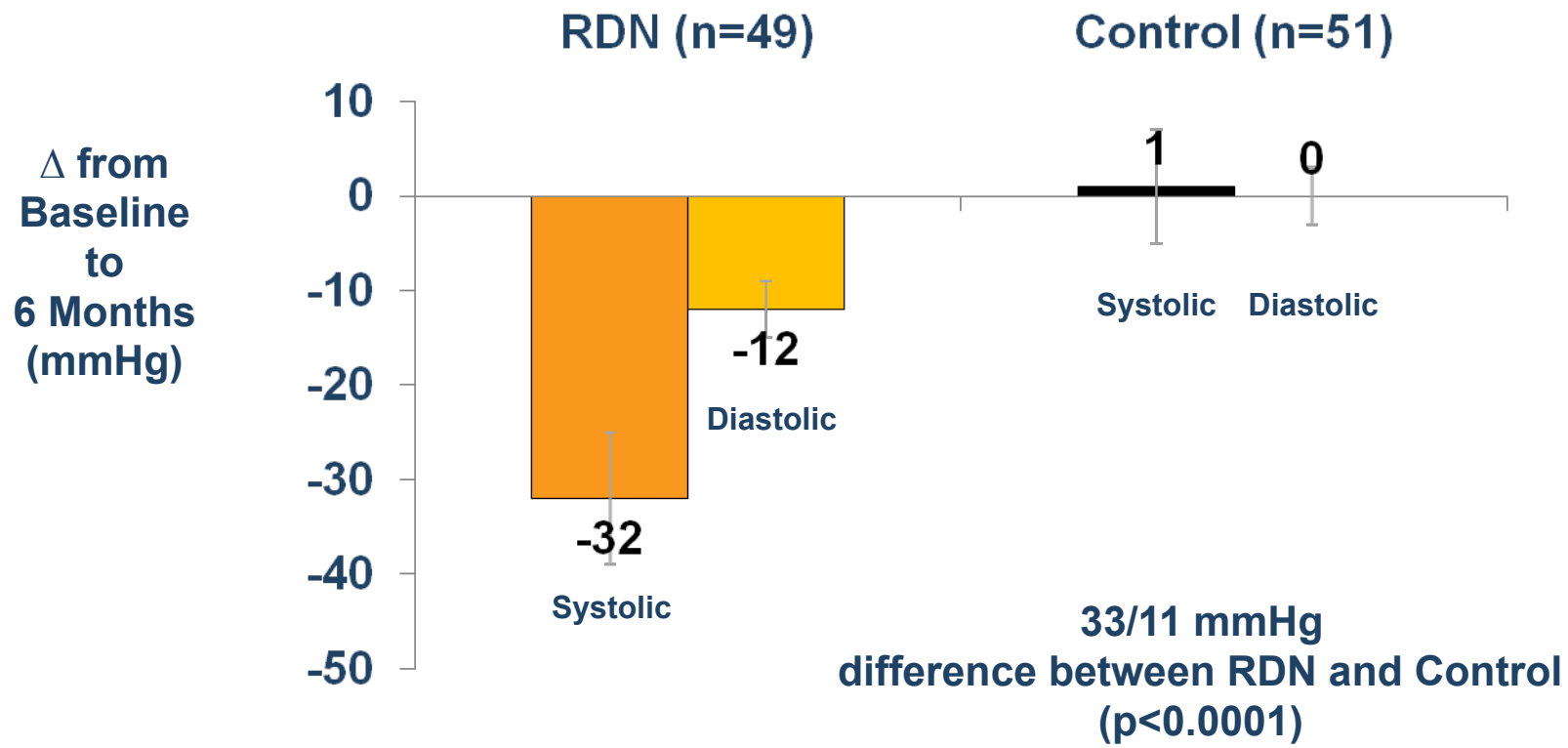


Symplicity HTN-2 Investigators. The Lancet. 2010.

