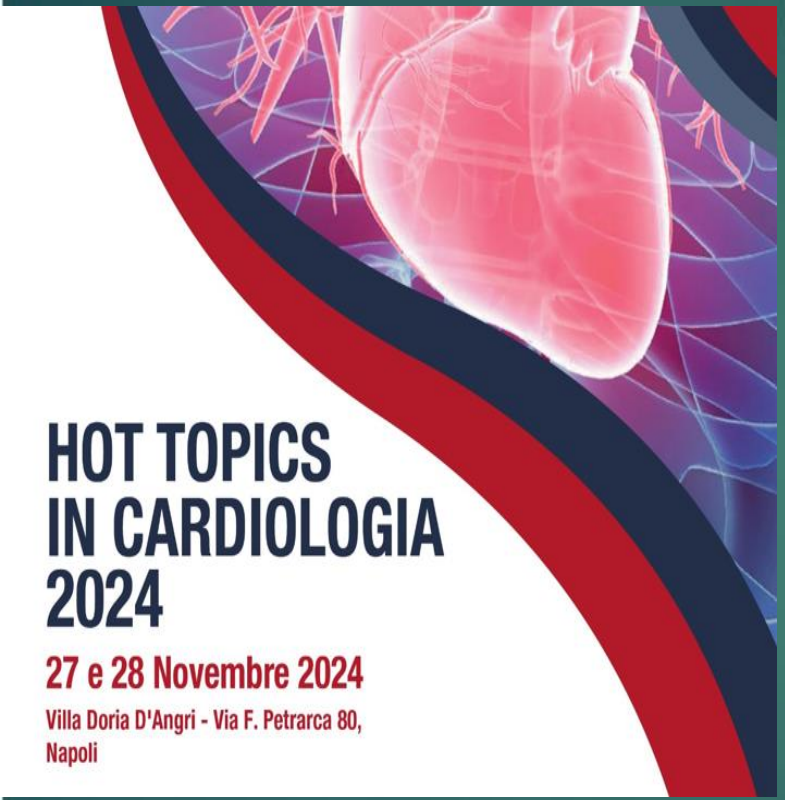


DENERVAZIONE RENALE PER IL TRATTAMENTO DELL'IPERTENSIONE RESISTENTE

Francesco Versaci, MD, FACC

Direttore UOC UTIC – Emodinamica e Cardiologia DEA II PO Latina Nord
Direttore Coordinamento Patologie Apparato Cardiovascolare ASL LT

ASL LATINA

Ore 15.55-16,05

Napoli, 28 novembre 2024

Villa Doria d'Angri

Disclosure Statement of Financial Interest

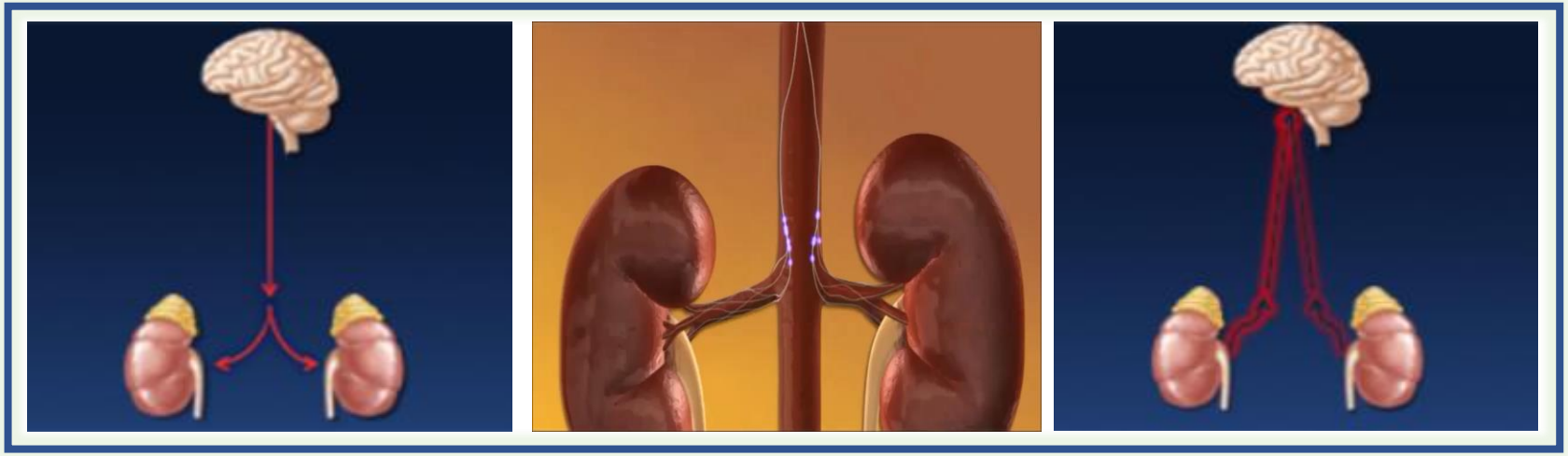
Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
• Consulting Fees/Honoraria	Sanofi, Translumina

