



INSTITUT
CARDIOVASCULAIRE
PARIS
SUD

La Denervation rénale

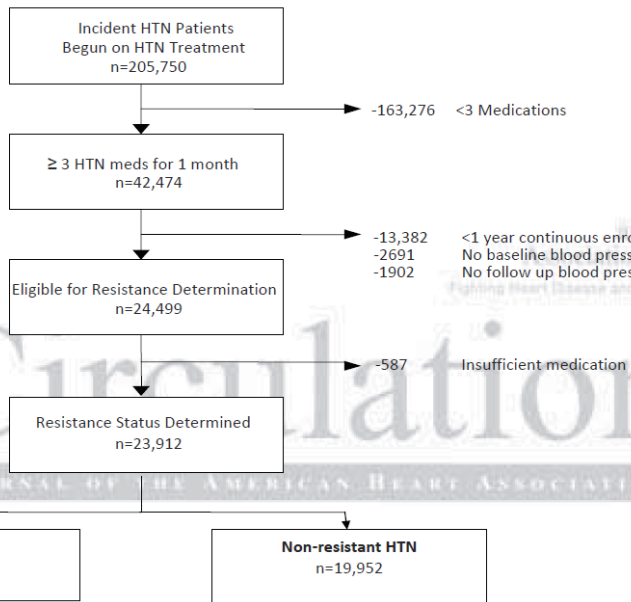
Hakim Benamer

*ICPS Massy, ICV-GVM la Roseraie, Aubervilliers
Hôpital Foch Suresnes*

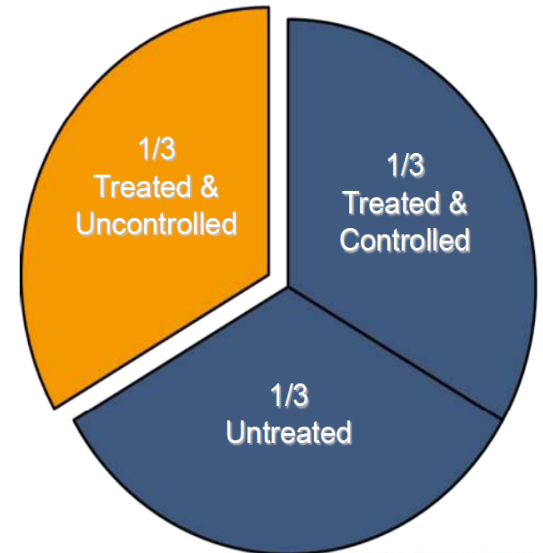
APPAC 2015 et CNCF

GENERALITES

Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients
 Stacie L. Daugherty, J. David Powers, David J. Magid, Heather M. Tavel, Frederick A. Masoudi, Karen L. Margolis, Patrick J. O'Connor, Joe V. Selby and P. Michael Ho

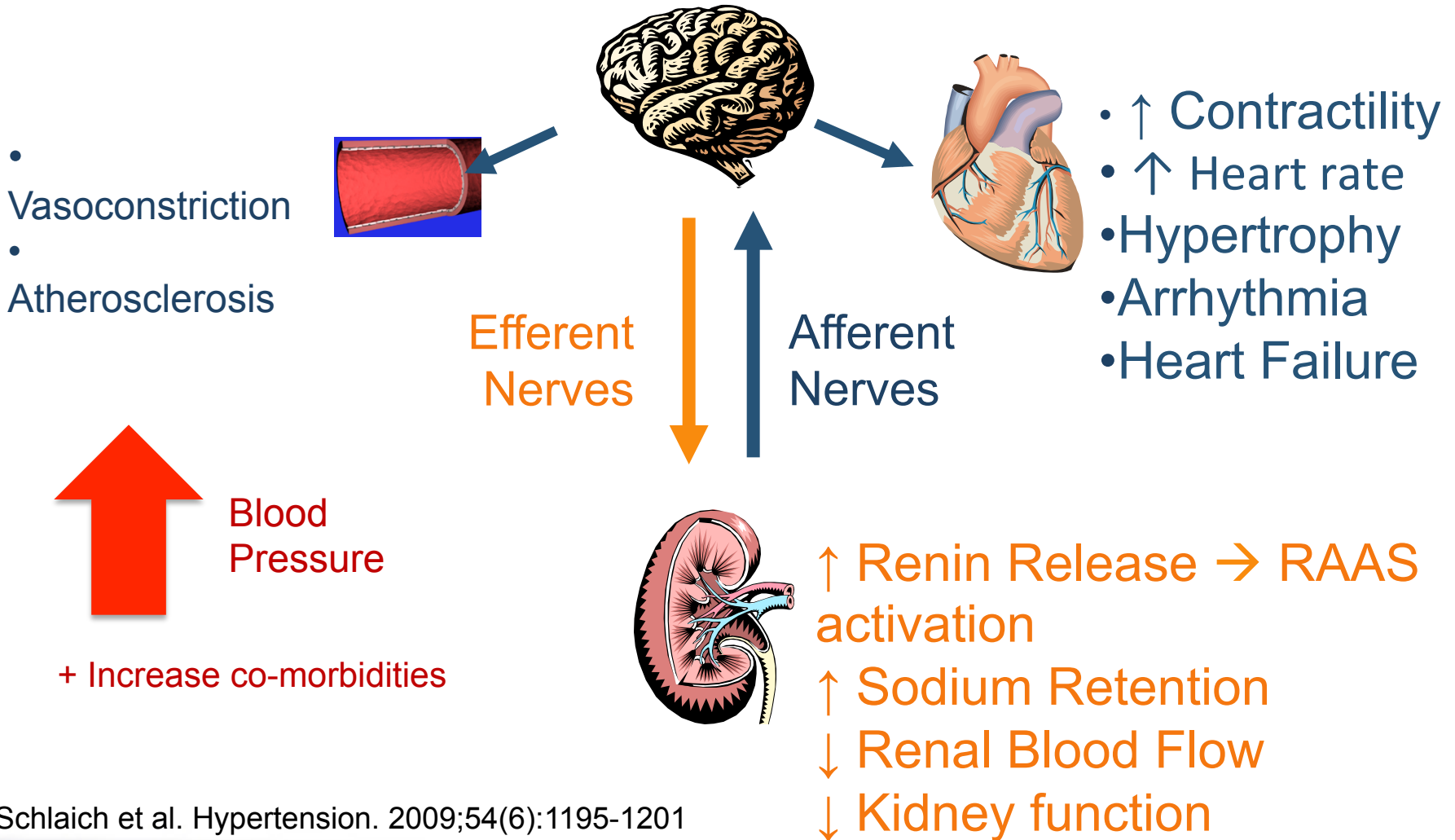


- 1 in 3 adults have hypertension
- 230 million people in EU5, US, & Japan
- 1 billion people worldwide
- 2x cardiovascular mortality for every 20/10 mmHg BP increase



Renal Sympathetic Nerve Activity:

Kidney as Origin & Recipient of Central Sympathetic Drive



L'histoire de la dénervation rénale

- 
- ✓ Etudes chirurgicales (1931, 1952, 1953)
 - ✓ Preuve du concept pour l'approche percutanée (2009)
 - ✓ HTN1 (2009)
 - ✓ HTN2 (2010)
 - ✓ New devices
 - ✓ Recommandations nationales (2011, 2012)
 - ✓ Recommandations Européennes (2013)
 - ✓ Registres locaux, nationaux, mondiaux
 - ✓ HTN3

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
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SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.

and




Jesse E. Thompson, M.D., Boston



Effective, but significant morbidity

Dr. Reginald H. Smithwick

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

		MSNA (burst/min)		BP (mmHg)
	* 59 year old male on 7 HTN meds			
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)

