CLINIQUE
Pasteur
TOULOUSE

Prise en charge interventionnelle de l'hypertension

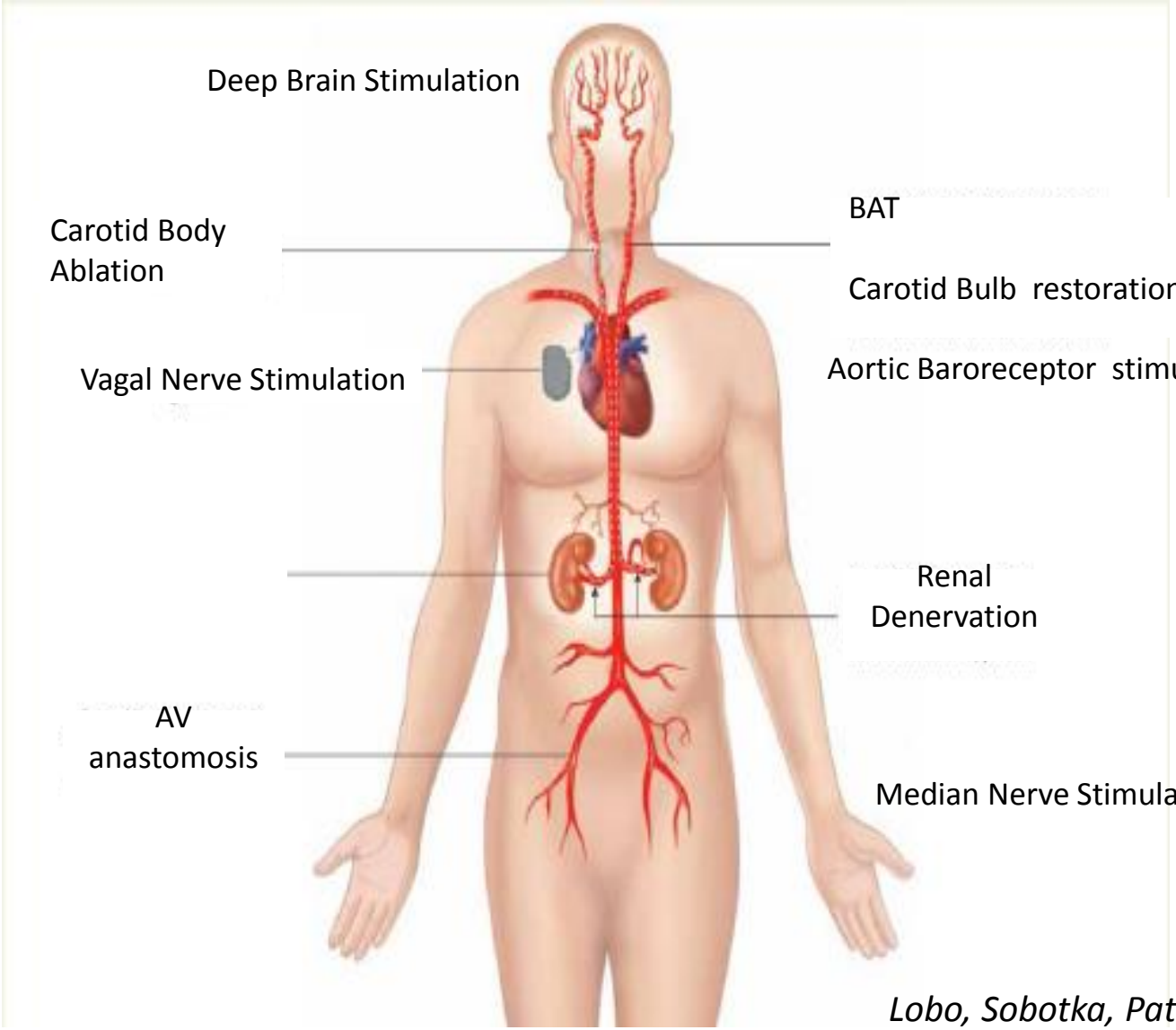
B.Honton
Clinique Pasteur
Toulouse

DÉCLARATION DE LIENS D'INTÉRÊT AVEC LA PRÉSENTATION

Intervenant : Benjamin HONTON, Toulouse

☑ Je n'ai pas de lien d'intérêt à déclarer

Cible des « Device Based Therapy »



Lobo, Sobotka, Pathak. EHJ 2016

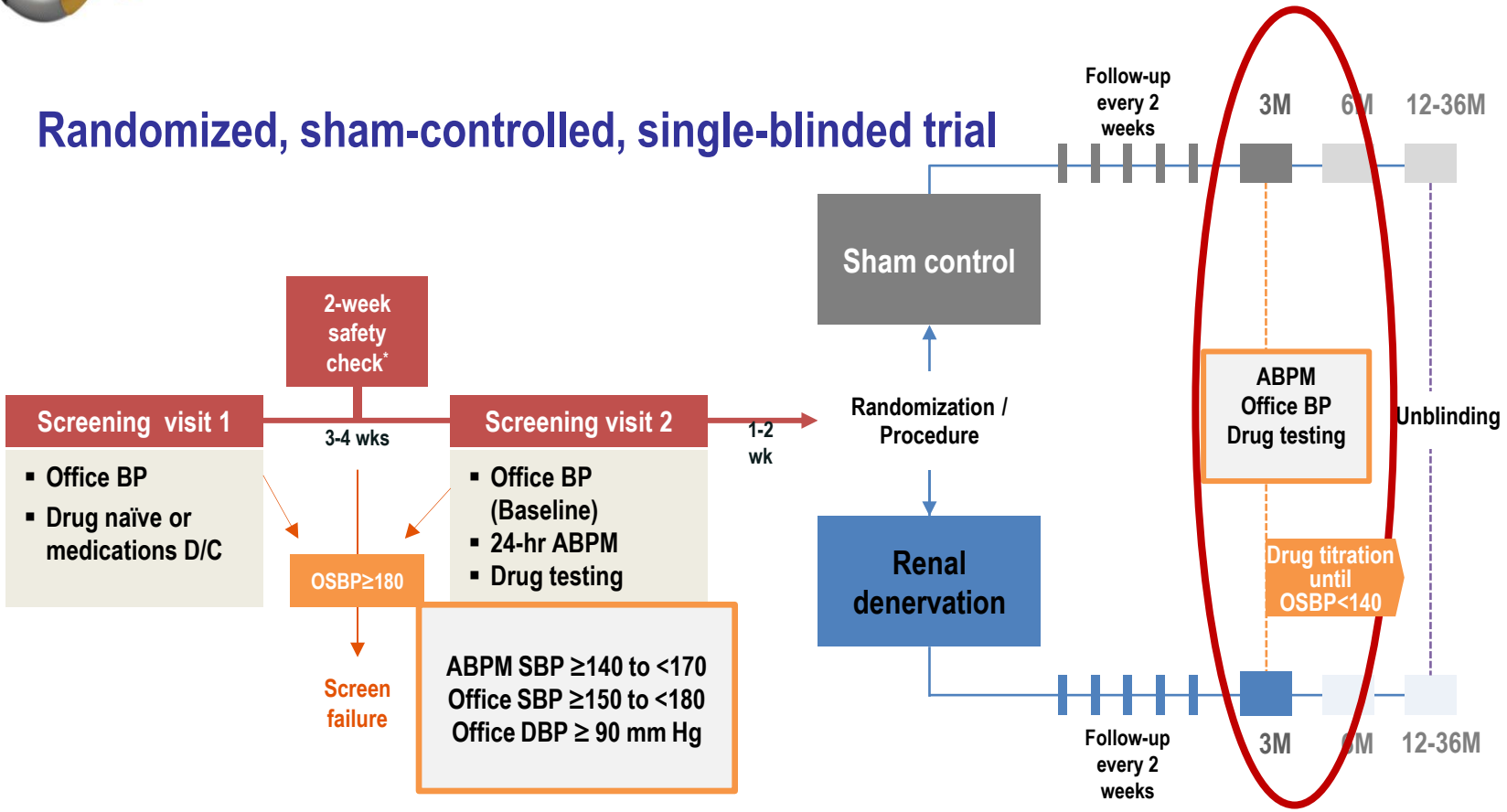
Dénervation Rénale

Current trials for RDN device-based therapies in patients with hypertension

Randomized, sham-controlled, feasibility; Not powered	SPYRAL HTN Global Clinical Trial Program	OFF – n=100 ON – n=100
Randomized, sham-controlled; Powered for ABP daytime difference of 6 mmHg	THE RADIANCE-HTN STUDY A Study of the ReCor Medical Paradise® System in Clinical Hypertension	SOLO – n=146 ON – n=146
Randomized, sham-controlled, feasibility; Not powered	REDUCE-HTN: REINFORCE Study	OFF – n=100
Randomized, sham-controlled, feasibility; Not powered	ABLATIVE SOLUTIONS Target BP I	OFF – n=100
Negotiations with FDA ongoing Probably 1st pivotal, powered for ABP	ENLIGHTNED GLOBAL IDE TRIAL	FIX – n=??? (>500)

SPYRAL HTN – OFF MED: Study Design

Randomized, sham-controlled, single-blinded trial



Interim analyses were planned after 40, 60, 80, and 100 patients

Kandzari D, et al. *Am Heart J*. 2016;171:82-91.

SPYRAL HTN – OFF MED: Baseline Characteristics

	RDN (N = 38)	Sham Control (N = 42)
Age (years)	55.8 ± 10.1	52.8 ± 11.5
Male	68.4% (26/38)	73.8% (31/42)
BMI (kg/m^2)	29.8 ± 5.1	30.2 ± 5.1
Diabetes (type 2)	2.6% (1/38)	7.1% (3/42)
Current smoker	10.5% (4/38)	23.8% (10/42)
Coronary artery disease†	0% (0/38)	7.1% (3/42)
Stroke and TIA†	2.6% (1/38)	0% (0/42)
MI/ ACS†	0% (0/38)	2.4% (1/42)
Office SBP (mm Hg)	162.0 ± 7.6	161.4 ± 6.4
Office DBP (mm Hg)	99.9 ± 6.8	101.5 ± 7.5
Mean 24-hour SBP (mm Hg)	153.4 ± 9.0	151.6 ± 7.4
Mean 24-hour DBP (mm Hg)	99.1 ± 7.7	98.7 ± 8.2