Patient Disposition



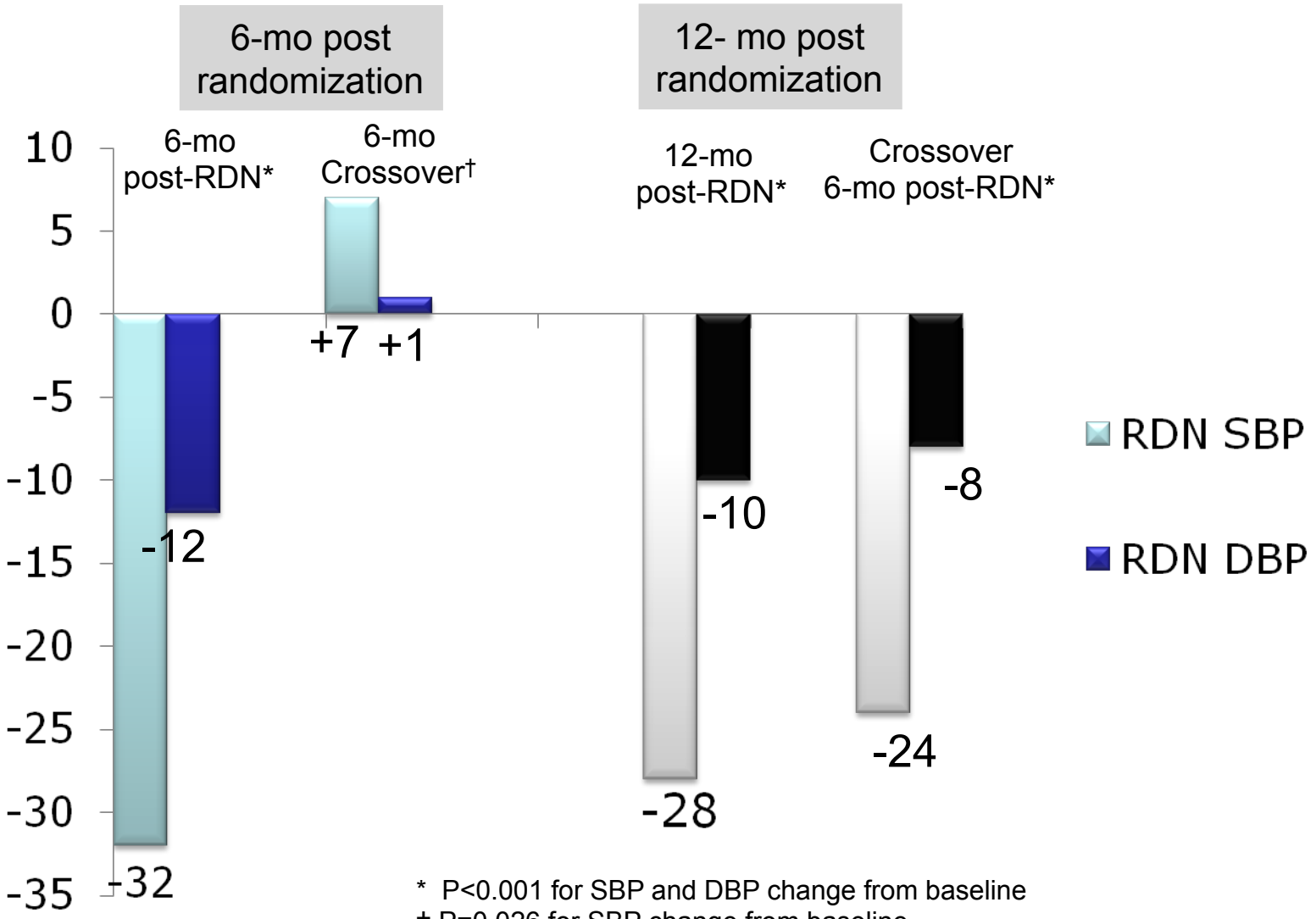
Primary Endpoint: 6-Month Office BP



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Symplicity HTN-2 Investigators. The Lancet. 2010.

Change in Office Blood Pressure (mm Hg)



* P<0.001 for SBP and DBP change from baseline
† P=0.026 for SBP change from baseline

Medication Changes at 6 and 12 Months Post-Renal Denervation

RDN (n=47)	6 month	12 months
Decrease (# Meds or Dose)	20.9% (9/43)	27.9% (12/43)
Increase (# Meds or Dose)	11.6% (5/43)	18.6% (8/43)

Crossover (n=35)	6 months post-RDN
Decrease (# Meds or Dose)	18.2% (6/33)
Increase (# Meds or Dose)	15.2% (5/33)

*Physicians were allowed to make changes to medications Once the 6 month primary endpoint was reached**

*Further analysis of Medications is ongoing

Procedural Safety

- No serious device or procedure related adverse events (n=52)
- Minor adverse events
  - 1 femoral artery pseudoaneurysm treated with manual compression
  - 1 post-procedural drop in BP resulting in a reduction in medication
  - 1 urinary tract infection
  - 1 prolonged hospitalization for evaluation of paraesthesias
  - 1 back pain treated with pain medications & resolved after one month
- 6-month renal imaging (n=43)
  - No vascular abnormality at any RF treatment site
  - 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)

Symplicity HTN-2 Investigators. The Lancet. 2010.

SUIVI POST DENERVATION
Fonction rénale

Δ Renal Function (baseline - 6M)	RDN Mean ± SD (n)	Control Mean ± SD (n)	Difference (95% CI)	p-value
eGFR (MDRD) (mL/min/1.73m^2)	0 ± 11 (49)	1 ± 12 (51)	-1 (-5, 4)	0.76
Serum Creatinine (mg/dL)	0.0 ± 0.2 (49)	0.0 ± 0.1 (51)	0.0 (-0.1, 0.1)	0.66
Cystatin-C (mg/L)	0.1 ± 0.2 (37)	0.0 ± 0.1 (40)	0.0 (-0.0, 0.1)	0.31

Symplicity HTN-2 Investigators. The Lancet. 2010.

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Dénervation Rénale dans notre pratique

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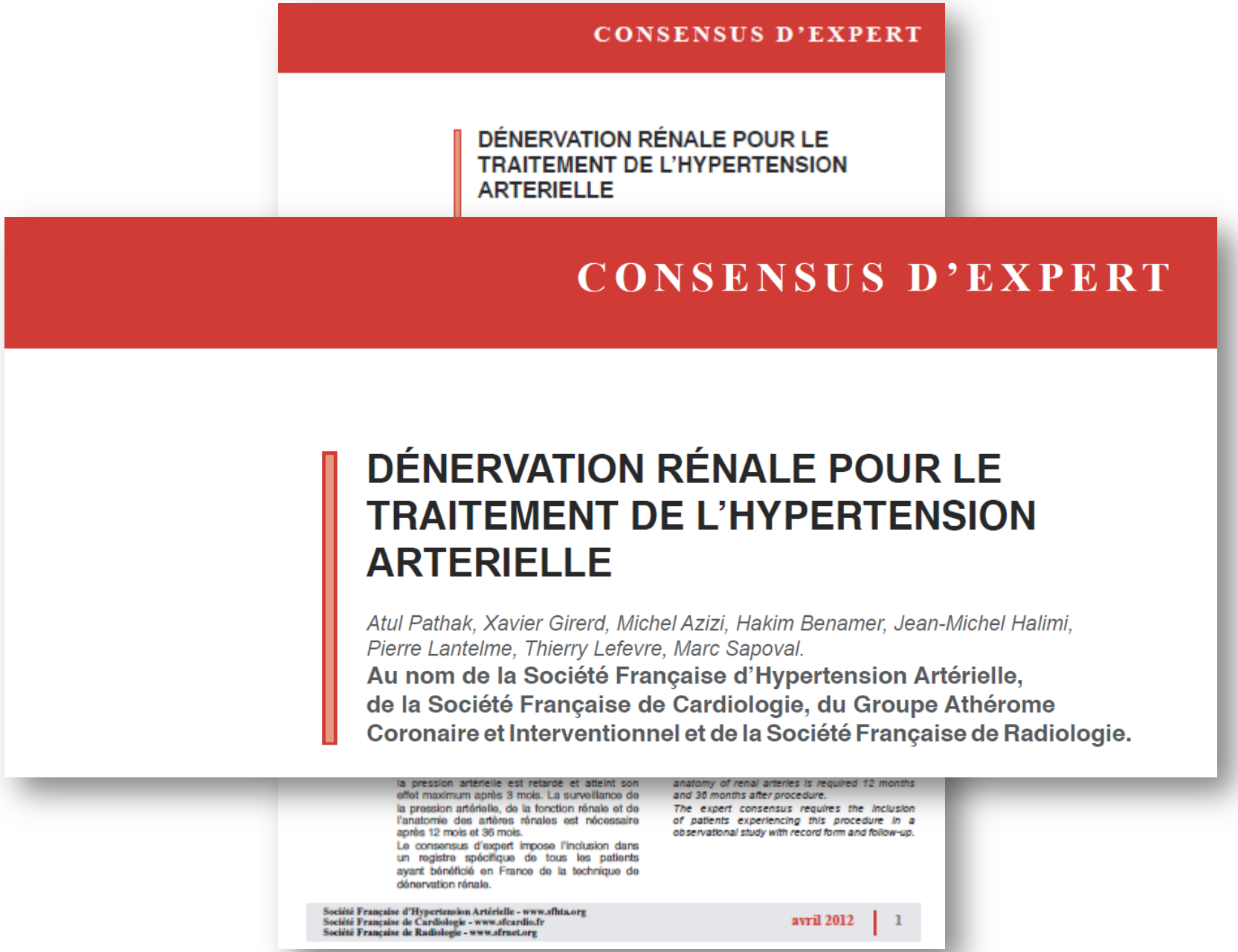
GRUPPO VILLA MARIA