Renal denervation to treat resistant hypertension: Guarded optimism

TABLE 2

The Symplicity HTN-1 and HTN-2 trials: Results

Primary efficacy outcomes ^a	SYMPPLICITY HTN-1 ¹⁴			SYMPPLICITY HTN-2 ¹⁵			
	Period	Number of patients	Change in office systolic blood pressure (SBP), mm Hg (mean, 95% CI)	Renal denervation group		Control group	
				Period	Change in office SBP, mm Hg (mean, SD), n = 49 ^b	Period	Change in office SBP, mm Hg (mean, SD), n = 51 ^b
	1 mo	41 of 45	-14/-10 (4/3)	1 mo	-20/-7	1 mo	0/0
	3 mo	39 of 45	-21/-10 (7/4)	3 mo	-24/-8	3 mo	-4/-2
	6 mo	26 of 45	-22/-11 (10/5)	6 mo	-32/-12 (23/11)	6 mo	1/0 (21/10)
	9 mo	20 of 45	-24/-11 (9/5)				
	12 mo	9 of 45	-27/-17 (16/11)				

Nonresponders 6 (13%) of 45 patients had an SBP reduction < 10 mm Hg

5 (10%) of 49 patients in the renal denervation group and 24 (47%) of 51 controls had no decline in SBP

4 (8%) of 49 patients in the renal denervation group and 6 (12%) of 51 controls needed drug increases before their 6-month follow-up

Renal denervation to treat resistant hypertension: Guarded optimism

TABLE 2

The Symplicity HTN-1 and HTN-2 trials: Results

	SYMPPLICITY HTN-1 ¹⁴	SYMPPLICITY HTN-2 ¹⁵												
Short-term safety outcomes	Renal artery dissection related to catheter placement before energy delivery (n = 1) Femoral artery pseudoaneurysm at access site (n = 3) (In initial and expanded cohorts)	Intraprocedural bradycardia requiring atropine (7/52 patients) Postprocedural drop in blood pressure (n = 1) Femoral artery pseudoaneurysm at access site (n = 1)												
Long-term safety outcomes	No renal vascular complications noted with postprocedure imaging studies on follow-up	No renal vascular complications noted with post-procedure imaging studies on follow-up												
		<table border="1"> <thead> <tr> <th>Renal denervation group</th> <th>Control group</th> </tr> </thead> <tbody> <tr> <td>Transient ischemic attack (n=1)</td> <td>Transient ischemic attack (n=2)</td> </tr> <tr> <td>Angina requiring a coronary stent (n=1)</td> <td>Angina requiring a coronary stent (n=1)</td> </tr> <tr> <td>Hypotension (n=1)</td> <td></td> </tr> <tr> <td>Hypertensive crisis (n=1)</td> <td></td> </tr> <tr> <td>Admission for nausea or vomiting possibly related to hypertension (n=1)</td> <td></td> </tr> </tbody> </table>	Renal denervation group	Control group	Transient ischemic attack (n=1)	Transient ischemic attack (n=2)	Angina requiring a coronary stent (n=1)	Angina requiring a coronary stent (n=1)	Hypotension (n=1)		Hypertensive crisis (n=1)		Admission for nausea or vomiting possibly related to hypertension (n=1)	
Renal denervation group	Control group													
Transient ischemic attack (n=1)	Transient ischemic attack (n=2)													
Angina requiring a coronary stent (n=1)	Angina requiring a coronary stent (n=1)													
Hypotension (n=1)														
Hypertensive crisis (n=1)														
Admission for nausea or vomiting possibly related to hypertension (n=1)														

Une sécurité Confirmée

Registre Monde Simplicity N=1162

- Renal artery re-intervention due to dissection (n=1) 0.09%
- Vascular complication
 - Vascular complication, pseudoaneurysm (n=4) 0.34%
 - Vascular complication, hematoma 0.09% (n=1)

Denervation Devices

Table 1 Details of the five CE-marked renal denervation devices

Catheter system	French	Energy	Electrodes/polarity	Design	Patients ^a	Longest follow-up ^a	BP changes at 6 months (mmHg) ^a	BP changes at longest follow-up (index a)	Study
Symlicity	6F	RF	1 unipolar	Single-tip	235	36 months (n = 34)	-32/-12 (n = 49)	-33/-16 (n = 34)	Symlicity HTN-1, ²² HTN-2 ^{7,9} (NCT00888433, NCT00664638)
EnligHTN	8F	RF	4 unipolar	Basket	46	6 months (n = 45)	-26/-10 (n = 45)	-26/-10 (n = 45)	EnligHTN-1 ²³ (NCT01438229)
Vessix V2	8F	RF	4-8 bipolar	Over-the-wire balloon	10	1 month (n = 10)	-30/-10 (n = 10)	-30/-10 (n = 10)	REDUCE-HTN (NCT01541865) ^b
OneShot	7/8F	RF	1 unipolar	helical, irrigated balloon	9	1 month (n = 9)	-31/-6 (n = 9)	-31/-6 (n = 9)	RHAS ⁵⁸
Paradise	7/8F	Ultrasound	1 transducer	fluid-filled balloon	15	12 months (n = 3)	-32/-17 (n = 11)	-25/-13 (n = 3)	REDUCE ⁵⁹

F, French; BP, blood pressure; RF, radiofrequency.

^aData are referring to manuscript published or orally presented.

^bHoppe UC, oral presentation during EuroPCR 2012, Paris, France.

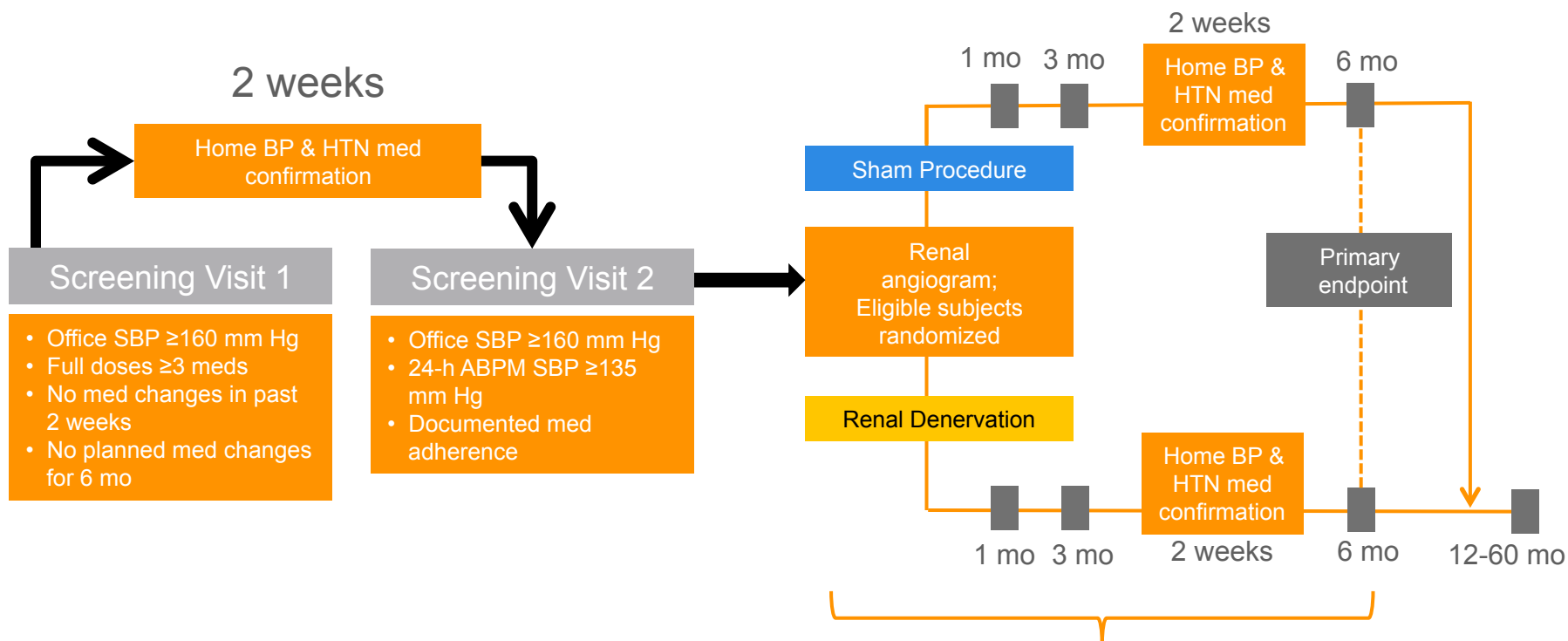
Simplicity HTN-3

- ✓ Blinded Randomized Trial vs Sham (2/1)
- ✓ 90 US centers.
- ✓ Resistant HBP with office sBP > 160 mmHG despite 3 treatments (at least one diuretic).
- ✓ Primary efficacy endpoint
sBP decrease > 15 mmHg at 6 months).
- ✓ Safety endpoint
Major Adverse Events at 6 months