24h - ambulatory BP Change from Baseline to 3 Months

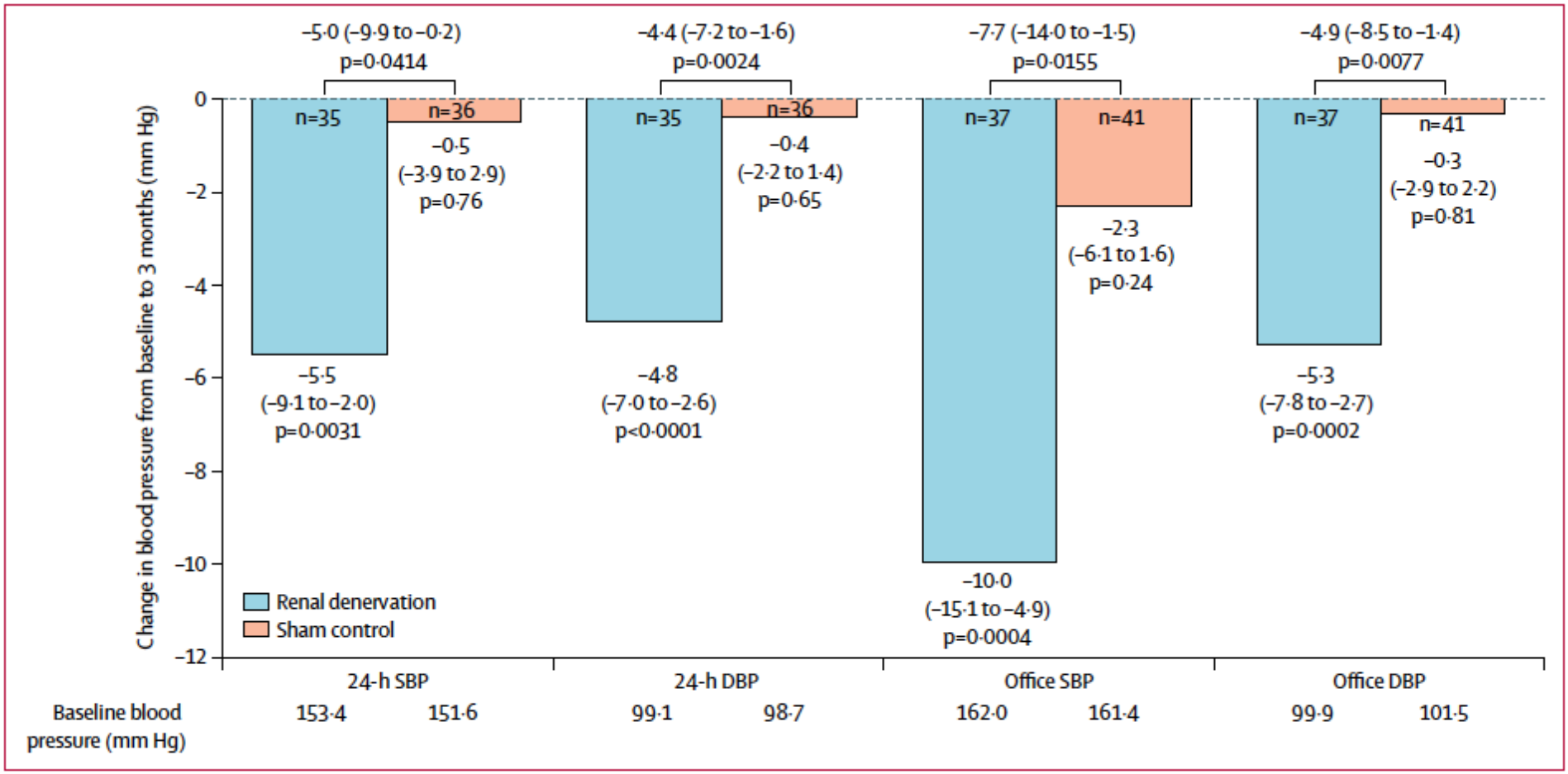
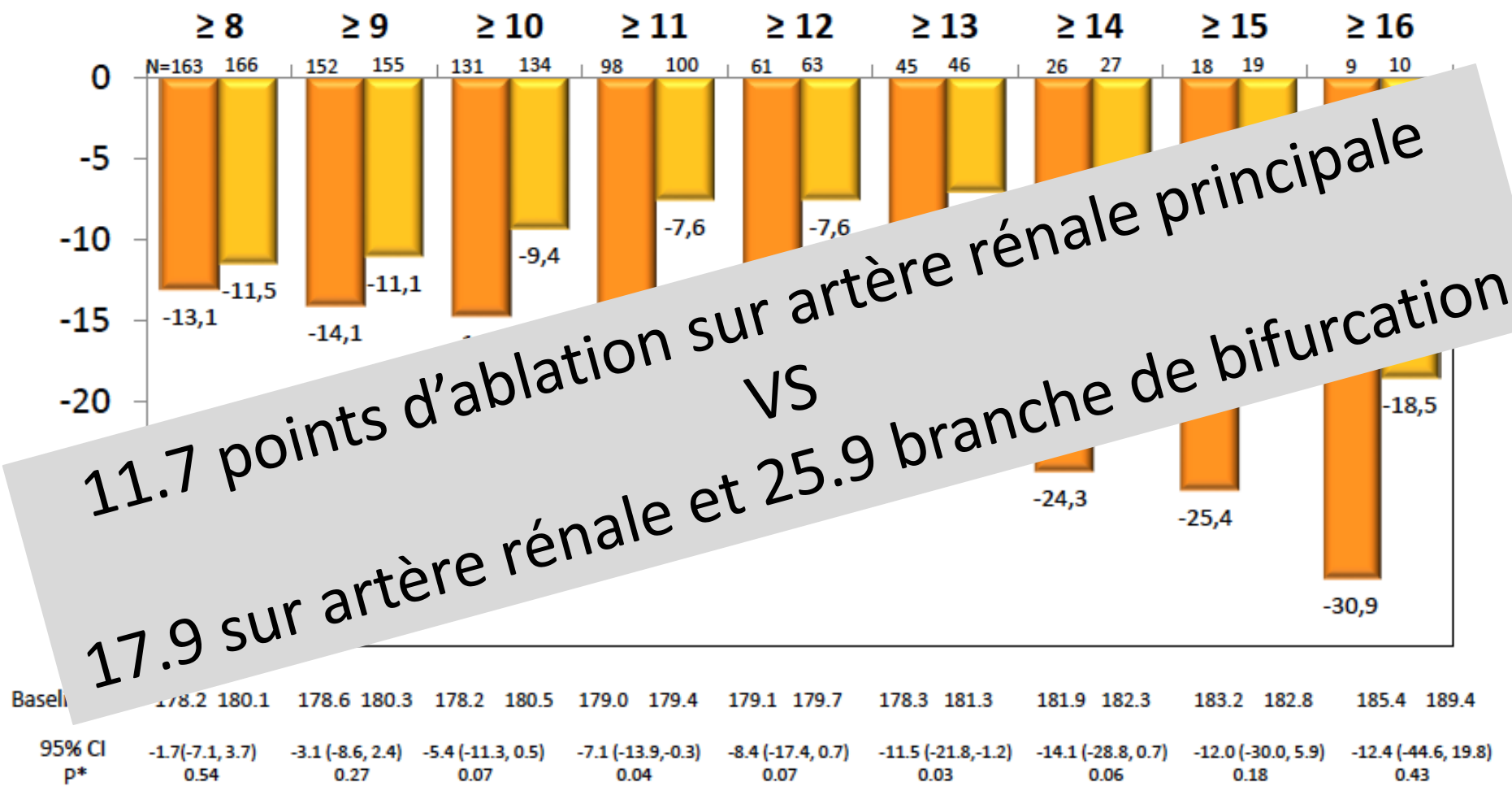


***Figure 3*: Changes at 3 months in office and ambulatory SBP and DBP for renal denervation and sham control groups**
95% CIs and unadjusted p values shown. SBP=systolic blood pressure. DBP=diastolic blood pressure.

SYMPLICITY 3



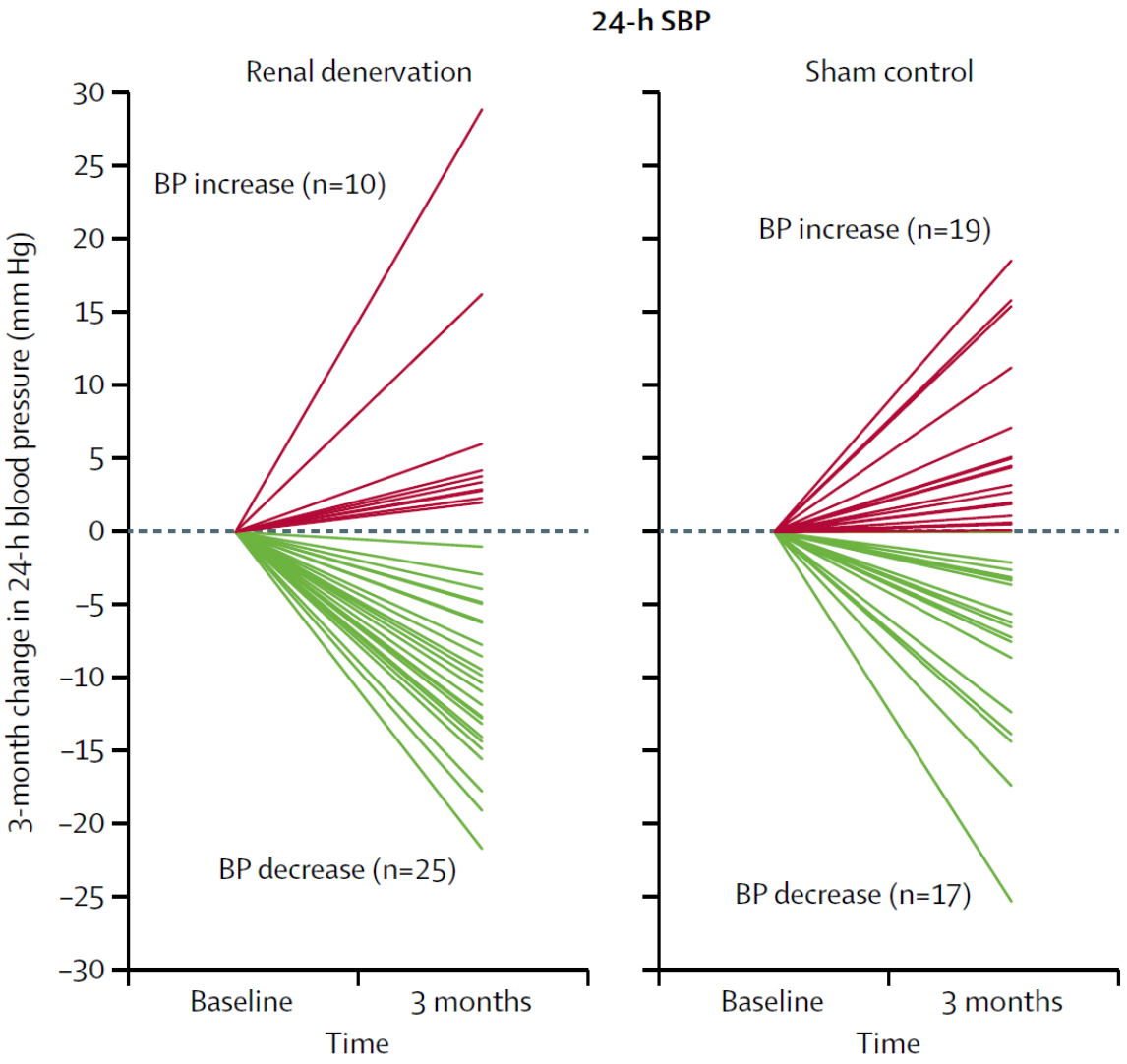
11.7 points d'ablation sur artère rénale principale
VS
17.9 sur artère rénale et 25.9 branche de bifurcation

Propensity scores using baseline characteristics as covariates were used to match sham control and denervation patients

*P value change in SBP for RDN compared with sham
Data presented are mean (SD)