GÉNÉRALE DE SANTÉ


CONSENSUS D'EXPERT
DÉNERVATION RÉNALE POUR LE TRAITEMENT DE L'HYPERTENSION ARTERIELLE
CONSENSUS D'EXPERT
DÉNERVATION RÉNALE POUR LE TRAITEMENT DE L'HYPERTENSION ARTERIELLE
Atul Pathak, Xavier Girerd, Michel Azizi, Hakim Benamer, Jean-Michel Halimi, Pierre Lantelme, Thierry Lefevre, Marc Sapoval.
Au nom de la Société Française d'Hypertension Artérielle, de la Société Française de Cardiologie, du Groupe Athérome Coronaire et Interventionnel et de la Société Française de Radiologie.
la pression artérielle est retardé et atteint son effet maximum après 3 mois. La surveillance de la pression artérielle, de la fonction rénale et de l'anatomie des artères rénales est nécessaire après 12 mois et 36 mois.
Le consensus d'expert impose l'inclusion dans un registre spécifique de tous les patients ayant bénéficié en France de la technique de dénervation rénale.
anatomy of renal arteries is required 12 months and 36 months after procedure.
The expert consensus requires the inclusion of patients experiencing this procedure in a observational study with record form and follow-up.
Société Française d'Hypertension Artérielle - www.sfhta.org
Société Française de Cardiologie - www.sfcardio.fr
Société Française de Radiologie - www.sfrnet.org
avril 2012 | 1

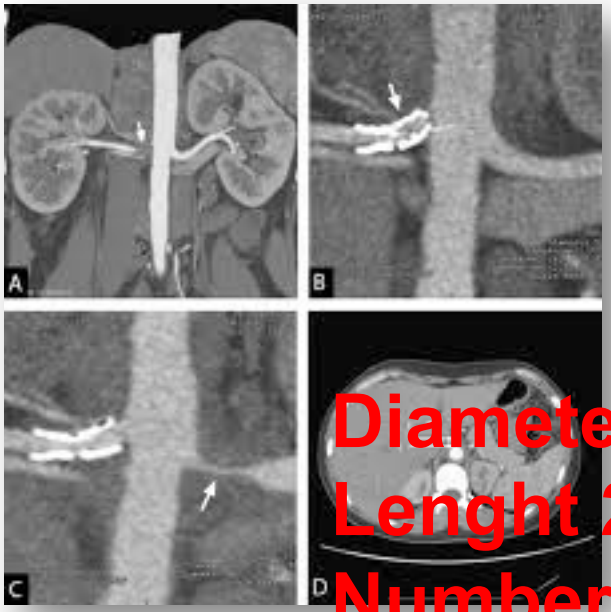
SELECTION du PATIENT
French Experts Consensus

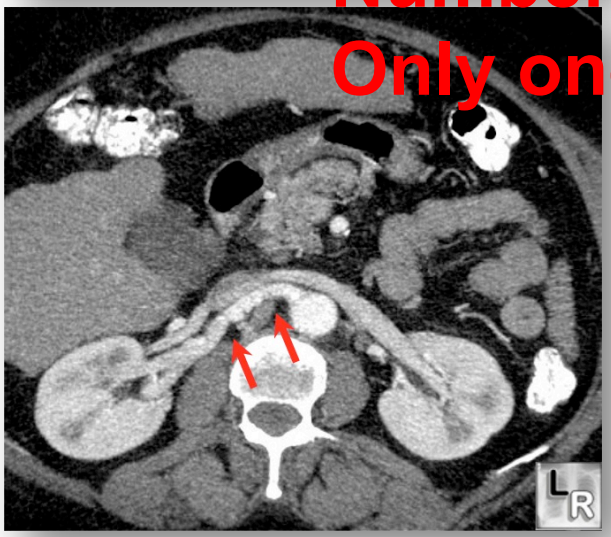
- Resistante Hypertension
- Eliminate a Secondary arterial hypertension
- Information for the patient
- Anatomic study of renal artery by scanner

SELECTION du PATIENT
French Experts Consensus

Contre indiqué

- Stenosis > 30% in a renal artery
- Fibromuscular dysplasia
- Age younger than 18 y
- Pregnancy
- eGFR < 45ml/min





Diameter > 4mm
Lenght 20mm (4 tirs)
Number of Renal arteries
Only one artery treated by kidney

Technic

Femoral access (6French)
Guiding catheter 45-55cm RDC1 ou LIMA
BHW 0,014 wire some time to improve the support
Flush NACL 0,9% with heparin
Nitro before the denervation
Anticoagulation with Heparin (ACT >300 sec)
Sedation and analgesia done by an anesthesiologist

Renal Artery and Denervation

Renal artery Spasm


Filtre : Filtrer 4
SUCCESS?