SYMPPLICITY HTN-3: Severe Drug-Resistant HTN

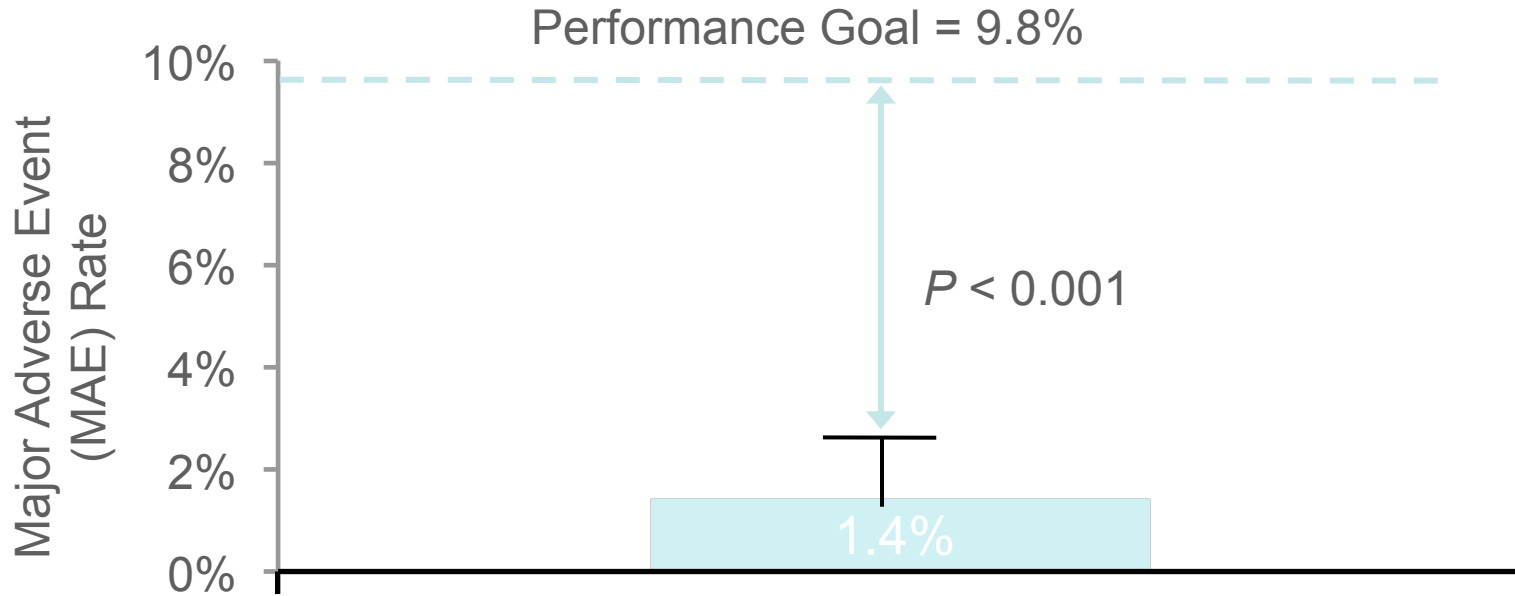
Office SBP ≥ 160 mm Hg

- 2:1 randomization, blinded and controlled
- Sham procedure in control patients that included renal angiogram
- 535 subjects randomized out of 1441 enrolled (63% screen failure rate)
- 2-week screening process, including maximum tolerated doses of antihypertensives



- Patients, BP assessors, and study personnel all blinded to treatment status
- No changes in medications for 6 M

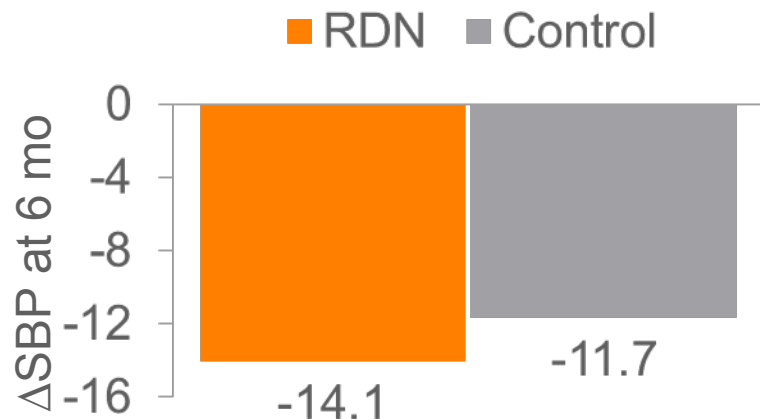
HTN-3 Results: Primary Safety Endpoint



Safety Measures	Renal Denervation (N = 364)	Sham Procedure (N = 171)	Difference (95% CI)	P
MAE	1.4% (5/361)	0.6% (1/171)	0.8% (-0.9%, 2.5%)	0.67

Primary Efficacy Endpoint

Office Systolic Blood Pressure at 6 Months, 5 mm Superiority Margin



	RDN	Control	P value
Baseline SBP	179.7	180.2	0.765
6 mo SBP	165.6	168.4	0.260

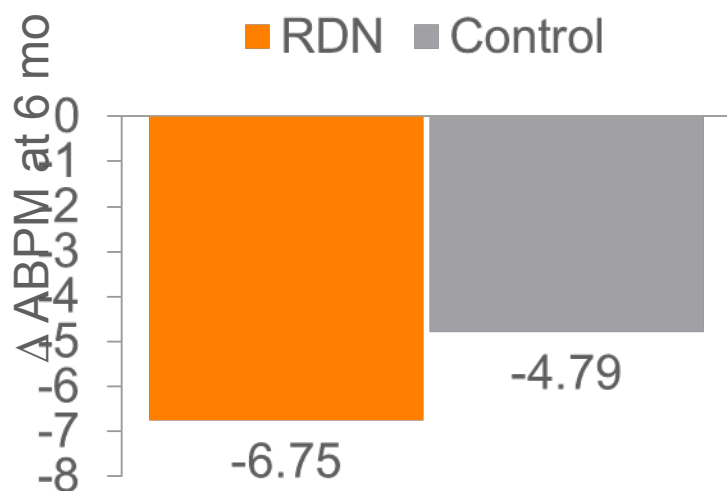
Change -14.1 -11.7 0.255¹
P < 0.001 *P* < 0.001

-2.39 (-6.89, 2.12), *P* = 0.255 (Primary analysis with 5 mm Hg superiority margin)

- Did not meet primary efficacy endpoint

Secondary Efficacy Endpoint

Ambulatory Systolic Blood Pressure at 6 Months, 2 mm Superiority Margin



	RDN	Control	P value
Baseline SBP	158.55	158.85	0.828
6 mo SBP	151.80	154.05	0.201
<i>Change</i>	<i>-6.75</i> <i>P < 0.001</i>	<i>-4.79</i> <i>P < 0.001</i>	<i>0.979</i>

-1.96 (-4.97, 1.06), $P = 0.979$ (ITT analysis with 2 mm Hg superiority margin)