Kandzari D. Euro PCR 2014

Large between-patient variability in the ABP response to RDN and sham procedure



SPYRAL HTN – OFF MED: Conclusion

- Biologic proof of principle for the short-term BP lowering effect of efficacy of RF catheter based-renal denervation in mild to moderate hypertensive patients off-antihypertensive medications
- No major safety events at 3 months
  - Despite a more complete denervation procedure that extended into renal artery branch vessels
- The results of this feasibility study is used to design of a larger pivotal trial

SPYRAL HTN – ON MED

Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial

Key inclusion criteria

- Moderate hypertension
  - SOPB : 150 – 170 mmhg AND DOBP >90 mmhg
  - SYSTOLIC DAY TIME ABPM : 140-170 mmhg
- **1-3** commonly used antihypertensive drugs
  - Toxicological analyses

SPYRAL HTN – ON MED: Baseline

	Renal denervation (N=38)	Sham procedure (N=42)
Age (years)	53·9 (8·7)	53·0 (10·7)
Male	33 (87%)	34 (81%)
BMI (kg/m²)	31·4 (6·4)	32·5 (4·6)
Race		
White	13 (34%)	15 (36%)
Black or African American	4 (11%)	5 (12%)
Asian	0	1 (2%)
Not reportable per local laws or regulations	18 (47%)	20 (48%)
Diabetes (all type 2)	5 (13%)	8 (19%)
Current smoker	8 (21%)	11 (26%)
Obstructive sleep apnoea	2 (5%)	10 (24%)
Peripheral artery disease	0	0
Coronary artery disease*	1 (3%)	1 (2%)
Stroke and transient ischaemic attack*	0	1 (2%)
Myocardial infarction or acute coronary syndrome	0	0
Office SBP (mm Hg)	164·6 (7·1)	163·5 (7·5)
Office DBP (mm Hg)	99·6 (6·9)	102·7 (8·0)
Mean 24 h SBP (mm Hg)	152·1 (7·0)	151·3 (6·8)
Mean 24 h DBP (mm Hg)	97·2 (6·9)	97·9 (8·4)
Office heart rate (bpm)	75·6 (11·8)	73·5 (10·4)
24 h heart rate (bpm)	75·3 (11·3)	75·6 (10·7)
Mean number of antihypertensive drug classes	2·2 (0·9)	2·3 (0·8)
Median number of antihypertensive drug classes	3·0 (1·0–3·0)	3·0 (1·0–3·0)
Prescribed drug classes		
1	11 (29%)	9 (21%)
2	7 (18%)	11 (26%)
3	20 (53%)	22 (52%)
Drug class		
Diuretic	22 (58%)	25 (60%)
Calcium channel blocker	27 (71%)	31 (74%)
ACE-I/ARB	31 (82%)	35 (83%)
Beta blocker	4 (11%)	6 (14%)

Kandzari D, Lancet 2018

SPYRAL HTN – ON MED: Resultats

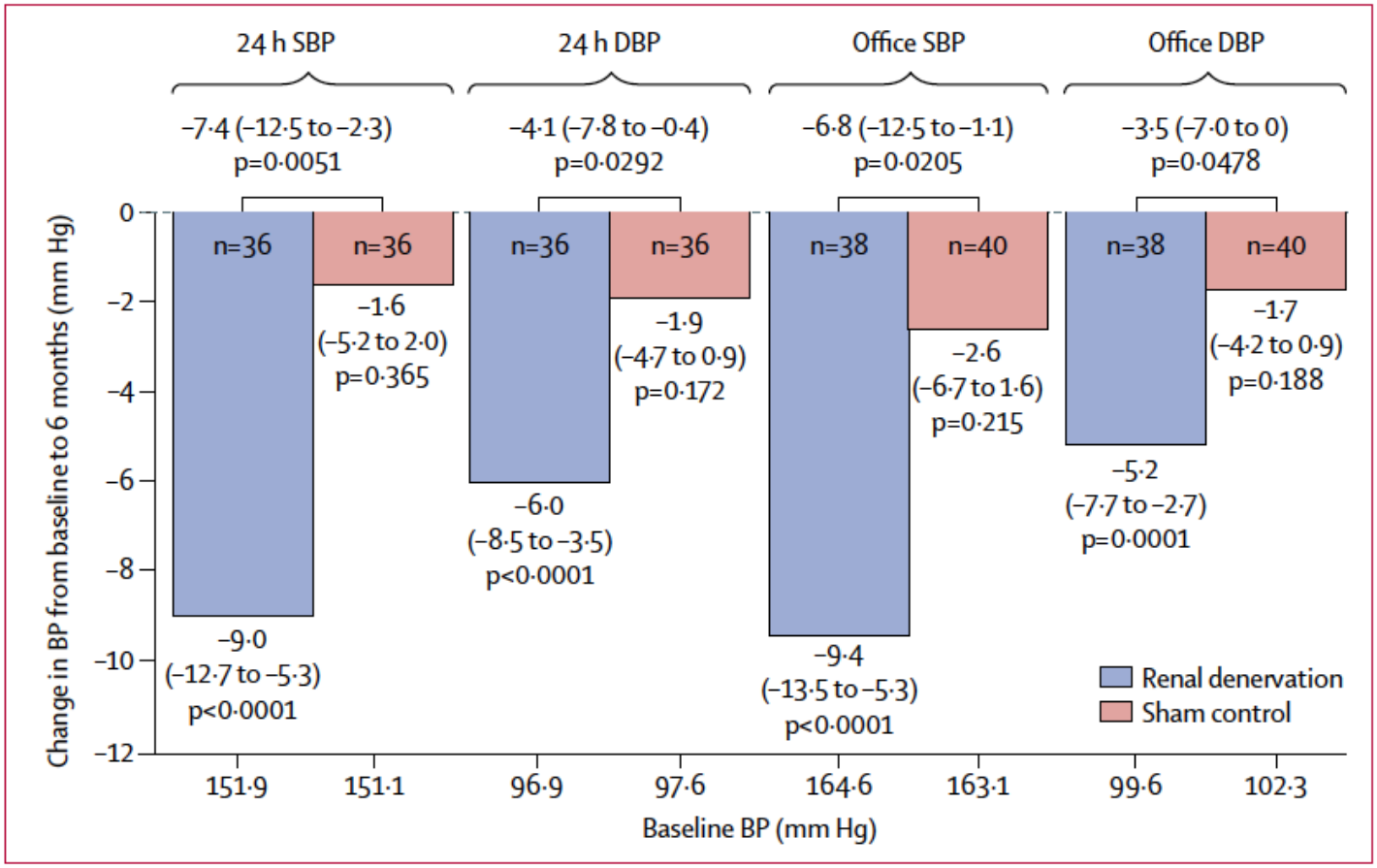


***Figure 2*: Change at 6 months in office and ambulatory systolic blood pressure and diastolic blood pressure for treatment and sham control patients**

Data are mean (95% CI). SBP=systolic blood pressure. DBP=diastolic blood pressure.

Kandzari D, Lancet 2018

SPYRAL HTN – ON MED: Resultats

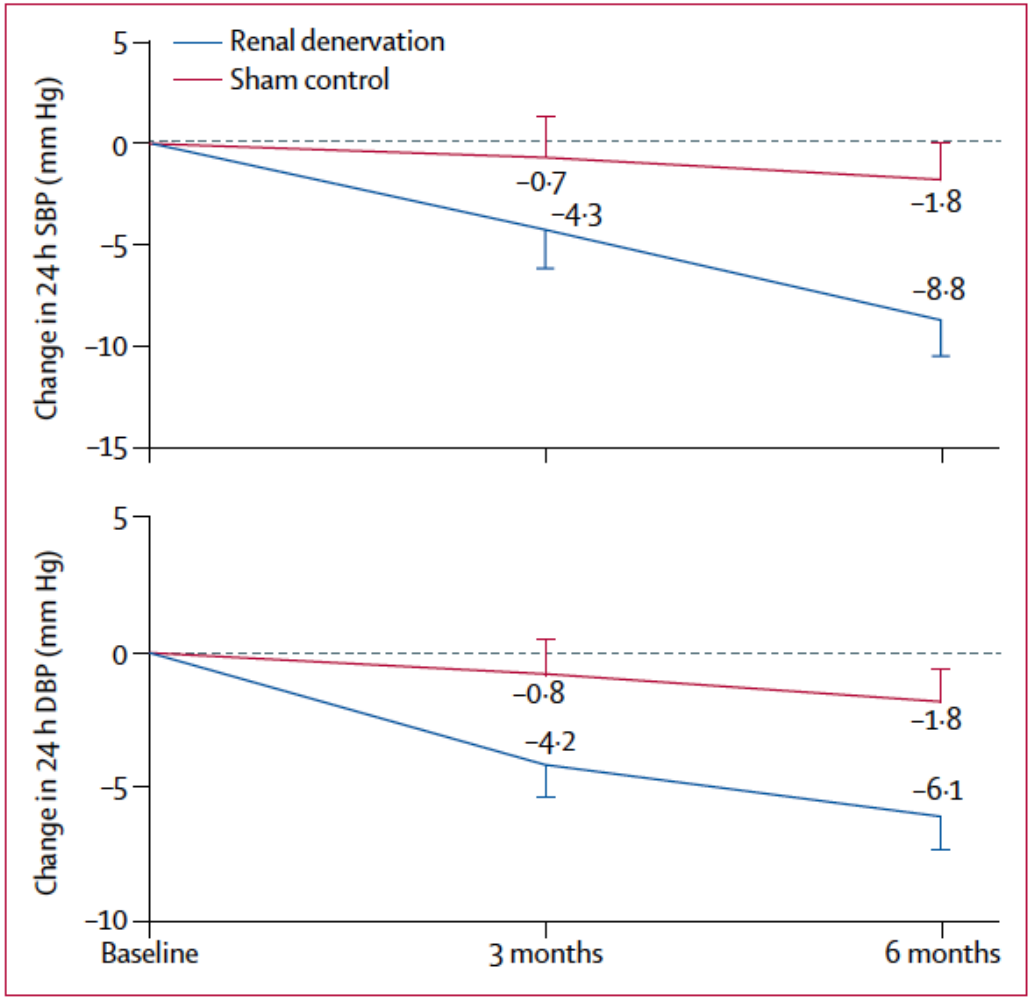
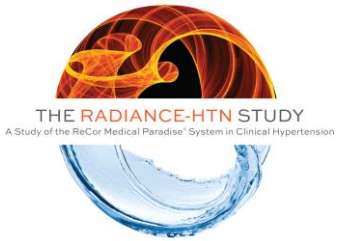


***Figure 3*: Mean changes in ambulatory 24 h blood pressure measurements at 3 and 6 months, adjusted for baseline values**