Notre Expérience

Clinical Characteristics

Patients	N = 33
Age (years)	63.6 +/- 11.7
Male, n (%)	32 (63.6)
Diabetes Mellitus type II, n (%)	12 (36.4)
Hypercholesterolemia, n (%)	17 (51.5)
Smoker, n (%)	4 (12.1)
BMI (Kg/m2)	29.3 +/- 5.1
Prior MI, n (%)	2 (6.1)
Prior CAD, n (%)	3 (9.1)
Prior Stroke, n (%)	7 (21.2)
Peripheral Disease, n (%)	1 (3.0)
Renal Insufficiency, n (%)	8 (24.2)
eGFR (ml/min)	92.2 +/- 35.1
Creatinine (mmol/l)	90.7 +/- 45.9

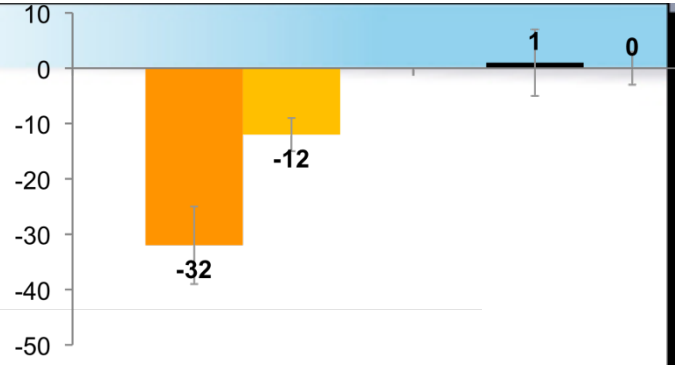
Medical Treatment of Hypertension

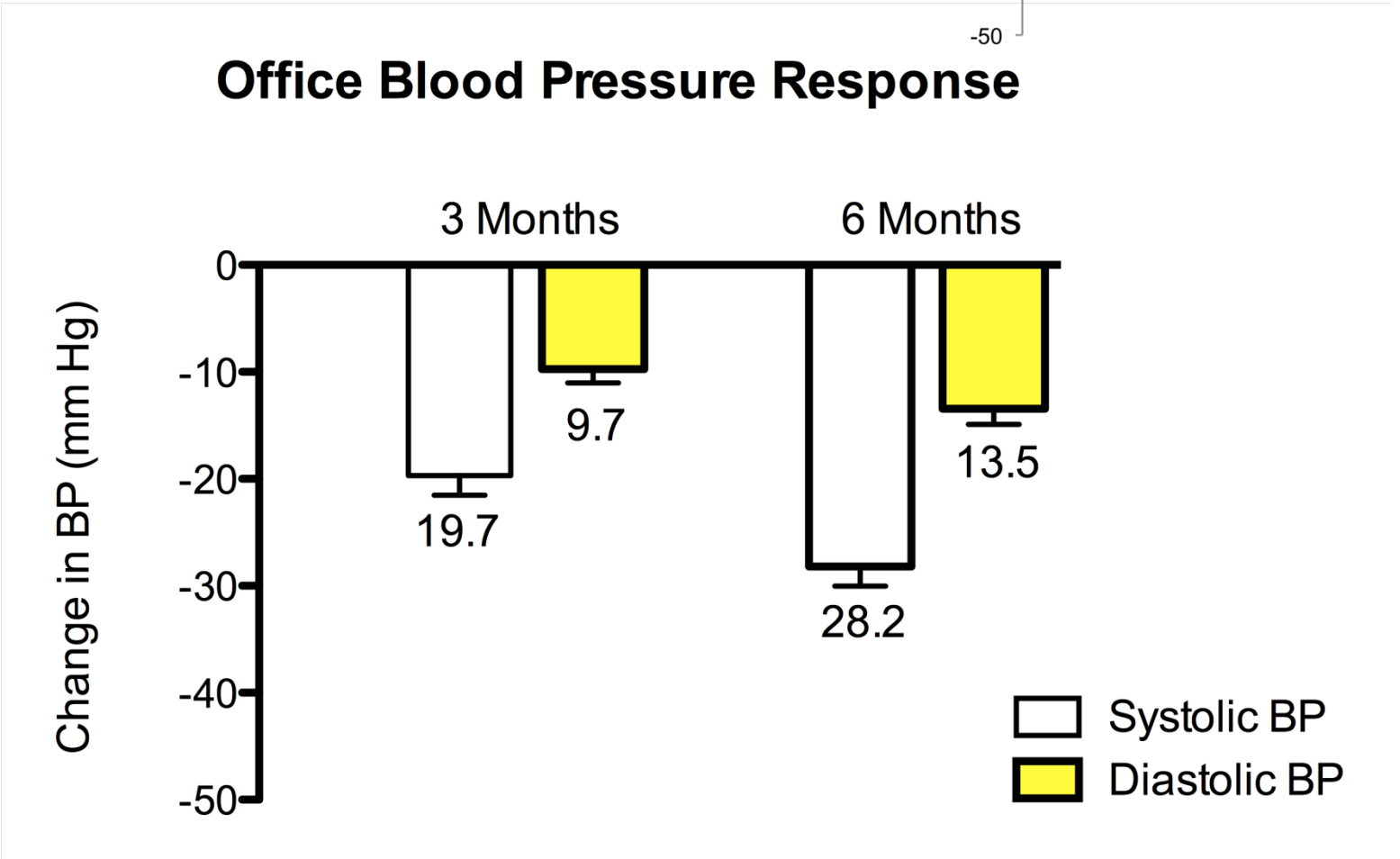
Patients	N = 33
Blood Pressure (Office) Préhospital (mmHg)	**181.1±21.9 / 100.8 ±16.8**
Blood Pressure (MAPA) Préhospital (mmHg) (55%)	**171.6±19.6 / 93.5±13.3**
Blood Pressure Inhospital (mmHg)	**169.9±28.2 / 93.0±19.7**
Number of anti-HTN meds (mean)	**4.6 ± 1.1**
ACE (%)	53.1%
ARB (%)	45.5%
ACE + ARB (%)	7.0%
Beta-blocker (%)	72.7%
Calcium channel blocker (%)	66.7%
Vasodilator (%)	60.6%
Diuretic (%)	97.0%