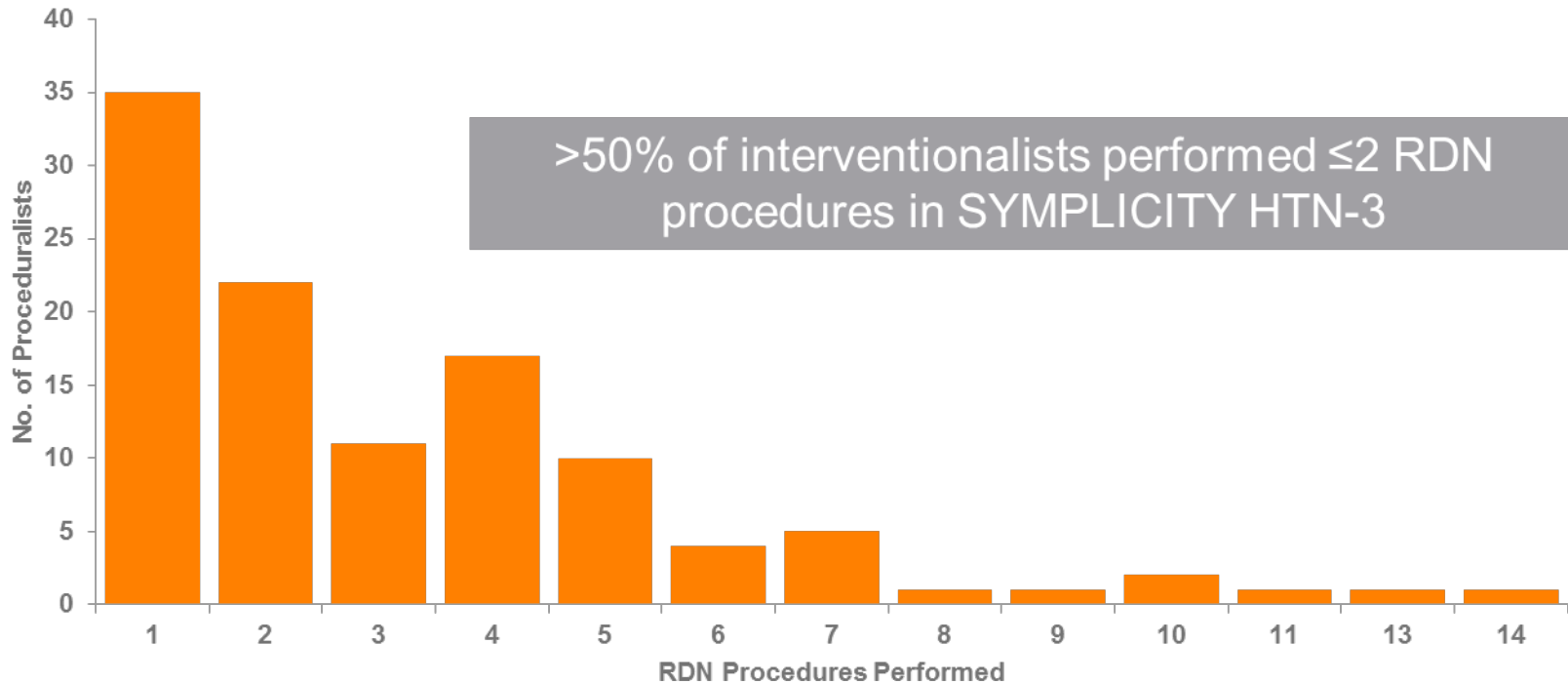
- Did not meet secondary efficacy endpoint

Pourquoi ce résultats d'HTN3?

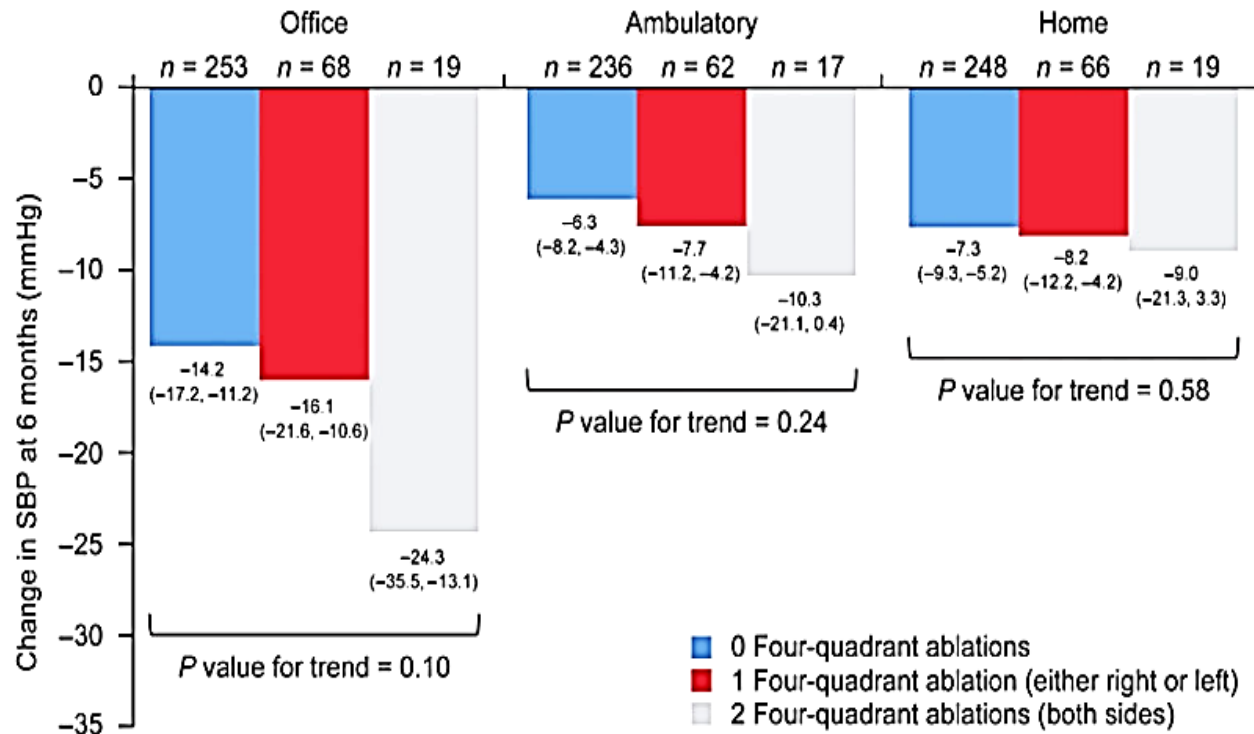
HTN-3: Procedural Experience

	HTN-1	HTN-3
No. of operators	20	112
No. of procedures per operator	6.0	3.3
No. of procedures per site	8.6	4.7

- a) 5X more operators vs HTN-1
- b) Greater heterogeneity of operator experience vs. HTN-1 and HTN-2
- c) Case proctoring was different and not comparable