Kandzari D, Lancet 2018



THE LANCET

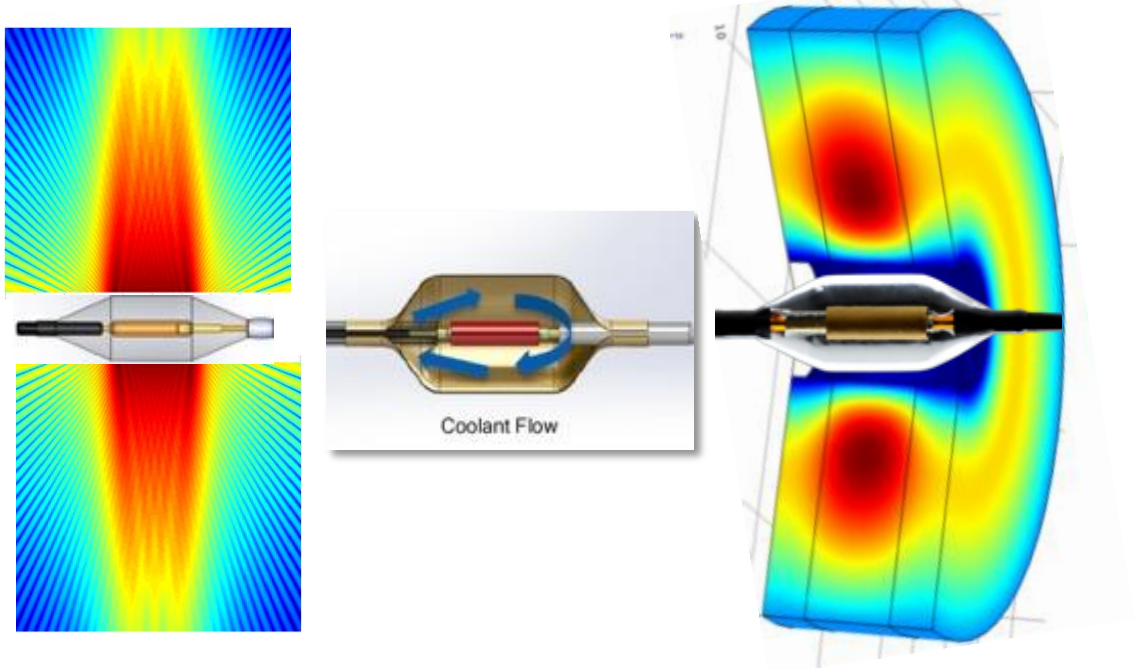
Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial

Michel Azizi, Roland E Schmieder, Felix Mahfoud, Michael A Weber, Joost Daemen, Justin Davies, Jan Basile, Ajay J Kirtane, Yale Wang, Melvin D Lobo, Manish Saxena, Lida Feyz, Florian Rader, Philipp Lurz, Jeremy Sayer, Marc Sapoval, Terry Levy, Kintur Sanghvi, Josephine Abraham, Andrew S P Sharp, Naomi DL Fisher, Michael J Bloch, Helen Reeve-Stoffer, Leslie Coleman, Christopher Mullin, Laura Mauri*, on behalf of the RADIANCE-HTN Investigators†*

RADIANCE-HTN SOLO

- Paradise® endovascular ultrasound ablation catheter (ReCor Medical, Palo Alto, CA, USA)
- Ring of ablative energy (depth of 1-6 mm) to interrupt renal nerve traffic
- Arterial wall protected by water circulating through balloon
- 2-3 ablations lasting 7 seconds each are delivered to each main renal artery

Ultrasonic Heating + Water Cooling → Thermal Profile



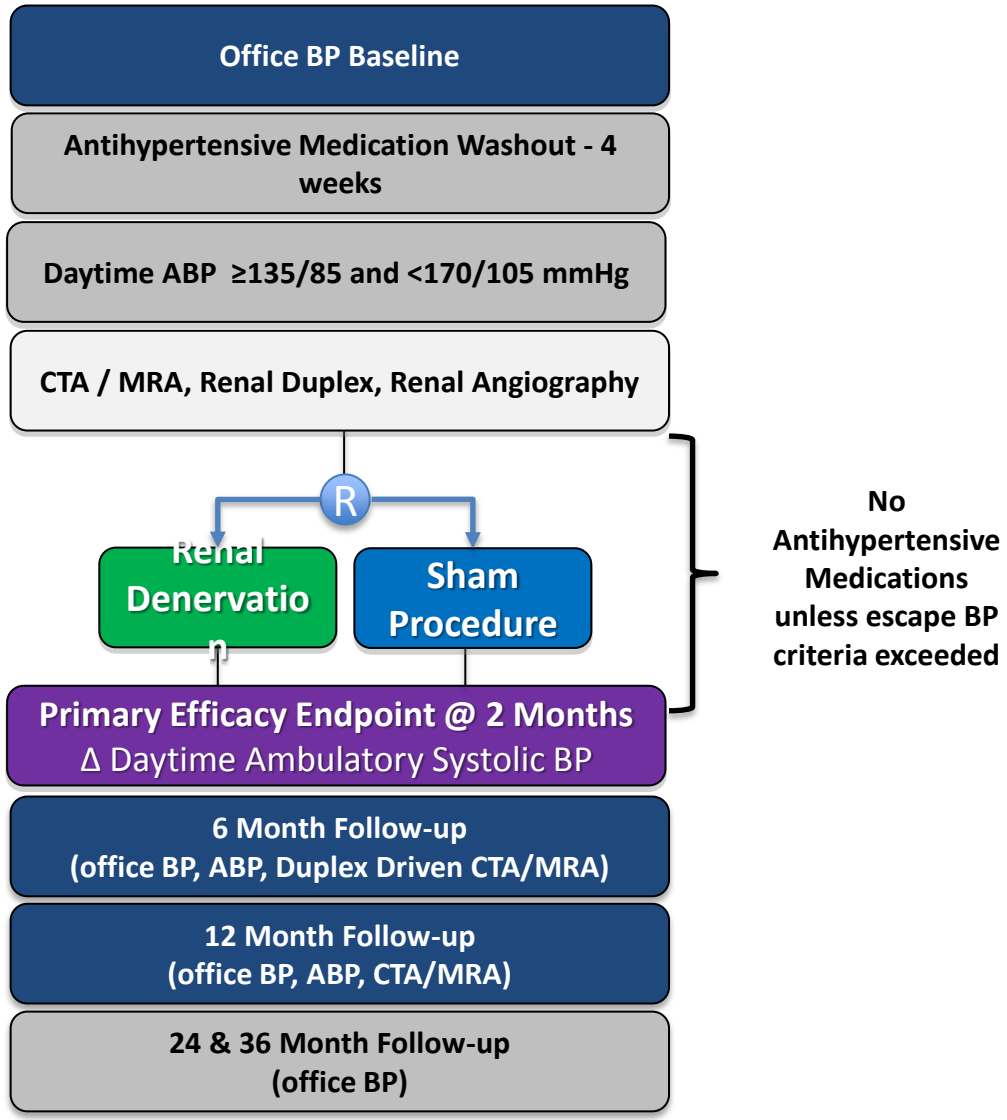
RADIANCE-HTN SOLO - Study Design

Blinded, sham-controlled, and randomized 1:1 (N=146)

Powered to detect 6 mmHg difference in ambulatory SBP between treatment arms with 80% power

Key Entry Criteria:

- Hypertension controlled on 1-2 anti-HTN meds or uncontrolled on 0-2 meds
- Off-medication daytime ABP ≥135/85 and <170/105 mmHg
- Age 18-75 years
- No prior cardiovascular or cerebrovascular events
- No Type I or uncontrolled Type II diabetes
- eGFR ≥40mL/min/m^2
- Eligible renal artery anatomy (bilateral diameter 4-8mm, length ≥25mm, and no stenosis ≥30%)

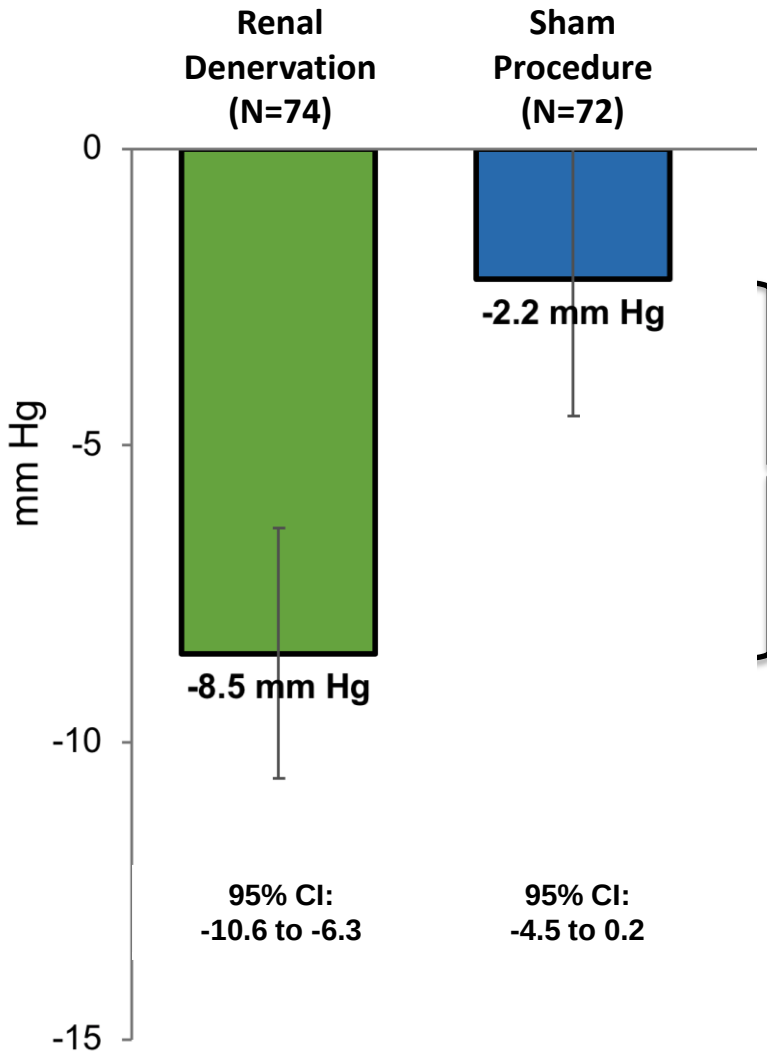


RADIANCE-HTN SOLO – Baseline / Procedure

Baseline Blood Pressures	Renal Denervation (N=74)	Sham Procedure (N=72)
Office BP after anti-HTN med washout (mm Hg)	155/100 ± 12/8	154/99 ± 16/9
Daytime ABP after anti-HTN med washout (mm Hg)	150/93 ± 8/5	150/94 ± 10/6
24-hour ABP after anti-HTN med washout (mm Hg)	143/87 ± 8/5	144/89 ± 10/6

	Renal Denervation (N = 74)	Sham Procedure (N = 72)	P Value
Treatment successfully delivered (min. 2 emissions bilaterally) (%)	96%	NA	--
Total Number of Emissions (N=72)	5.4 ± 1.0	NA	--
Total Emission Time (seconds) (N=72)	38 ± 7	NA	
Procedure time (arterial sheath insertion to removal) (min)	72 ± 23	38 ± 13	<0.001
Contrast volume (cm^3)	141 ± 69	79 ± 41	<0.001
Fluoroscopy exposure (min)	14 ± 7	5 ± 12	<0.001

Primary Efficacy Endpoint (ITT):
Change in Daytime Ambulatory Systolic BP at 2 Months