Renal Nerves and the SNS

Efferent Renal Sympathetics

Afferent Renal Sympathetics

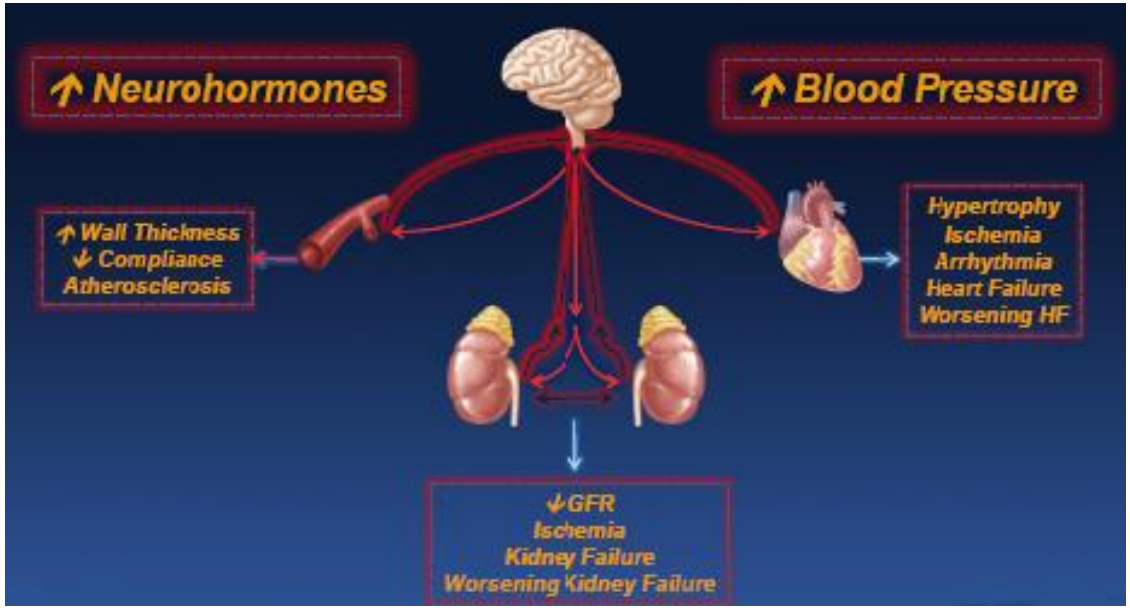


- **Decreased Renal Blood Flow**
- **Increased Renin Release**
- **IncreasedSodium Reabsorption**

The Kidney is a source of central Sympathetic activity, sending signals to the CNS