Predictors of blood pressure response in the SYMPLICITY HTN-3 trial

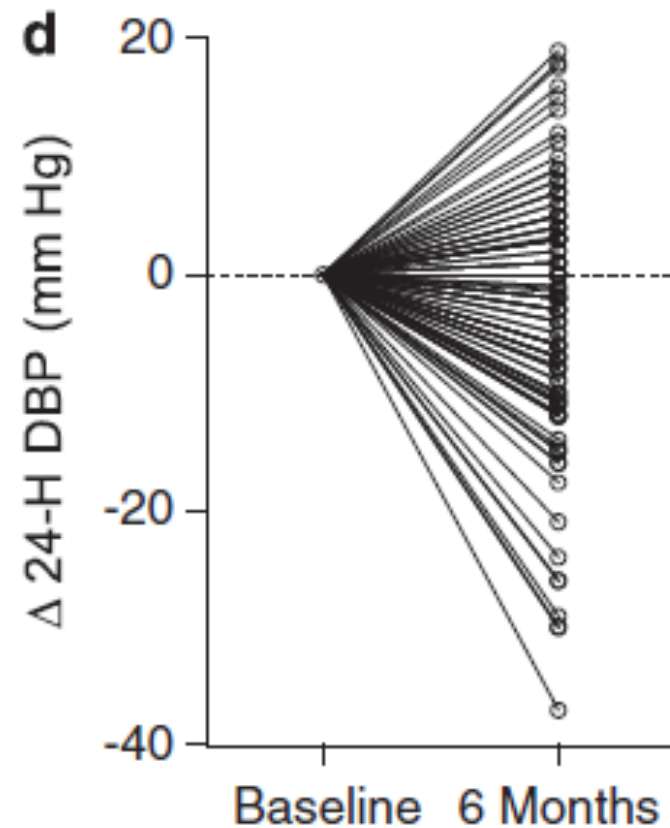
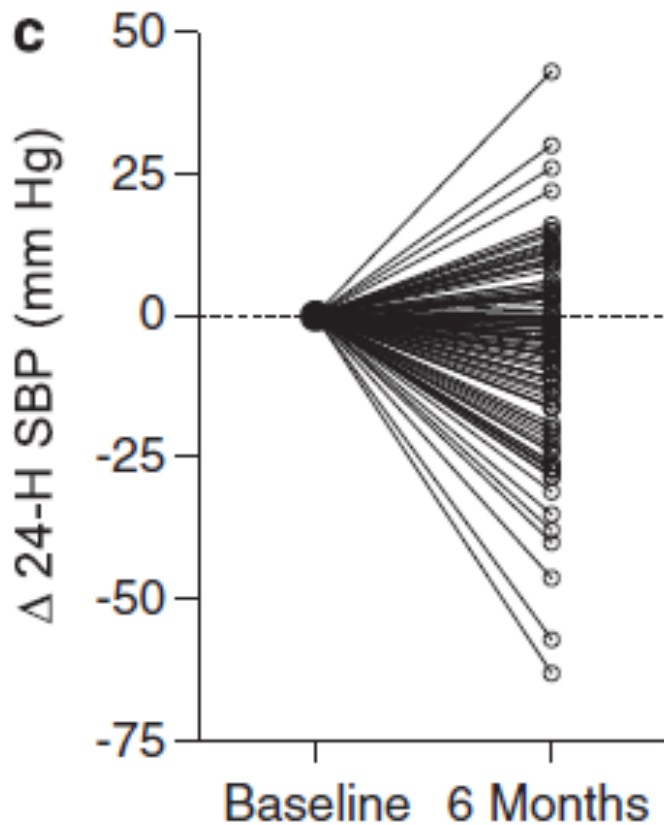


Baseline SBP (mmHg)	0 Four-quadrant ablations	1 Four-quadrant ablations	2 Four-quadrant ablations
Office	179.6	178.8	186.9
Ambulatory	158.7	161.2	159.9
Home	168.5	171.3	170.4

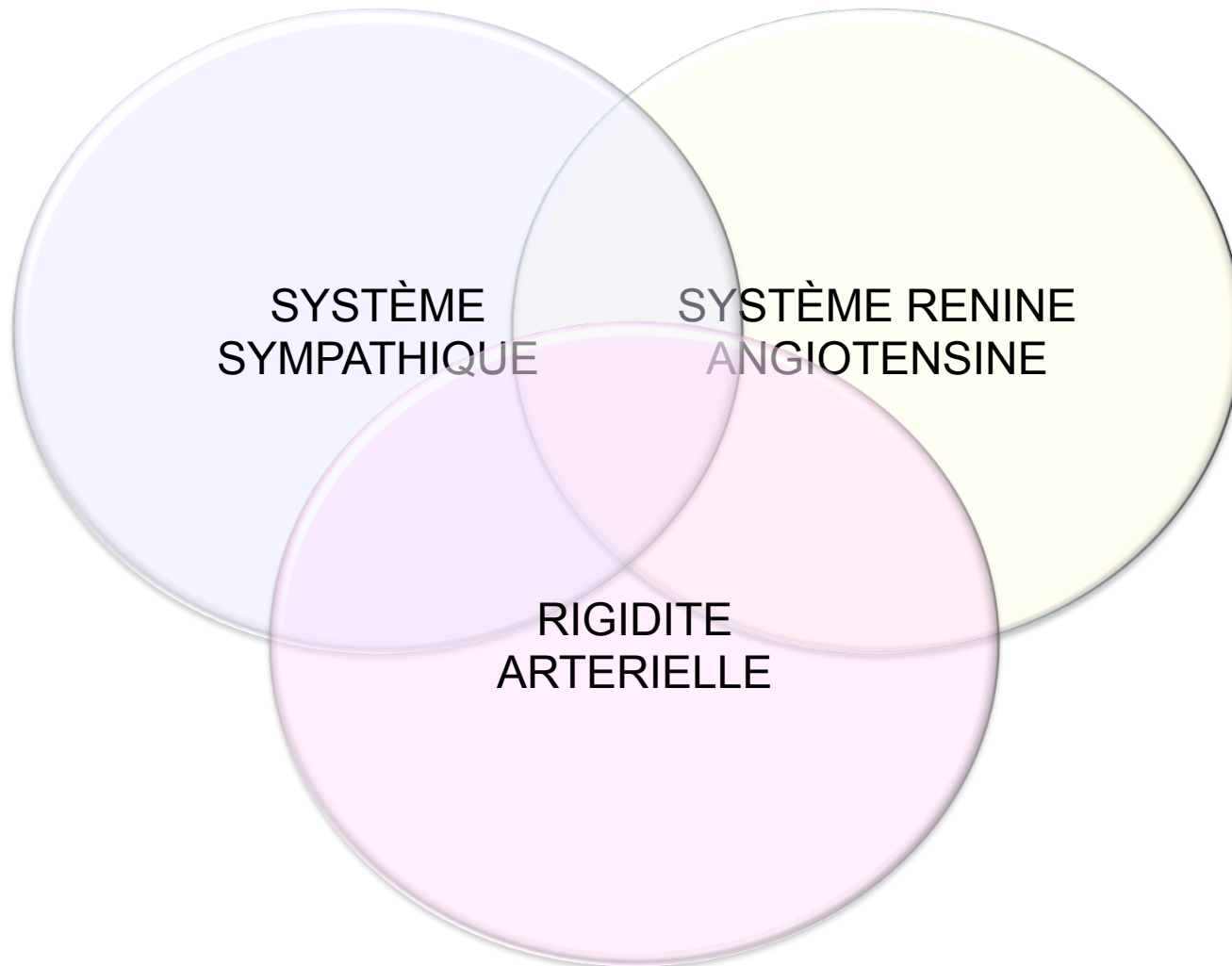
Change in office, ambulatory, home SBP at 6 M based on ablations in four quadrants of the renal artery for both kidneys, one kidney, or neither kidney. Four-quadrant ablation: 1 superior, 1 inferior, and 2 anterior/posterior ablations

Hétérogénéité de Réponse à la dénervation

Cohorte Européenne ENCORED

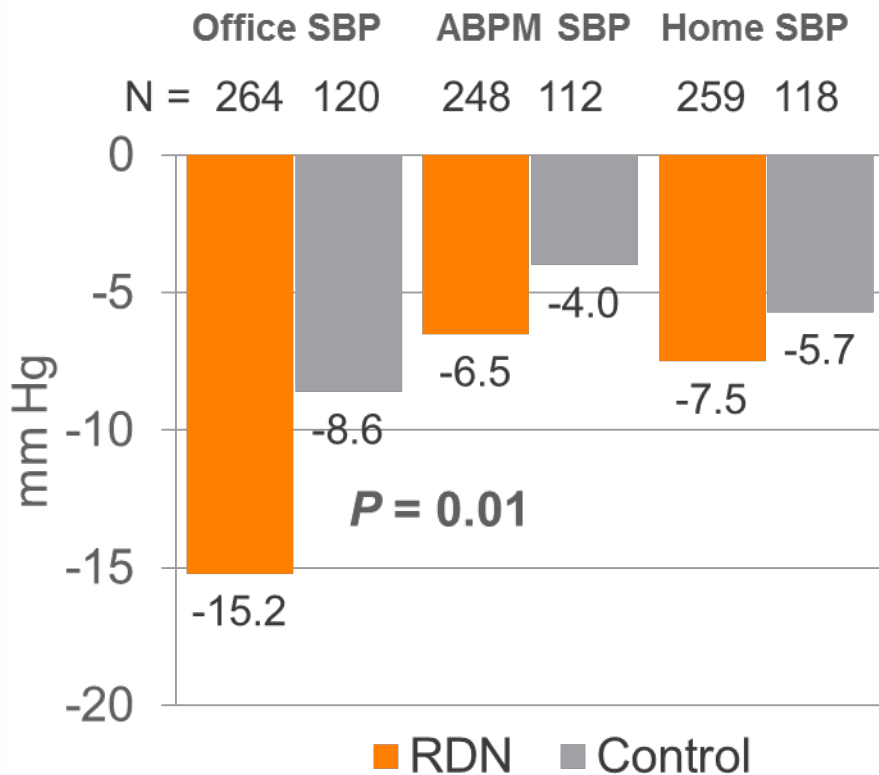


HTA C'est QUOI?