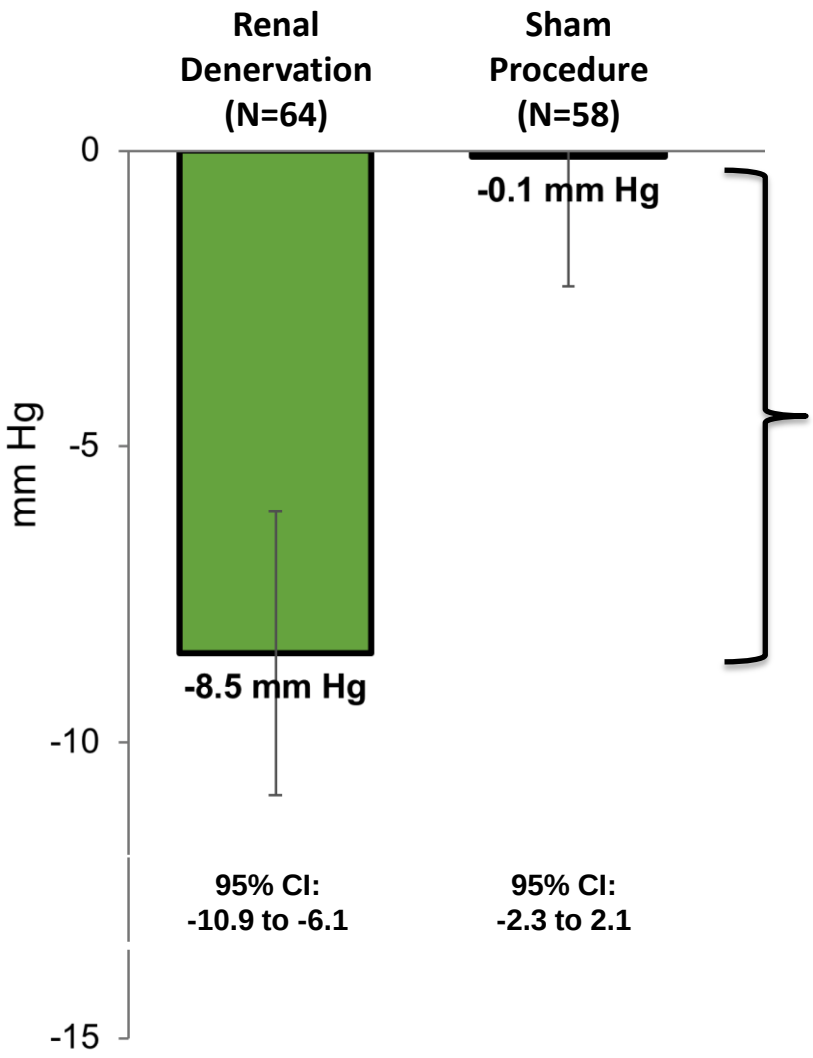


Between Group Difference Adjusted for Baseline BP

-6.3 mm Hg
(95% CI, -9.4 to -3.1)
P<0.001

Change in Daytime Ambulatory Systolic BP at 2 Months

Analyse Per-Protocol



Between Group Difference Adjusted for Baseline BP

-8.2 mm Hg
(95% CI, -11.5 to -5.0)
p<0.001

Per-Protocol Excluded:

- Patients resuming medications prior to 2 mo
- Patients not meeting entry criteria
- Renal Denervation patients with incomplete Tx
- Patients without 2-month ABP collection

10 Renal Denervation patients excluded

- 5 received antihypertensive meds prior to 2 mo

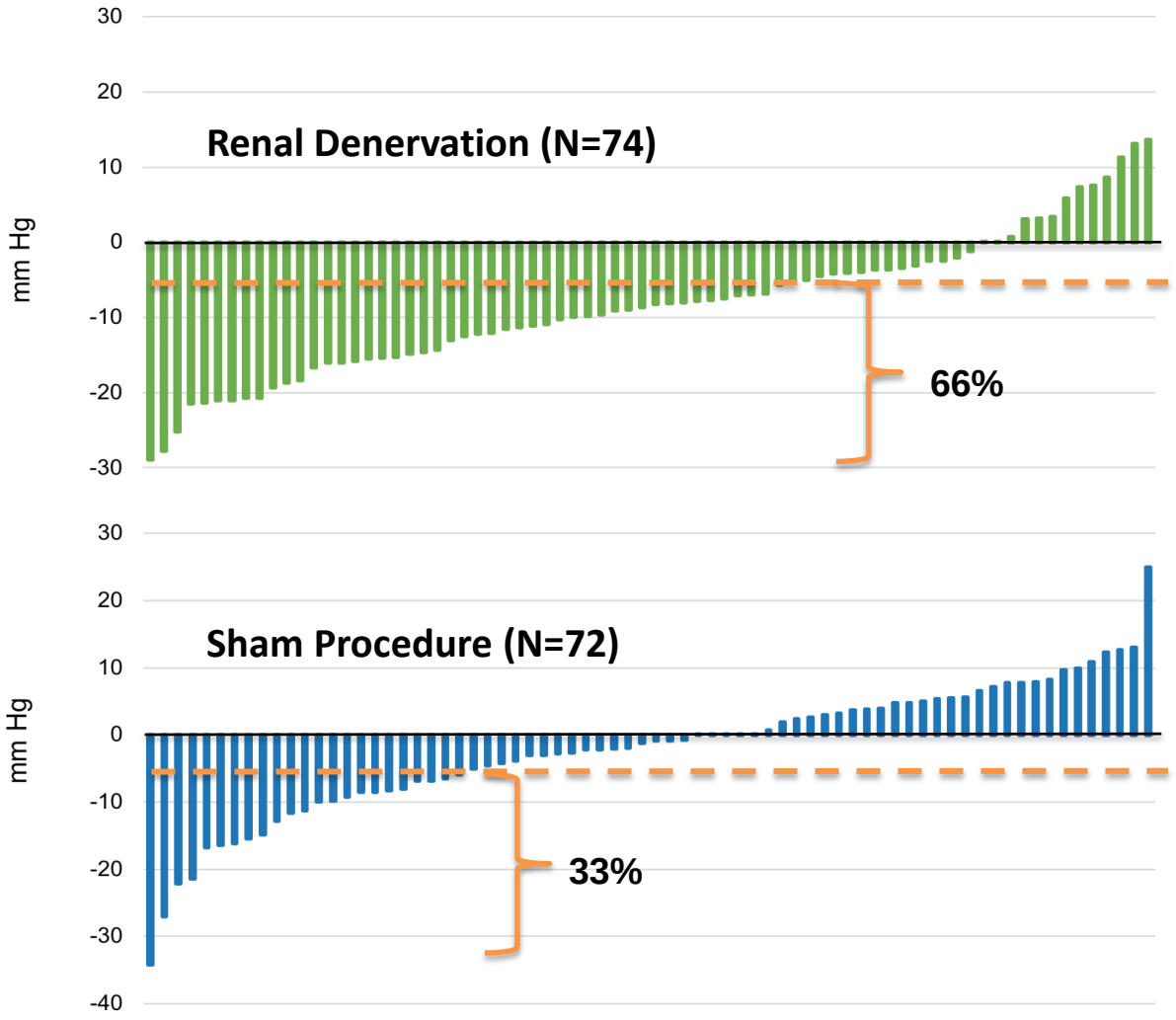
14 Sham Procedure patients excluded

- 13 received antihypertensive meds prior to 2 mo

One month Safety Event

Event	Renal Denervation (N = 74)	Sham Procedure (N = 72)
Major adverse event (%)	0%	0%
Death within 30 days	0%	0%
Acute renal failure within 30 days	0%	0%
Embolic event resulting in end-organ damage within 30 days	0%	0%
Renal artery or other vascular complication requiring intervention within 30 days	0%	0%
Hypertensive crisis within 30 days	0%	0%
New renal artery stenosis of more than 70% within 6 months[†, ††]	0%	0%

Individual Patient Response at 2 Months:
Change in Daytime Ambulatory Systolic BP at 2 Months (ITT Population)