Procedural Characteristics

Femoral Access	33 (100%)
6F catheter	33 (100%)
Total number of ablations	11.8 ± 3.3
Procedural duration (min)	57.7 +/- 18.8
Closure device	33 (100%)
Vascular complication	0
Dissection or any complication	0

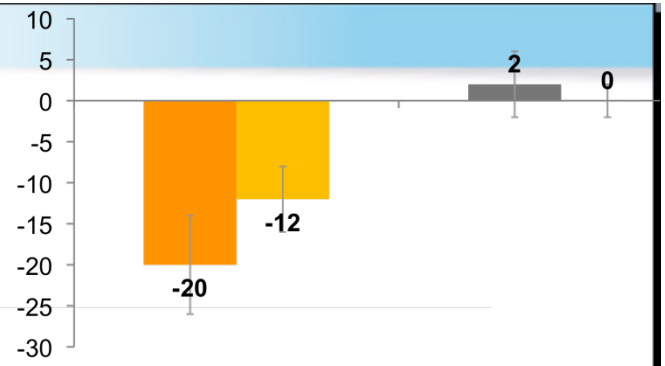
Results

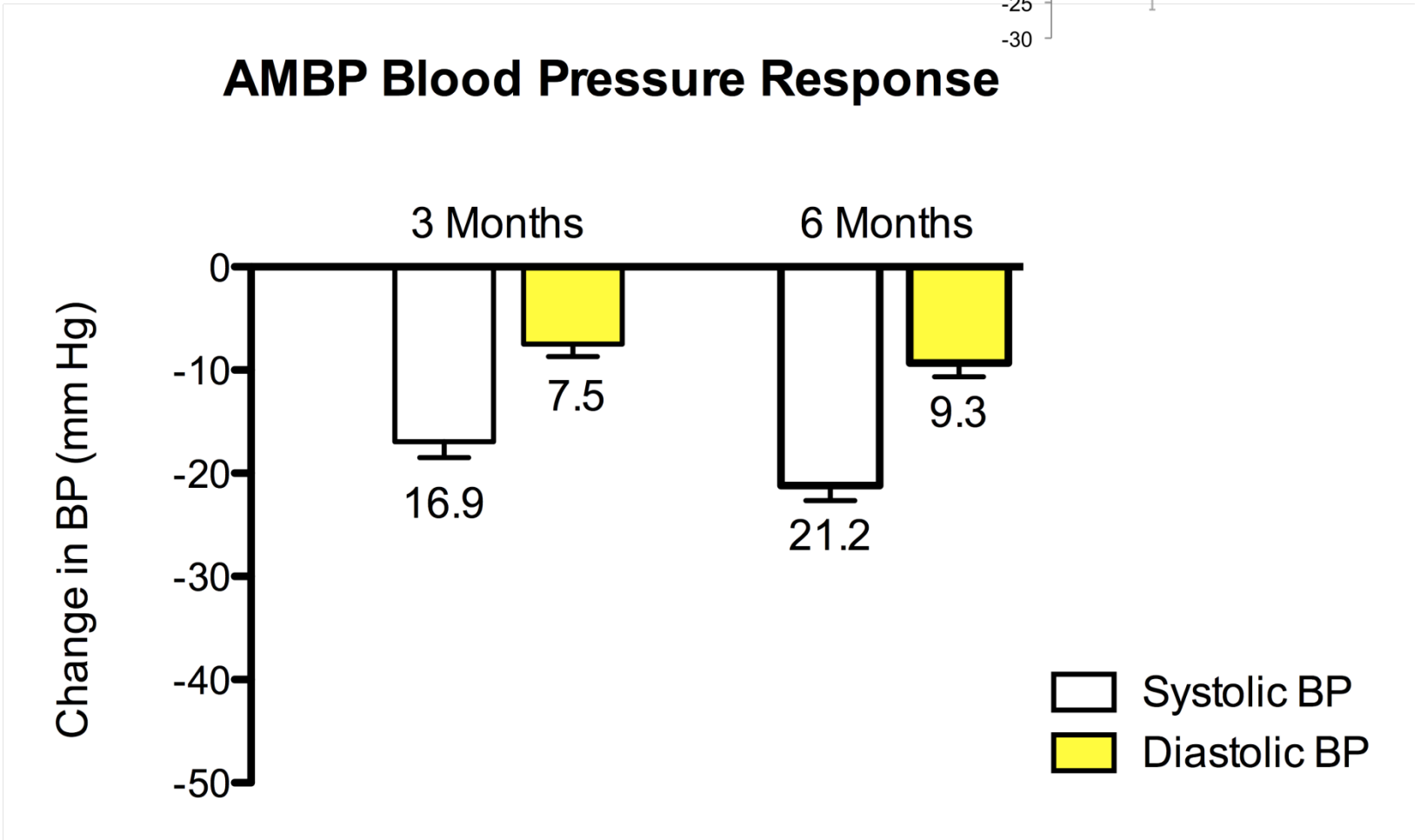




Repeated measures ANOVA: P<0.001 for Systolic & Diastolic BP vs. baseline

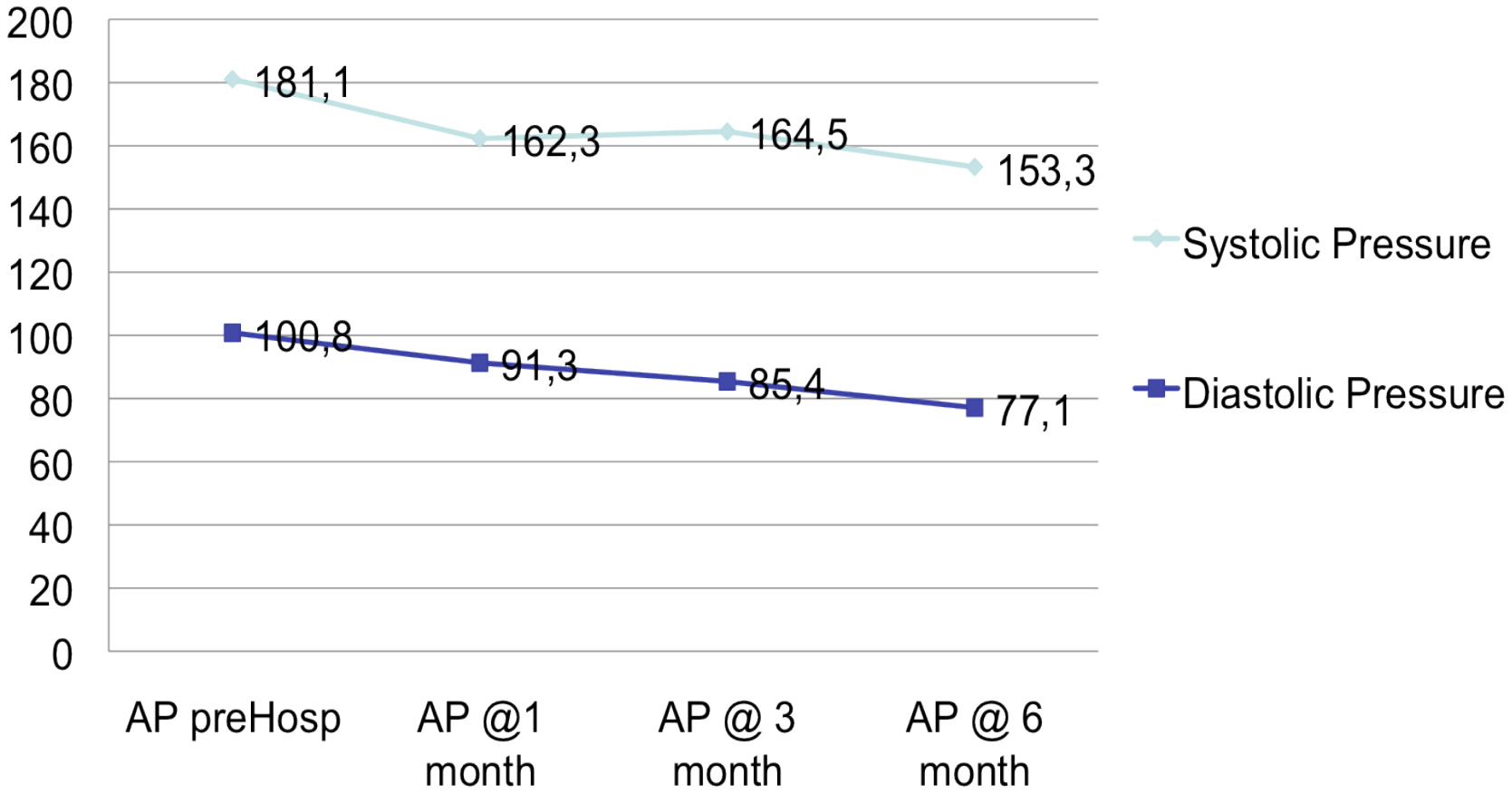
Results





Repeated measures ANOVA: P<0.001 for Systolic & Diastolic BP vs. baseline