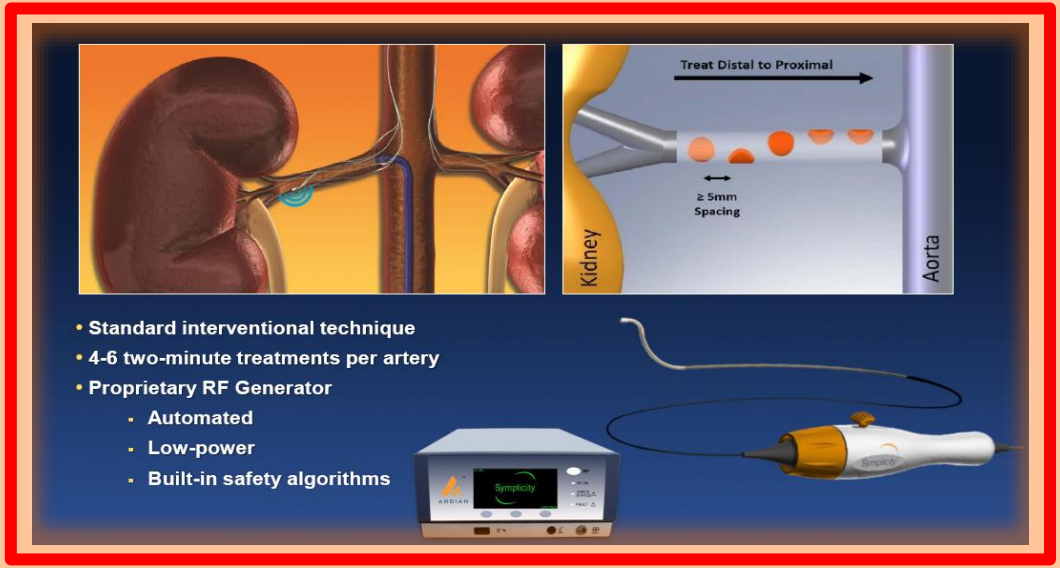
DiBona GF, et al. Am J Physiol Regul Integr Comp Physiol. 2010;298: R245–R253.
Schlaich MP, et al. Hypertension. 2009;54:1195-1201.

Chronic Effect of Increased Sympathetic Nerve Activity



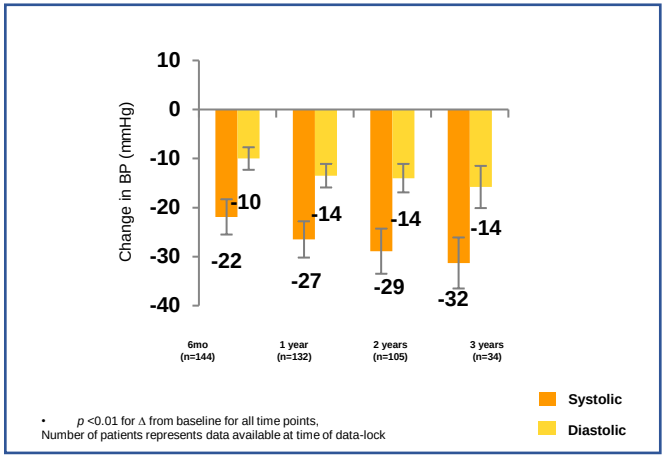
Schlaich MP, et al. Hypertension. 2009;54:1195-1201.

Renal Nerve Anatomy Allows a Catheter-Based Approach



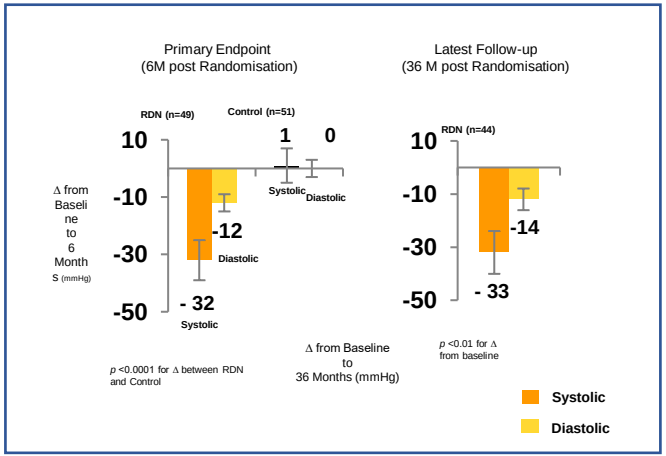
Renal Denervation by Radiofrequency: Update