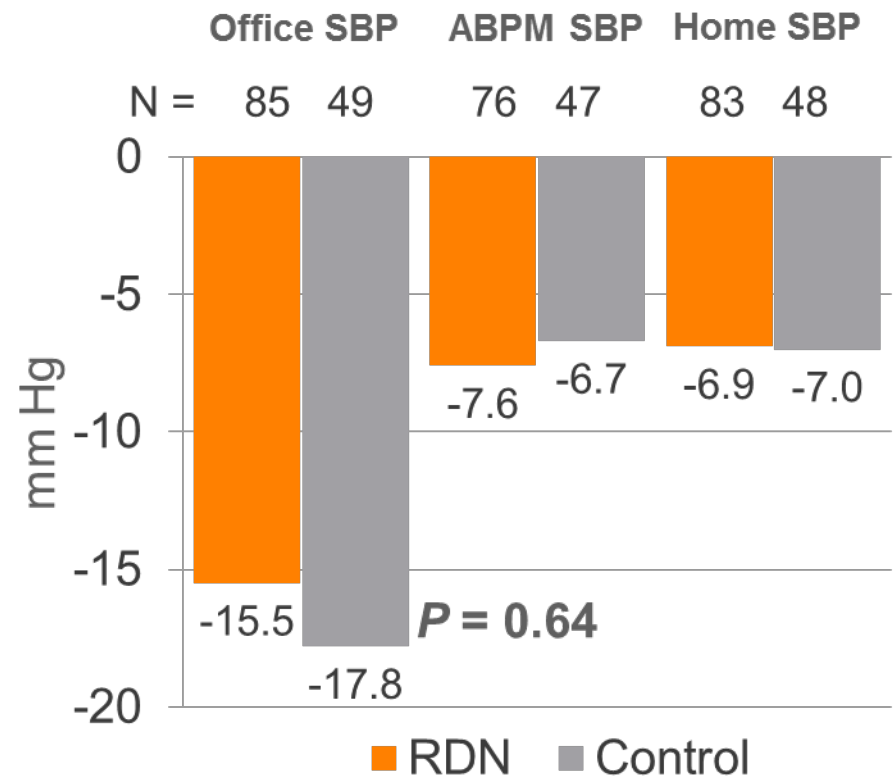


HTN-3: Different Control Response in African American Population

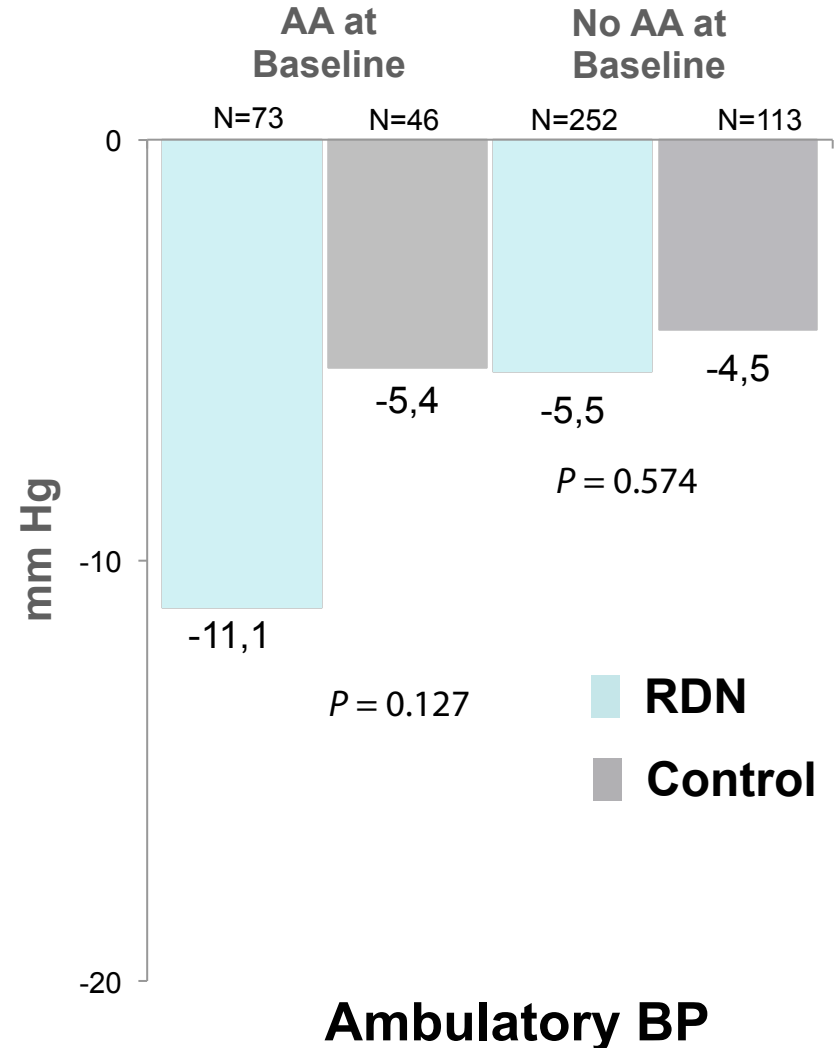
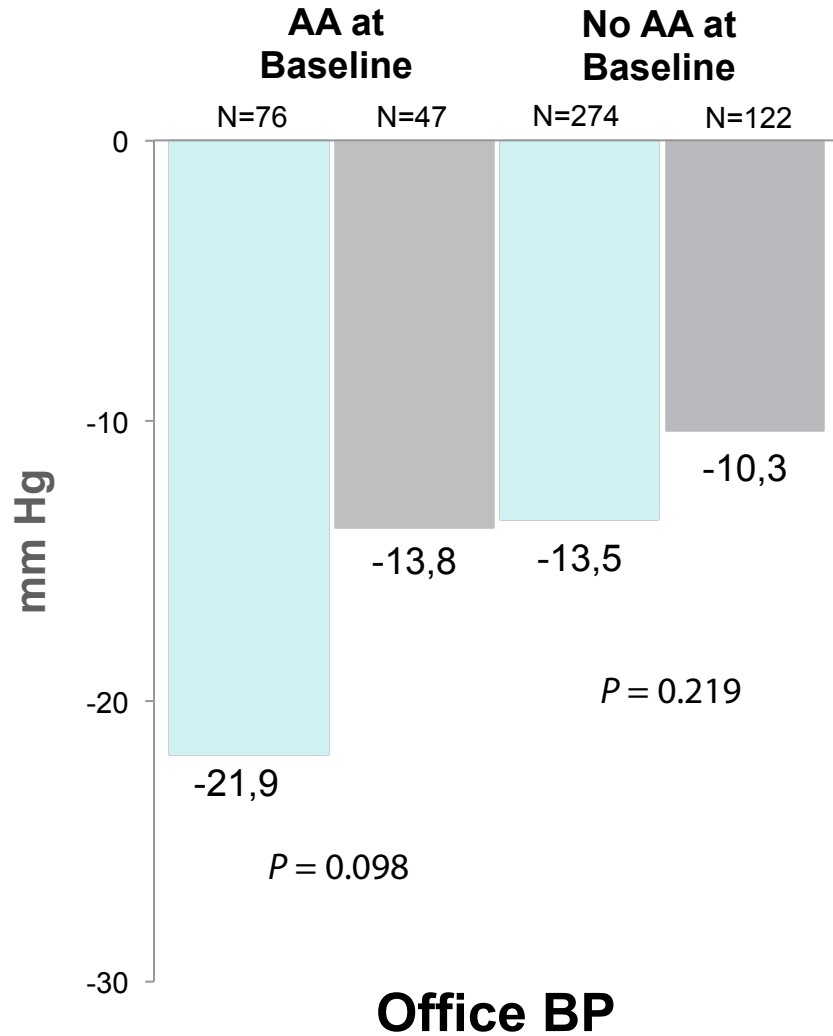
Non-African Americans



African Americans



Aldosterone Antagonist Subgroup Efficacy



Non c'est pas mort !