RESULTS


200
180
160
140
120
100
80
60
40
20
0
181,1
162,3
164,5
153,3
100,8
91,3
85,4
77,1
AP preHosp
AP @1 month
AP @ 3 month
AP @ 6 month
Systolic Pressure
Diastolic Pressure

Results

Medication Change

Anti-HTN reduction: N=4

Anti-HTN increase: N=3

Adverse Events

Procedure-Related

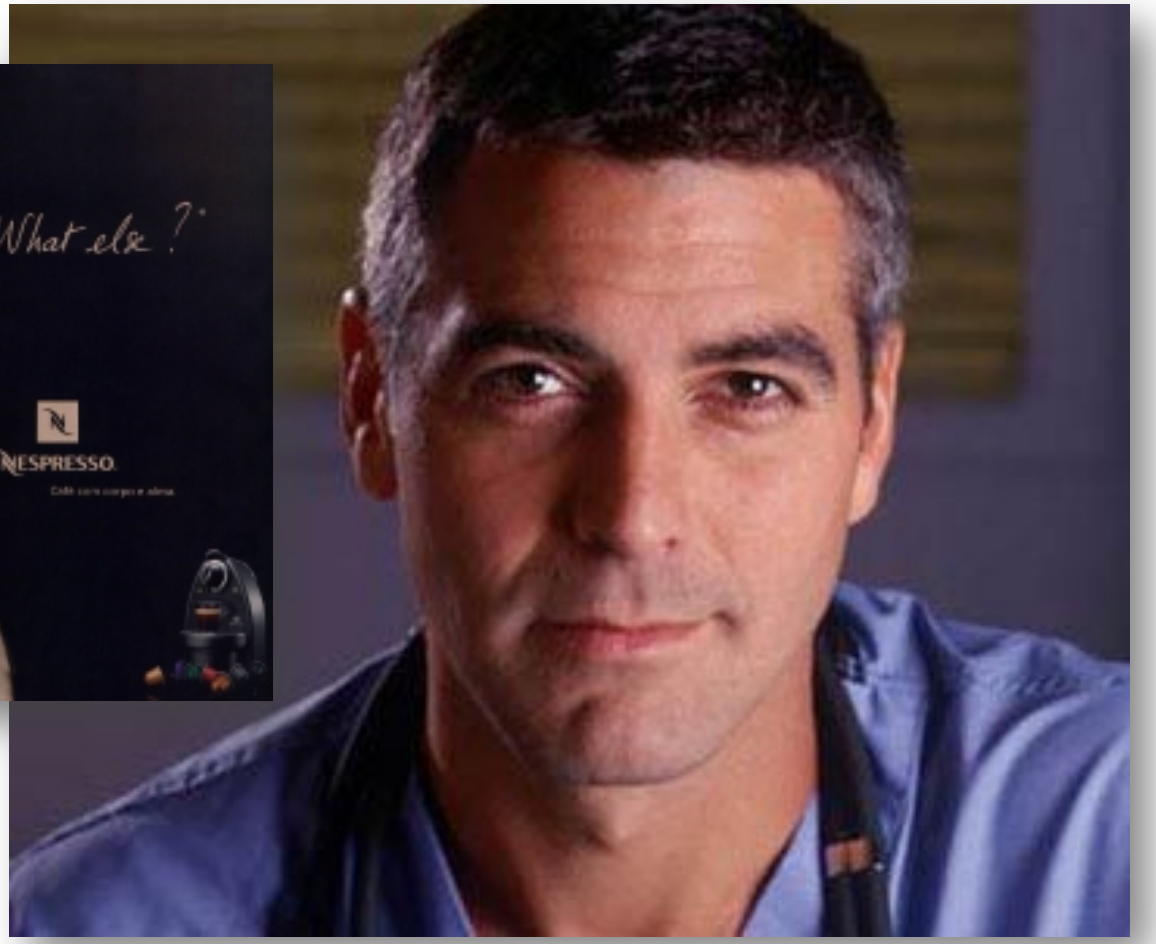
Orthostatic hypotension	N=0
Electrolyte disturbance	N=0
Arrhythmia	N=0

Other

One admission with hypertensive encephalopathy

No stroke or MI

WHAT ELSE ?