Symplicity HTN-1: Significant, Sustained Blood Pressure Reductions to at Least 3 Years



Krum H, et al. Lancet 2014 Feb 15;383:622-9

Symplicity HTN-2: RDN Superior to Medical Management, Reductions Sustained to 36M



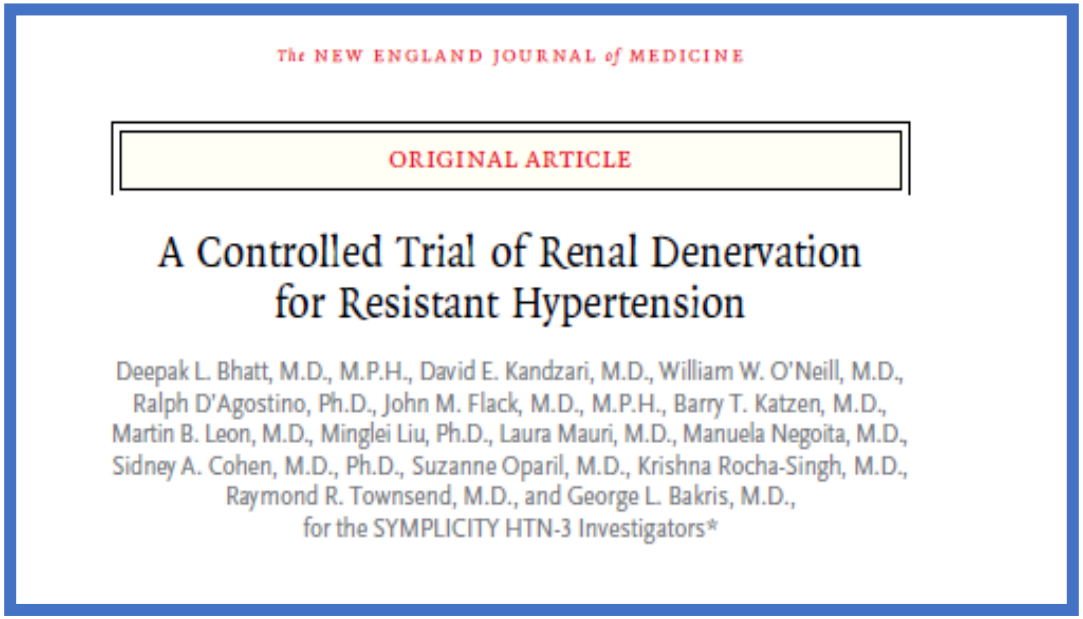
Esler MD, et al. Eur Heart J 2014 Jul;35 826):1752-9

RDN Technologies Avaible and in Development

Technology	Device Name (Manifacturer)	Key Characteristics
Radiofrequency	Symplicity Flex (Medtronic, Inc)	Single-electrode catheter
	Spyral (Medtronic, inc)	Spiral-electrode catheter
	EnlighHTN (St.Jude Medical, Inc)	Multielectrode Catheter
	OneShot (Covidien, Manfield, MA)	Irrigated, spiral-electrode catheter
	Vessix V2 (Boston Scientific Corp.)	Multielectrode catheter with bipolar energy deliver
	ThermoCool (Biosense Webster, Inc)	Irrigated, multielectrode catheter
	Iberis (Terumo)	Single-electrode, radial artery access system
	Verve Medical System	Multielectrode, retrouretic access system
Ultrasound	Paradise (ReCor Medical)	Nonfocused endovascular ultrasound energy system
	TIVUS (Cardiosonic)	Nonfocused endovascular ultrasound energy system
	Kona System (Kona Medical)	Externally applied, low-intensity ultrasound
	Sound 360 (Sound Innovations, Inc)	Endovascular ultrasound energy system
Cryoablation	Not yad named (friedrich-Schiller Universuty	Standard cryoablation catheter
Brachitherapy	CyberHeart	Catheter based, beta-radiation Brachiterapy
Pharmacological	Not yad named (Universuty of Athens)	0.1 mg vincristine delivered from six holed proprietary balloon catheter
	Bullfrog (Mercator MedSystems, Inc)	Guanethidine microinjecyion into the adventitia
	Peregrine (Ablative Solutions)	Ethanol Microinjection into the adventitia
	ApexNano system (Apexnano Ther)	Magnetic Nanoparticles impregnated with Botox

SYMPLICITY HTN-3

results to be announced a mystery or a story foretold?