The French DENERHTN study Renal denervation + standardized antihypertensive treatment vs. standardized antihypertensive treatment alone: 6 months BP efficacy data

M. Azizi (1), M. Sapoval (1),
on behalf of the DENERHTN Investigators (2)

(1) Georges Pompidou European Hospital, Paris (FRANCE)

(2) French Network of ESH excellence Centers (FRANCE)

Conflicts of interest : Vessix, Boston , Recor, Cordis, CVRX

Objective and Study design

1. Objective :

To compare the efficacy, safety and cost-effectiveness of renal denervation (RDN) using the single electrode Symplicity catheter added to a protocol-driven and stepped-care optimized antihypertensive treatment (SOAT) strategy with the same medical strategy alone in patients with confirmed essential RH

2. Methodology :

- Investigator-initiated, multicentre, randomized, controlled, open-label, parallel, superiority trial with blind assessment of the primary endpoint
- Primary endpoint: changes in daytime ambulatory SBP from baseline to 6 months
- Statistical hypothesis: Δ daytime ambulatory SBP : 10 mmHg, SD: 18 mmHg, α risk: 5%, β risk: 20%; NSN: 53 per group, attrition rate: 10 to 15%, Total number of patients: 120

3. Duration of the trial:

1st patient 1st visit: June 2012; Last patient last visit: 21/05/2014
Enrollment : 17 months; follow-up : 6 months

Funding : French Ministry of Health

Inclusion criteria

1. Men or women, aged : 18 to 75 yrs
2. Essential hypertension (complete work-up within the past 2 yrs)
3. RH: office BP ≥ 140 or 90 mmHg despite a stable medication regimen including full tolerated doses of ≥ 3 AHT, including a diuretic
4. eGFR ≥ 40 ml/min/1.73 m² (MDRD)
5. Suitable renal anatomy (renal CT- or MR angiogram in the past year)



➤ 4-week treatment with indapamide SR 1.5 mg + ramipril 10 mg (or irbesartan 300 mg) + amlodipine 10 mg (5 mg)



Confirmed RH by daytime ABP ≥ 135 or 85 mmHg



Randomisation 1:1 stratified on centres: RD + SOAT vs. SOAT alone

Standardized optimal antihypertensive treatment (NICE UK guidelines)

		Monthly visits							
4 weeks		M1	M2 STEP 1	M3 STEP 2	M4 STEP 3	M5 STEP 4	M6		
Standardized triple therapy: <i>Indapamide 1.5 mg + Ramipril 10 mg / Irbesartan 300 mg + Amlodipine 10 mg</i>									
Randomisation		+ Spiro. 25 mg		+ Spiro. 25 mg Biso. 10 mg		+ Spiro. 25 mg Biso. 10 mg Prazo . 5 mg		+ Spiro. 25 mg Biso. 10 mg Prazo . 5 mg Rilme .1 mg	
		 Adjustment of the AHT medication done according to HBP Goal <135 and 85 mmHg							
ABPM	X								X
eGFR 8-item Morisky	X	X		X		X		X	X

Clinical and biological characteristics of the patients at randomisation

	Renal denervation (n=53)		Control (n=53)	
Age (years)	55.2	10.8	55.2	10.1
Male sex, N (%)	34 (64.2)		32 (60.4)	
Caucasians, N (%)	42 (79.2)		41 (77.4)	
BMI (kg/m ²)	30.7	4.8	29.7	4.5
eGFR (ml/min/1.73 m ²)	88	24	90	24
Daytime ambulatory SBP (mmHg)	155.5	16.4	151.0	16.0
Daytime ambulatory DBP (mmHg)	93.2	15.4	92.0	10.8
Nighttime ambulatory SBP (mmHg)	141.3	17.4	135.5	14.3
Nighttime ambulatory DBP (mmHg)	81.9	16.2	79.4	10.5

Data are expressed as mean ± SD.

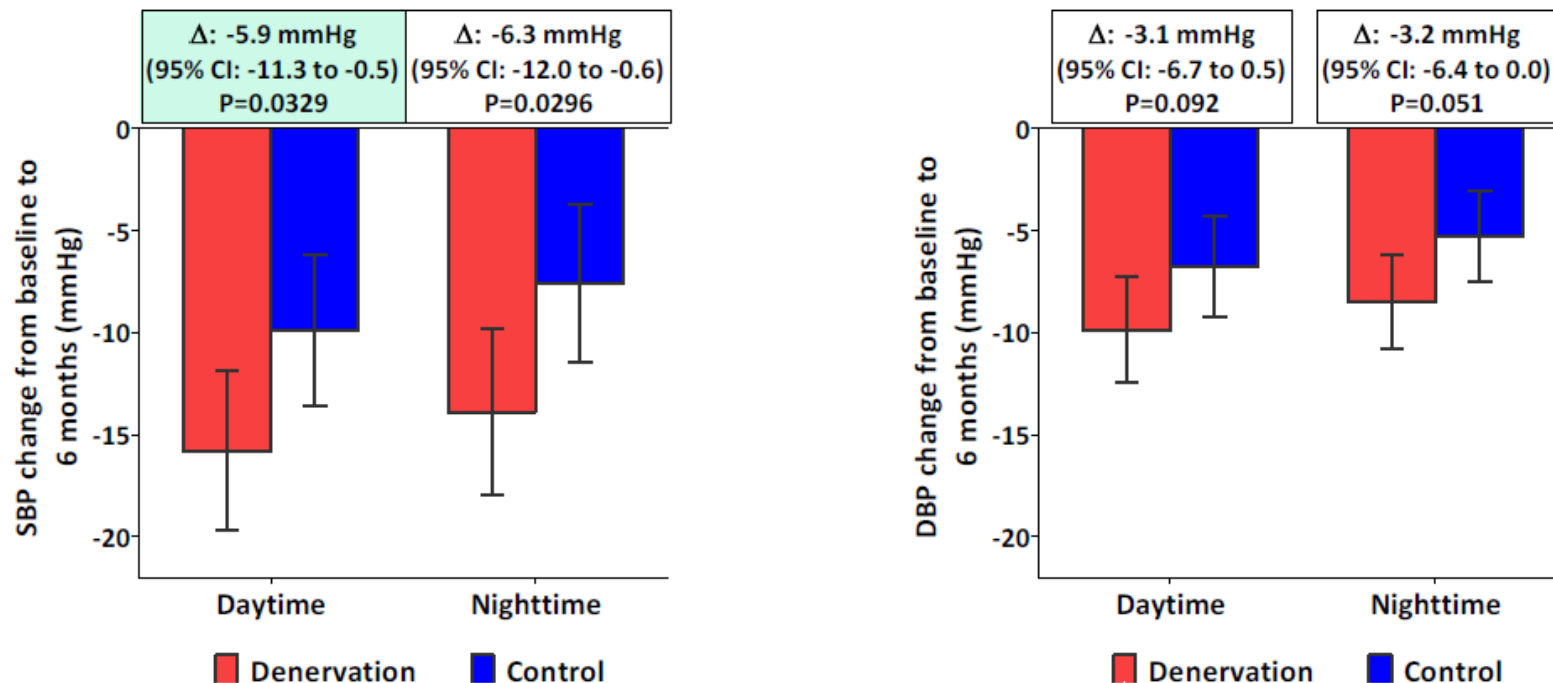
Standardized antihypertensive treatment at randomisation

	Renal denervation (n=53)	Control (n=53)
Indapamide 1.5 mg, N (%)	53 (100.0)	53 (100.0)
Ramipril 10 mg, N (%)	46 (86.8)	43 (81.1)
Irbesartan 300 mg, N (%)	7 (13.2)	10 (18.9)
Amlodipine 10 mg, N (%)	51 (96.2)	49 (92.4)
Amlodipine 5 mg, N (%)	2 (3.8)	4 (7.6)