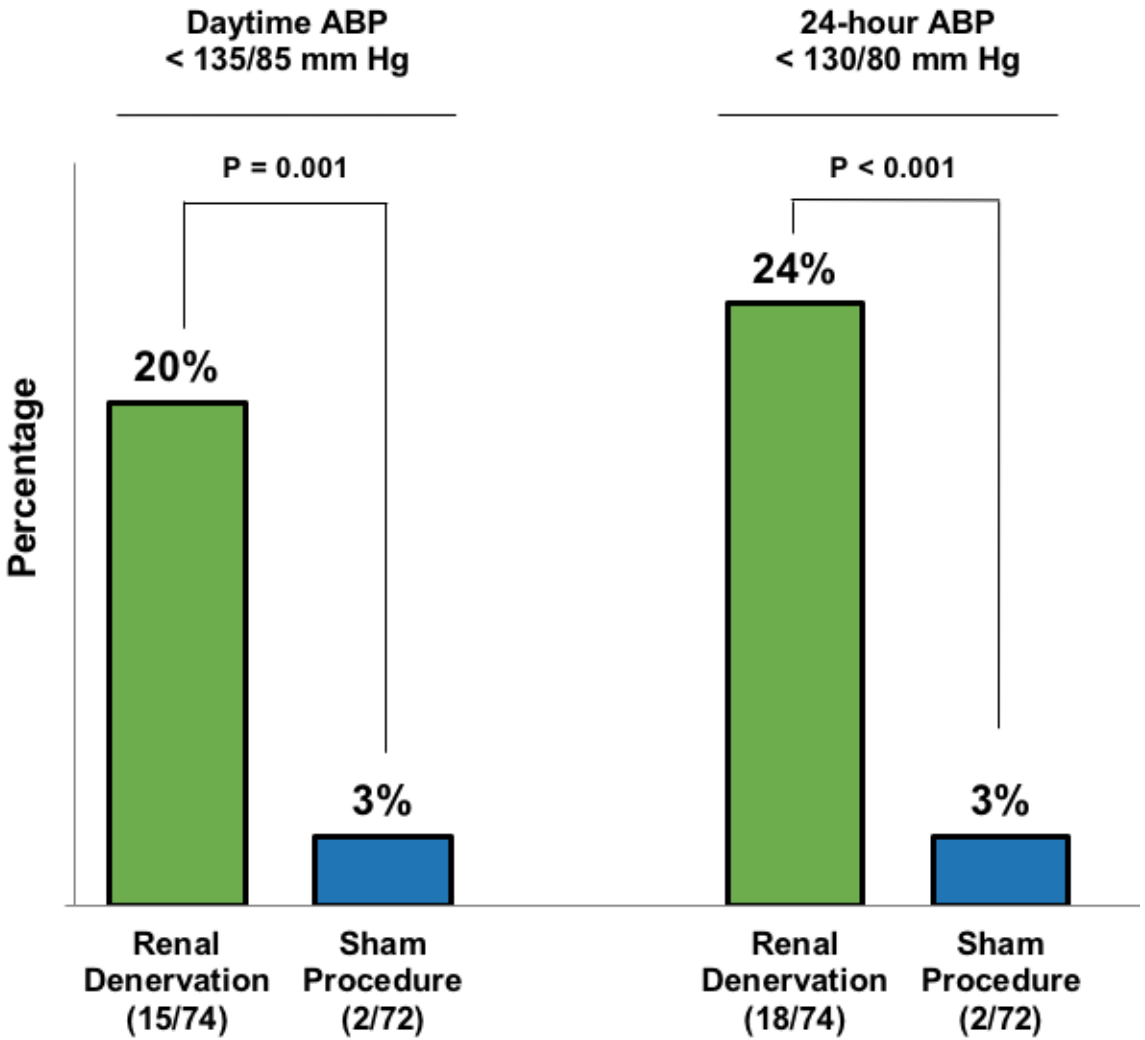


% Patients with ≥ 5 mm Hg Decrease

Renal Denervation: 66%
Sham Procedure: 33%

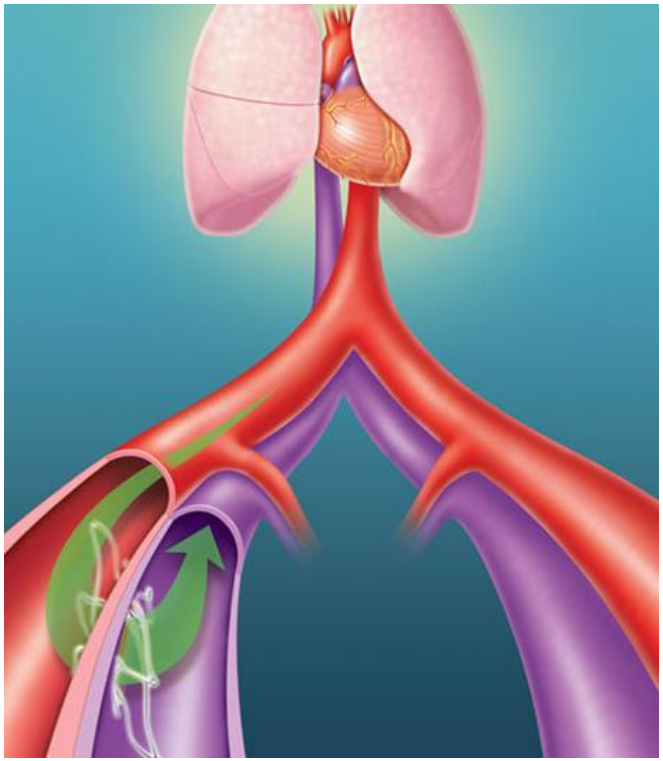
P<0.001

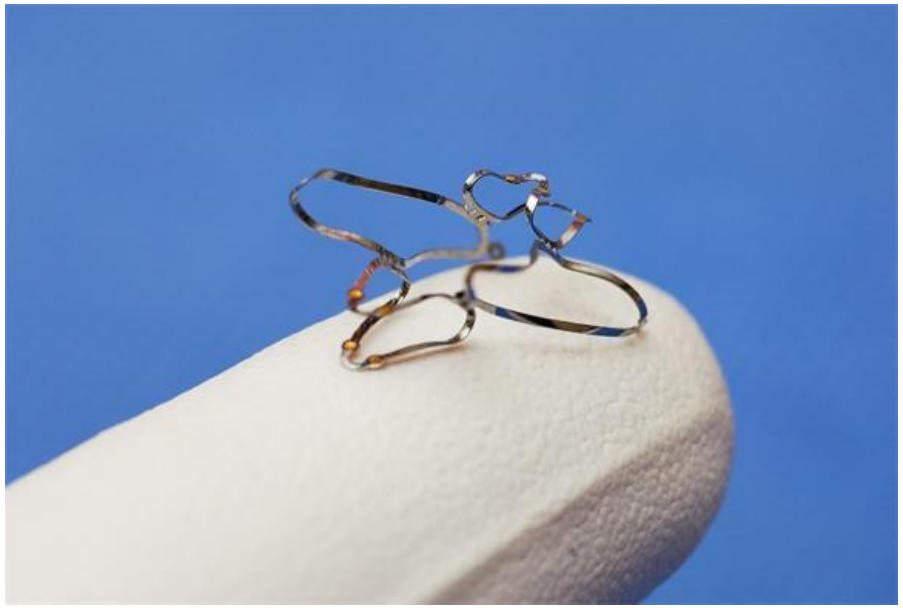
Patients Achieving Control
Without the Addition of Antihypertensive Medications



Anastomose Artério-veineuse

Rox Coupler

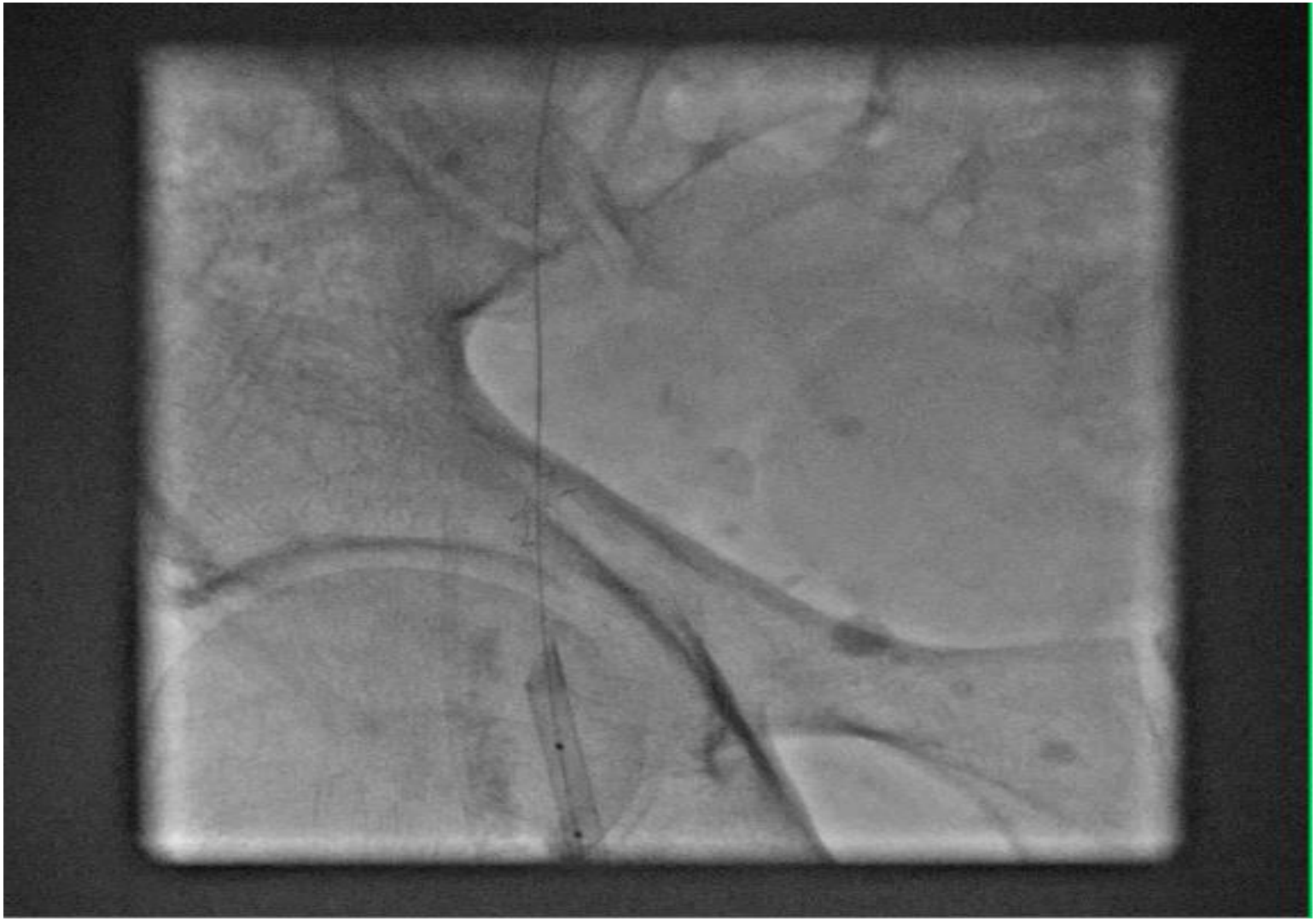




Creation of a fixed external iliac arterio-venous anastomosis with the ROX COUPLER

Self-expanding nitinol device permits a controlled shunt volume of 800 to 1000 ml/mn

ROX Coupler – Angio Final



Physiology

Shunt via proximal AV anastomosis

↑Right Atrial Pressure

↑Cardiac Output

↓Systemic Vascular Resistance

- ANP release → vasodilatation
- Bainbridge reflex

→ ↑ heart rate

→ peripheral sympatho-inhibition

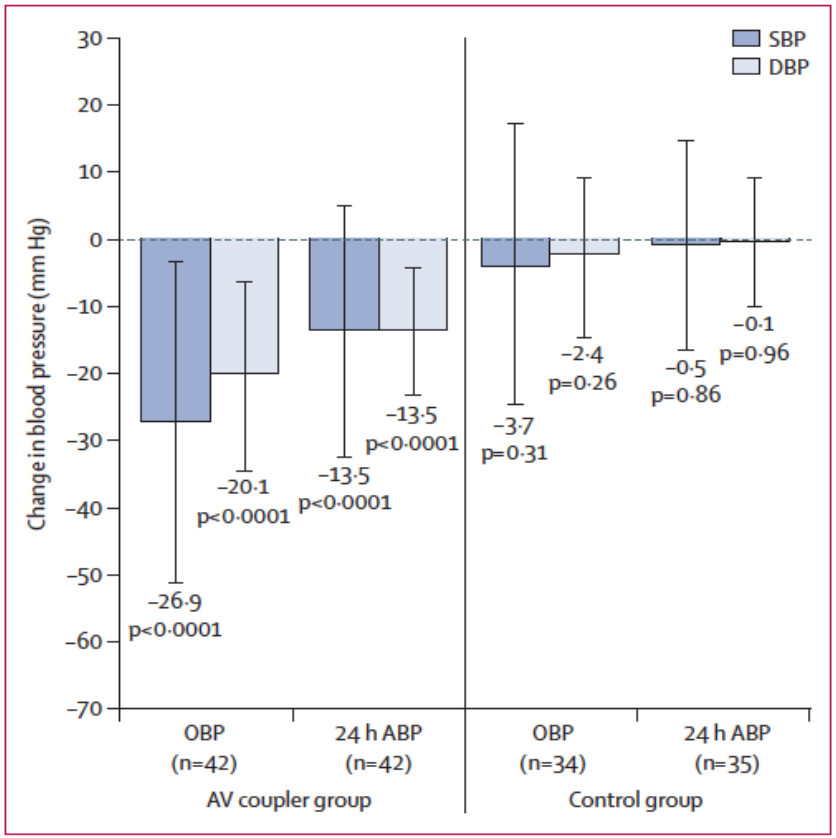
- ↑ venous oxygenation & ↑ pulmonary blood flow
- Activation of pulmonary arterial mechanoreceptors
- Venous baroreceptor activation