Dr Goug ROSS

Externally Applied Focused Ultrasound
Kona Medical

low-intensity focused ultrasound (LIFU)

Figure 1. Kona Medical noninvasive treatment system based on Doppler signals from the renal artery.

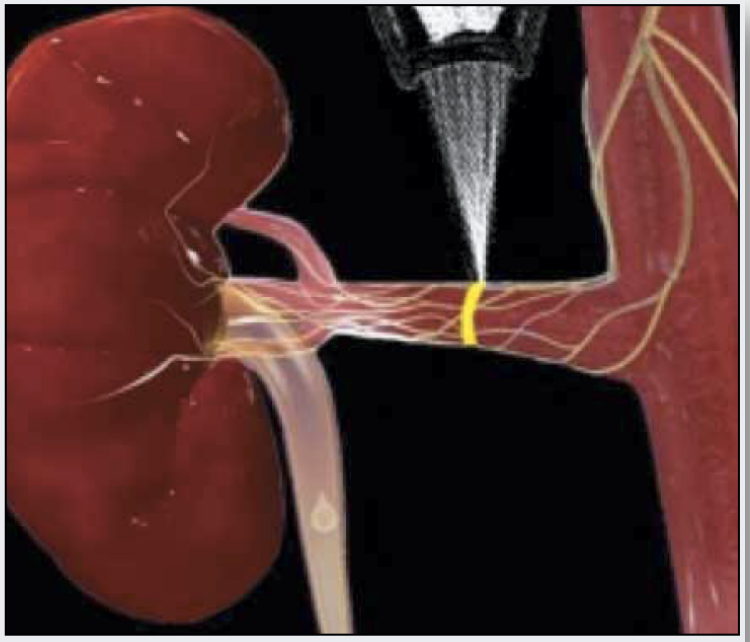


Figure 2. The concept of "outside-in" energy delivery to the renal nerves without instrumentation of the vessel.

Kona has shown in animal studies that a heat/vibratory cloud at one plane along the artery is highly effective at long-term inhibition of renal nerves with no visible effect on any portion of the artery at any time point.

The TIVUS System CardioSonic Ltd.

Solution for renal denervation is a high-intensity, nonfocused ultrasonic (US) catheter system named TIVUS (Therapeutic IntraVascular UltraSound)

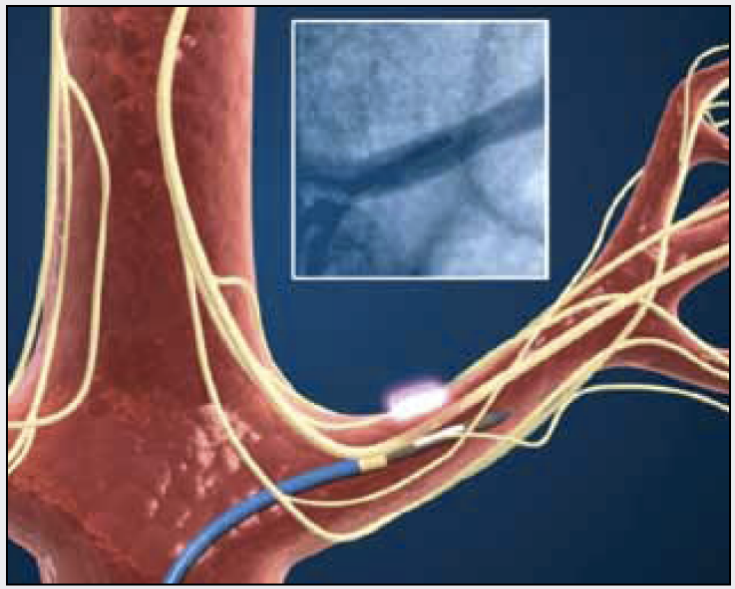


Figure 3. The 0.014-inch guidewire-based TIVUS catheter positioned within the renal artery lumen through a 6-F flexible sheath. Note that the ultrasound-emitting element (positioned superiorly) does not make direct contact with the vessel wall (inset).

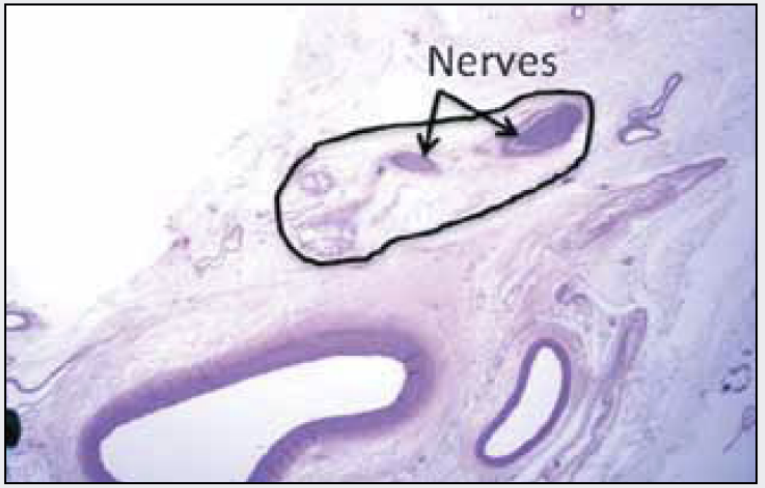


Figure 4. Hematoxylin and eosin histological section through the renal artery and surrounding adventitial 30 days post-treatment with the TIVUS catheter. Note that the renal intimal and medial layers are free of damage, whereas renal nerves in the adventitial (circled in black with arrows) show evidence of vacuolar degeneration consistent with nerve cell death.