Baseline-adjusted changes (95%CI) in ambulatory BP from randomisation to 6 months

Right renal artery: 6 ablations [IQR: 5 to 6]
 Left renal artery: 5 ablations [IQR: 5 to 6]

1 mild groin hematoma
 2 lumbar pain



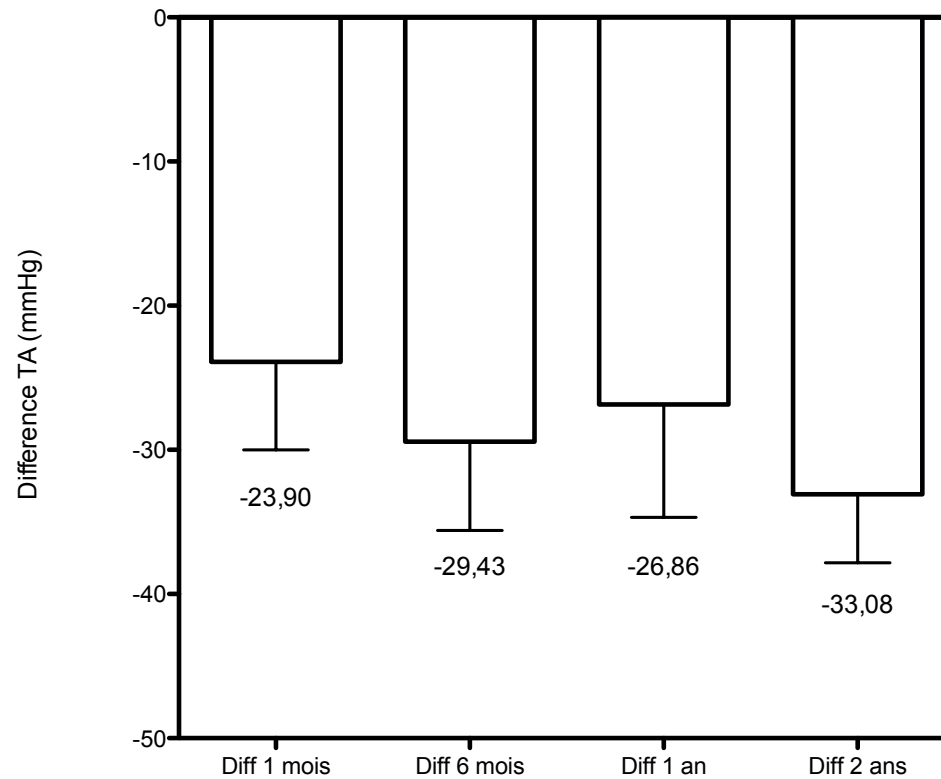
	Renal denervation	Control	P
% pts with daytime BP < 135/85 mmHg	41.7	28.3	0.1582
% patients with ΔSBP ≥ -20 mmHg	41.7	20.3	0.0229

Notre expérience

Plus de 75 pts aujourd'hui

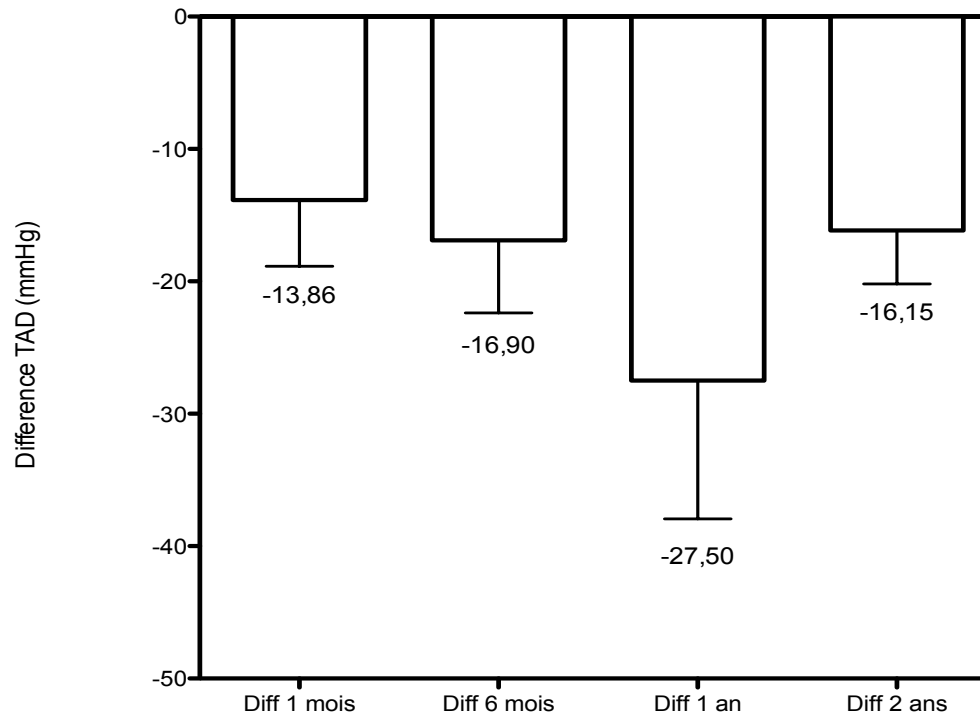
	Renal denervated patients (n=64)
Baseline systolic BP (mmHg)	172±20,68
Baseline diastolic BP (mmHg)	97±18,59
Age (years)	62,95±12,017
Sex (male)	39 (61,9%)
Race (white)	38 (62,3%)
BMI (kg/m ²)	29,02±4,86
Type 2 diabetes	24 (40%)
Hypercholesterolaemia	31 (51,7%)
eGFR (mL/min/per 1.73m ²)	84,83±32,78
eGFR>40	51 (82,3%)
Serum creatinine (umol/L)	94,03±42,77
Number of antihypertension medications	5,12±1,10
Patients on 5 or more medications	35 (55,6%)

Résultats: différentiel TAS



Diff 1 mois -23,90 ± 27,93
Diff 6 mois -29,43 ± 28,25
Diff 1 an -26,86 ± 20,72
Diff 2 ans -33,08 ± 17,16

Résultats: différentiel TAD




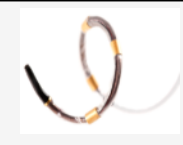



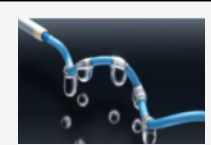

Diff 1 mois -13,86 ± 22,90

Diff 6 mois -16,90 ± 25,14

Diff 1 an -27,50 ± 25,57

Diff 2 ans -16,15 ± 14,54

Renal Denervation Technologies

	MDT Symplicity	MDT Spyral	STJ EnlightN	COV OneShot	ReCor Gen-2 Paradise	JNJ ThermoCo ol	BSC Vessix
							
CE Mark	✓	No	✓	✓	✓	No	✓
Catheter Design	Catheter with single electrode	Pigtail Catheter 4 electrodes	Basket with four electrodes	Balloon catheter helical electrode and cooling	Balloon catheter; internal cooling; Circumferential treatment	Pigtail catheter with 5 electrodes and cooling	Balloon catheter 4-8 electrodes
Balloon	No	No	No	✓	✓	No	✓
Guidewire	No	✓	No	✓	✓	No	✓
Energy	Monopolar RF	Monopolar RF	Monopolar RF	Monopolar RF	Ultrasound	Monopolar RF	Bipolar RF
Power	8W	Unknown	8W	25W	~12W	Unknown	~1W
Energy Delivery Time	2 min.	1 min.	60 sec	2 min.	30 sec.	Unknown	30 sec.
Total Treatment Time	16-24 min.	2 min.	4 min.	4 min.	3 min.	Unknown	2 min.

CONCLUSIONS

✧ REALITES:

- ✧ Ca marche (publi/registre)
- ✧ HTA non contrôlée
- ✧ Sûre (peu de complication)
- ✧ Outils existent
- ✧ Réservé à l'HTA Resist.

FANTASMES

- Pas chez tout le monde
- Fréquente
- Pas de complications
- Parfait
- Seule indication à l'avenir