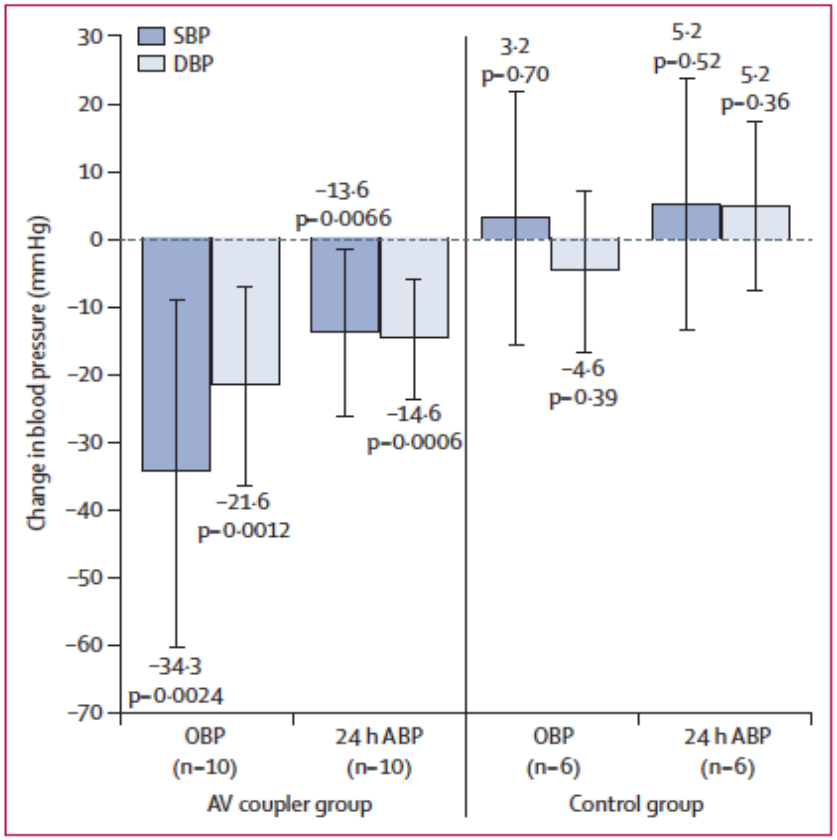
↑ arterial compliance
↓ reflected pulse wave
↓ effective arterial volume

↑ tissue oxygen delivery
→ ↓ chemoreceptor activity
→ ↓ sympatho-excitation due to cerebral / renal hypoperfusion
→ ↓ sodium and water retention

Efficacy

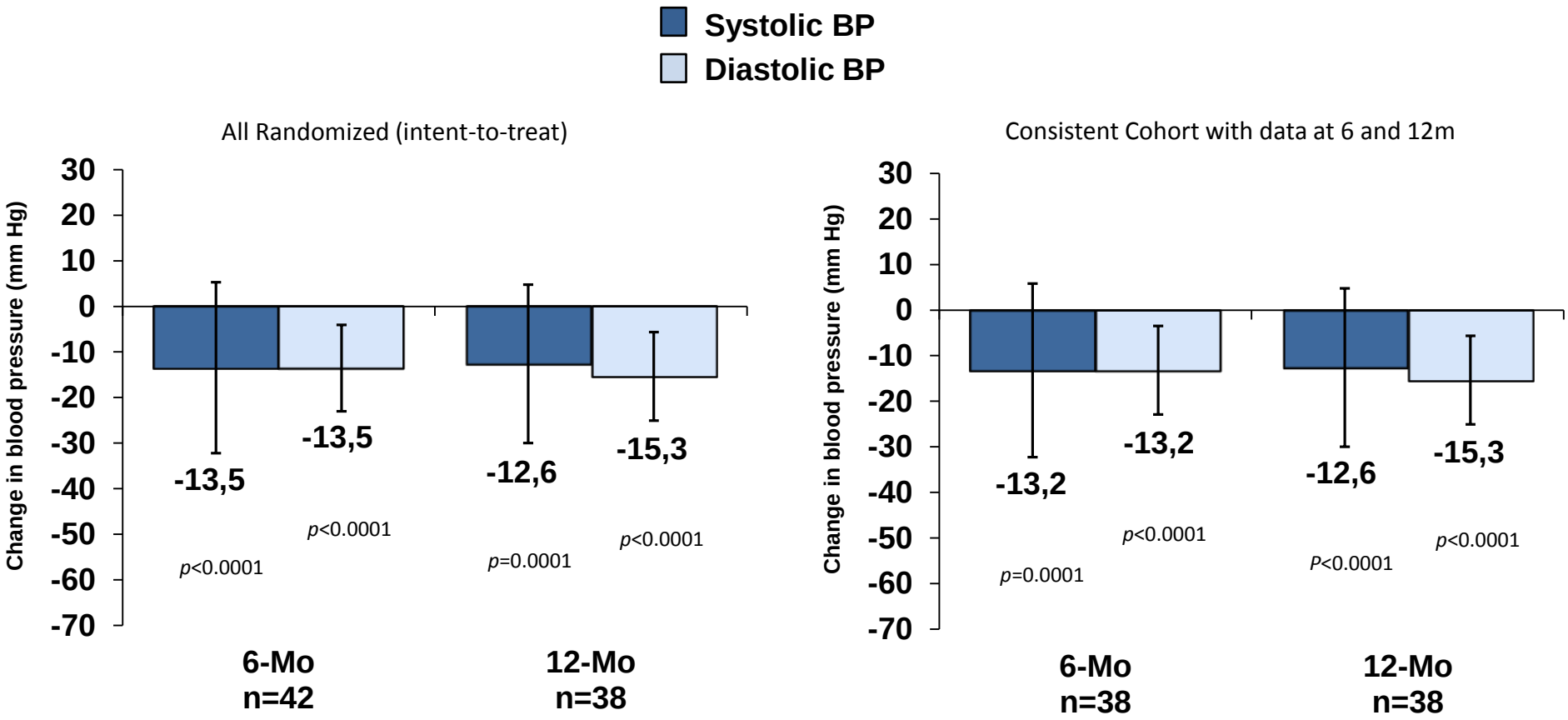
Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial





Lobo and al. Lancet 2015

Mid Term - Efficacy



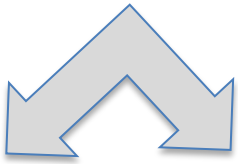
Change in 24-hr ABPM at 6 and 12 Months

Mid Term - Safety

Procedural complication	
Arterial deployment*	3 (7·1%)
Intimal dissection iliac artery	1 (2·4%)
Transient bradycardia	1 (2·4%)
Contrast reaction	1 (2·4%)
Urinary retention	1 (2·4%)
Anaemia	1 (2·4%)
Transient or localised pain	2 (4·8%)
Nausea or lethargy	1 (2·4%)
Deep venous thrombosis	1 (2·4%)
Lower limb pain	1 (2·4%)
Device-related event	
Venous stenosis	12 (28·6%)