The procedure requires no direct mechanical contact with the arterial wall, thereby minimizing potential damage to the vessel intima.

PARADISE Technology ReCor Medical, Inc.

The PARADISE technology (Percutaneous Renal Denervation System) includes a 6-F compatible catheter with a cylindrical transducer that, emits ultrasound energy circumferentially, allowing for a more efficient renal denervation procedure.

Figure 5. The PARADISE catheter. The ultrasound transducer is centered within a fluid-filled balloon.

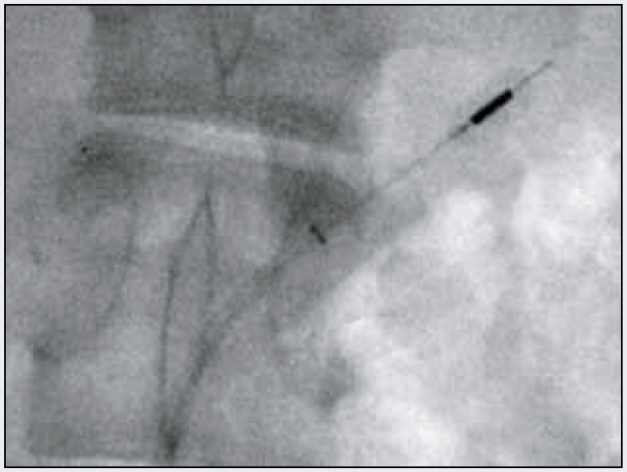


Figure 6. The PARADISE catheter deployed within a renal artery.

ReCor Medical is currently completing the REDUCE first in-man study, which has shown clinically relevant blood pressure reductions in patients with resistant hypertension out to 3 months. These results are to be confirmed by the REALISE study, which is starting in the first quarter of 2012 at a renowned European site.

Bullfrog Microinfusion Catheter Mercator MedSystems, Inc.

Mercator MedSystems, Inc. proposes to reduce resistant hypertension by producing a partial denervation of the kidneys with localized administration of guanethidine monosulfate to the adventitia and perivascular tissue of the renal arteries

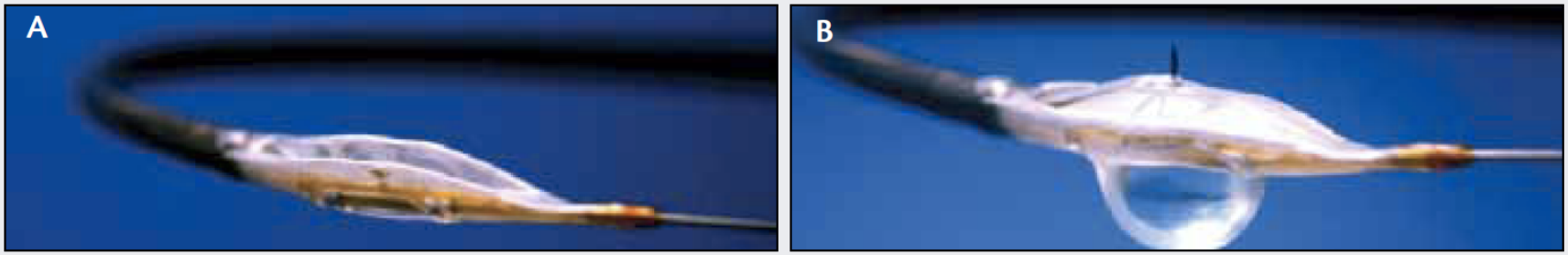


Figure 7. The deflated (A) and inflated (B) Bullfrog microinfusion catheter. Balloon walls sheath the needle (0.9 mm in length and 130 µm in diameter) and protect the vessel during catheter placement. When the balloon is inflated, the needle slides through the vessel wall, allowing drug delivery to the adventitia and perivascular tissue. The balloon is then deflated, and the catheter is moved to another target site or removed from the body.

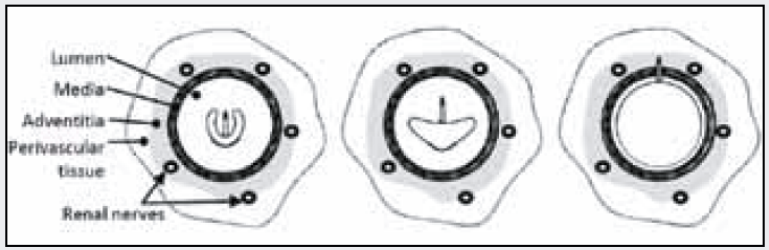


Figure 8. As the Bullfrog balloon inflates, the microneedle slides through the media and into the adventitia and perivascular tissue.

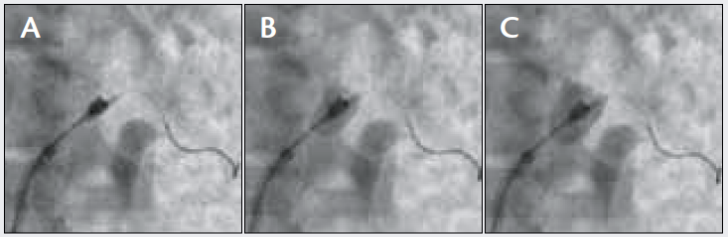


Figure 9. Renal artery drug delivery with Bullfrog catheter. Bullfrog catheter inflated in a porcine left renal artery (A). After a 0.5-mL adventitial infusion (B). After a 1-mL adventitial infusion (C). Note that the contrast mixed with drug provides an immediate visual feedback to confirm adventitial delivery.

Conclusions

Dénervation rénale avec le catheter symplicity

- Simple et sûre
- Réduction significative de la pression artérielle
- Sélection rigoureuse des patients +++
- Suivi est important pour s'assurer de l'efficacité et sécurité à long terme
- Nécessité d'avoir plus d'études et de partager les expériences

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GRUPPO VILLA MARIA

GÉNÉRALE DE SANTÉ