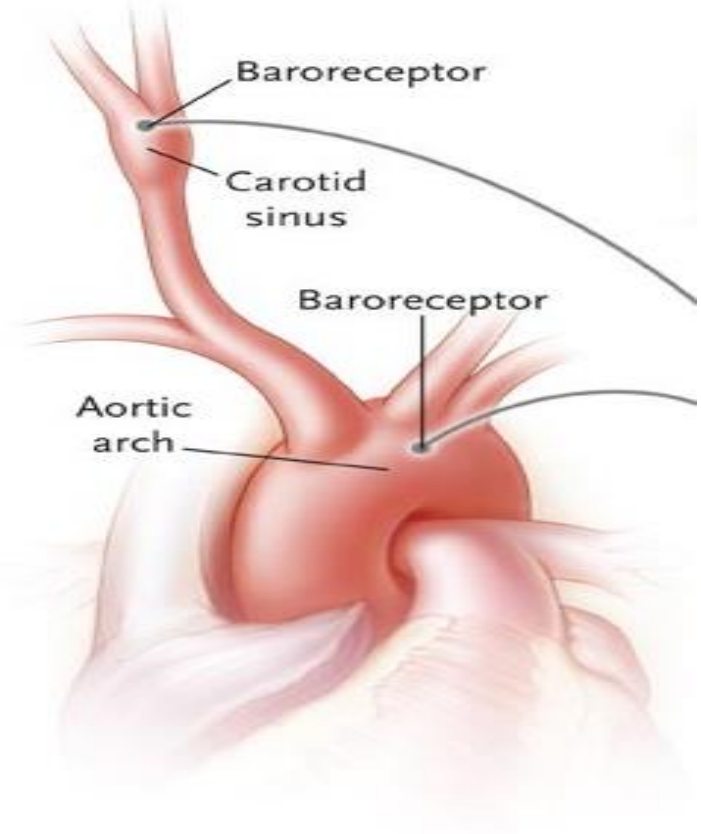
Lobo and al. Lancet. 2015

Baroreflex

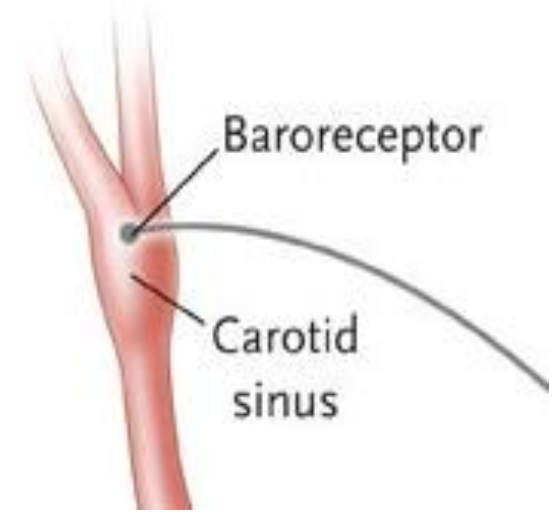


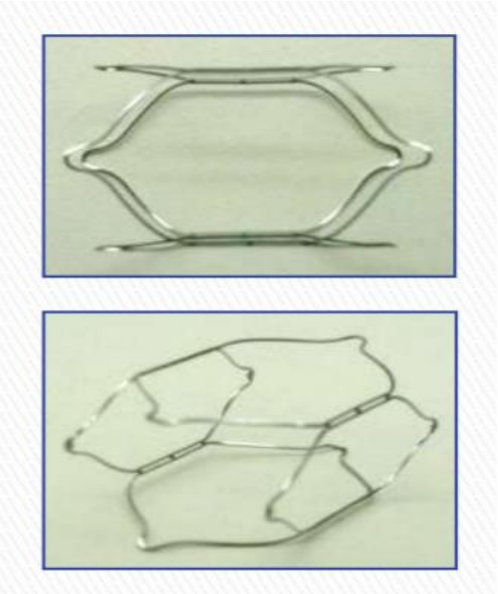
Baromodulation

Barostimulation

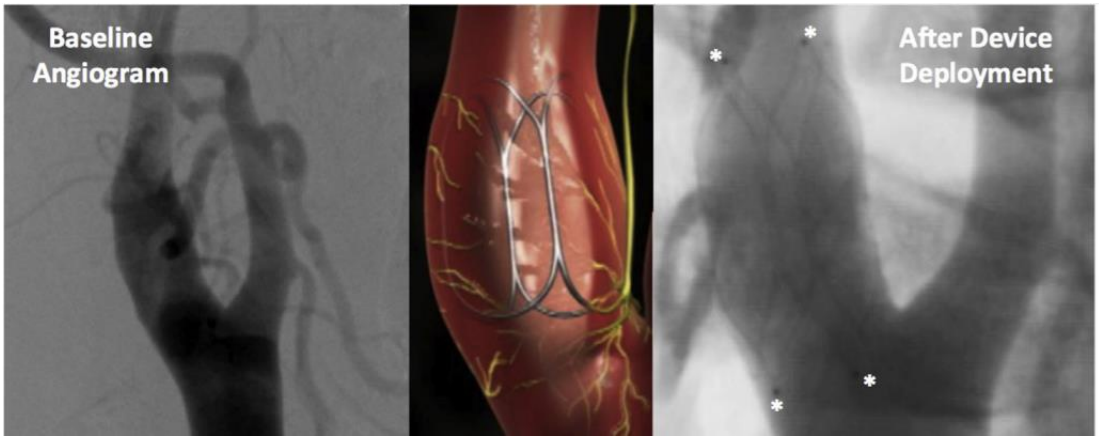


Modulation du Barorecepteur



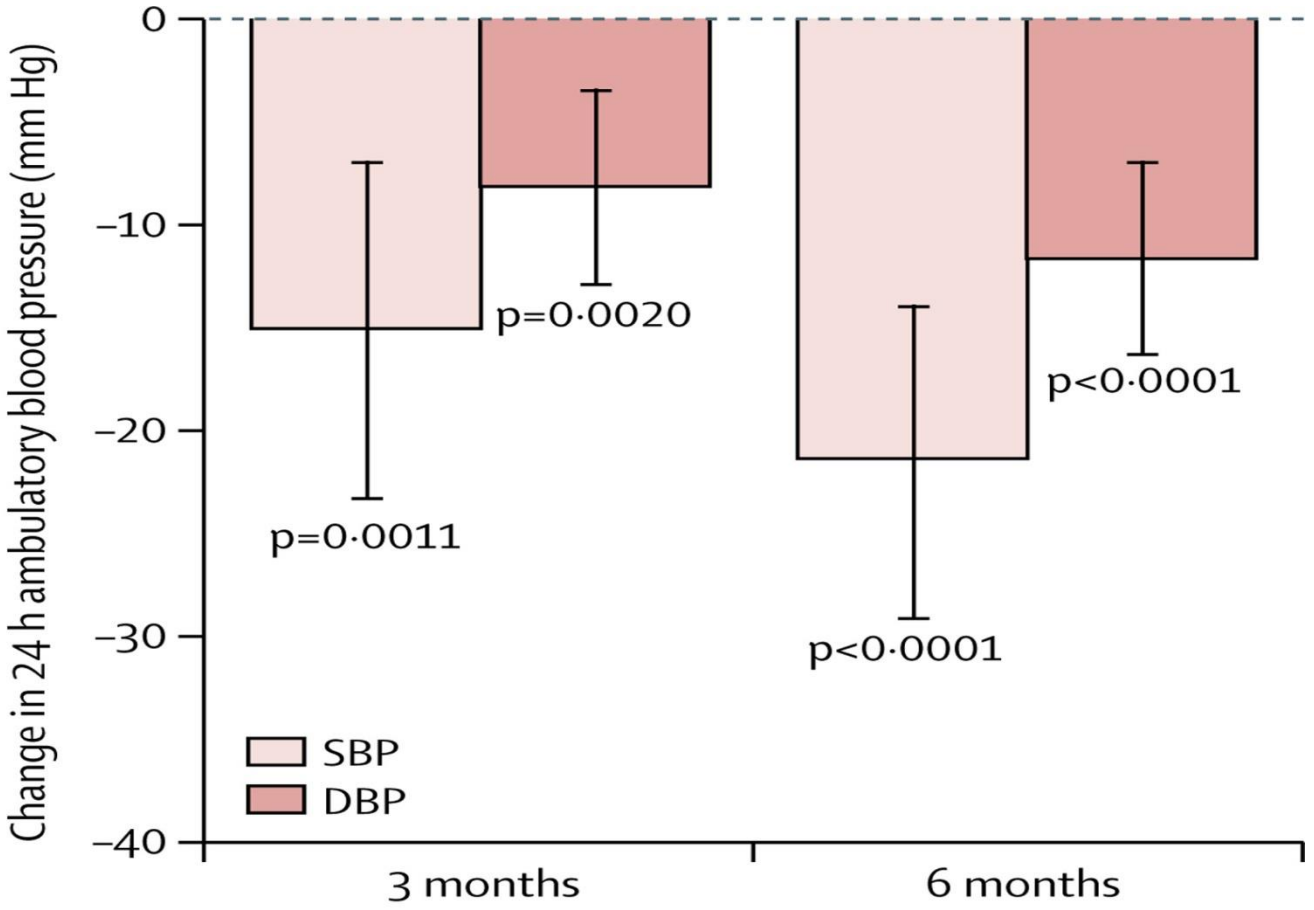


Mobius HD



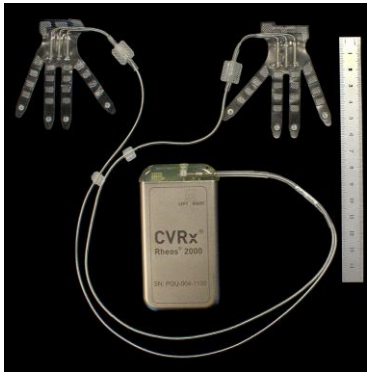
CALM – FIM Study (Safety)

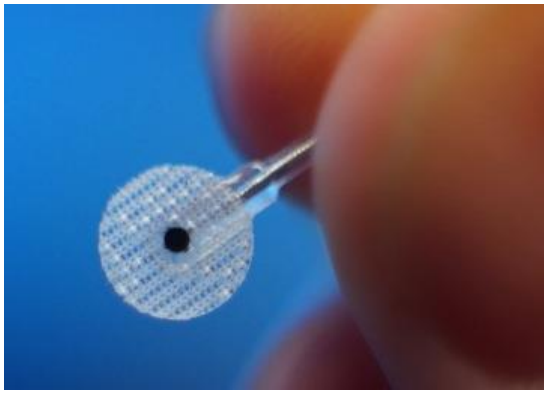
n= 30

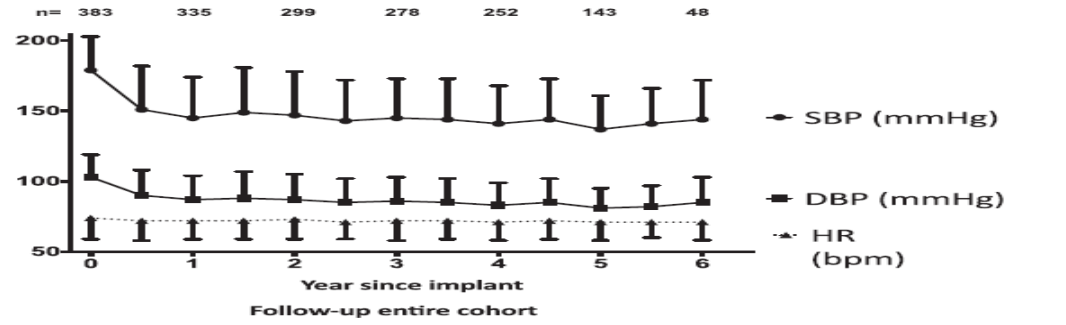


	3 months	6 months
Baseline SBP (mm Hg)	166	166
Baseline DBP (mm Hg)	100	100

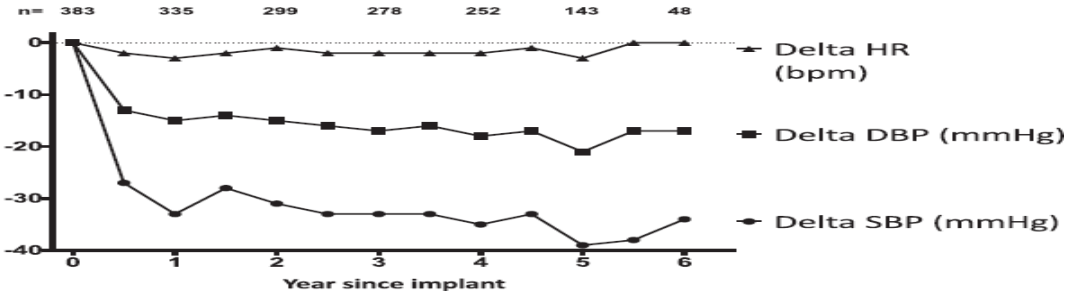
Stimulation du Barorecepteur





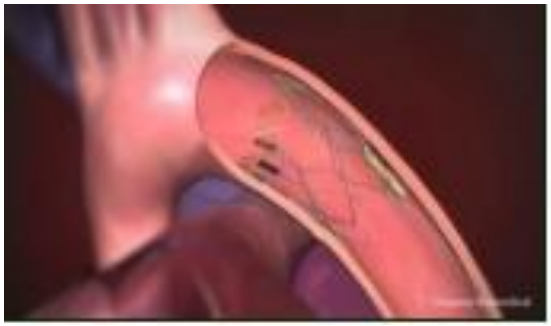


Follow-up entire cohort

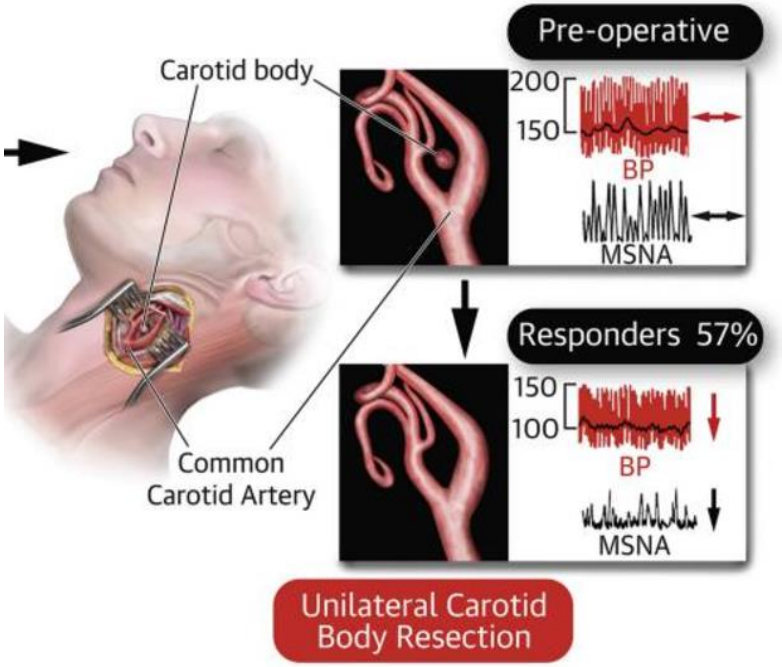


Autre thérapie …

AORTIC BARORECEPTEUR STIMULATION

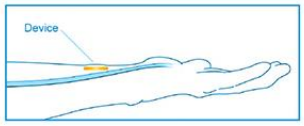


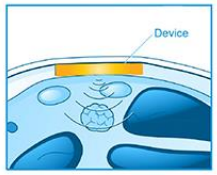
CAROTID BODY ABLATION



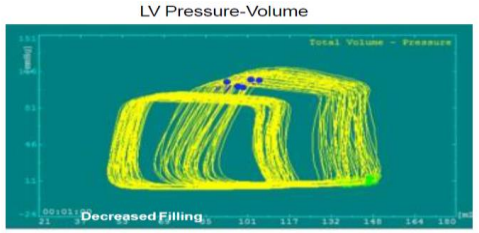
DEEP BRAIN STIMULATION

ELECTROSTIMULATION





SHORT AV PACING



Atrial pacing versus AV sequential pacing with short AV interval (40ms).
Acute Porcine Model

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 3021–3104
doi:10.1093/eurheartj/ehy339

2018 ESC/ESH Guidelines for the management of arterial hypertension

Device-based therapies for hypertension

Recommendation	Class[a]	Level[b]
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.[367,368]	III	B

Conclusion

Reduction de 7.7 mmhg SOBP

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Reduction 20% Evenement CV

Retour au stade de recherche clinique

Dynamique constructive - Nombreuses interrogations