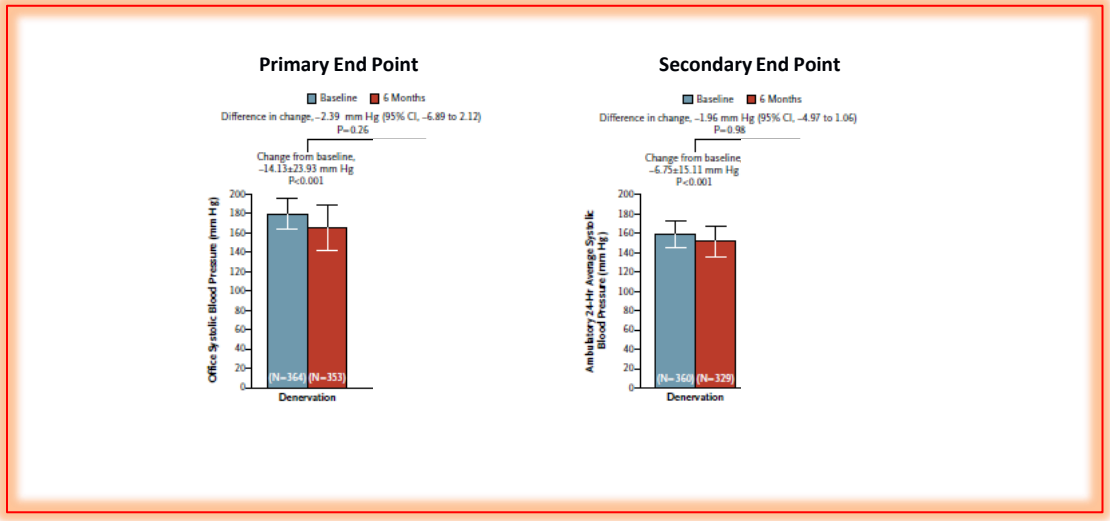
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

SYMPLICITY HTN-3 results to be announced a mystery or a story foretold?



Bhatt DL, et al. Engl J Med. 2014 Apr 10;370(15):1393-401

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

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

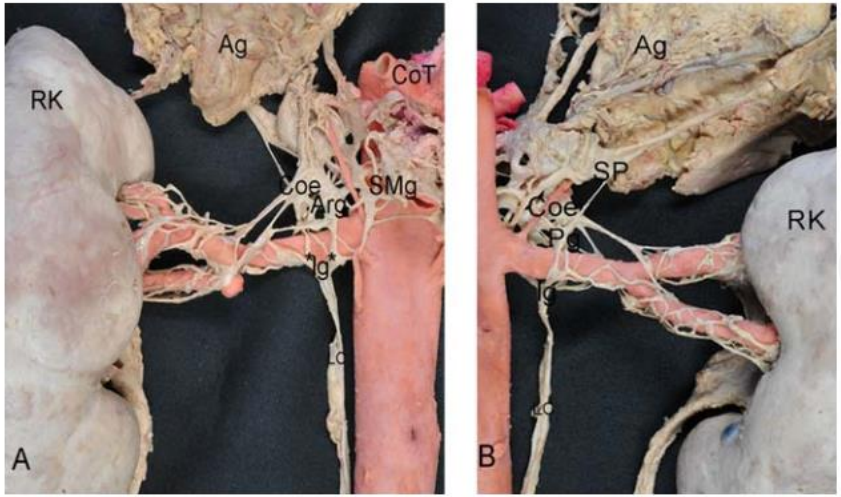
Device-based therapies for hypertension

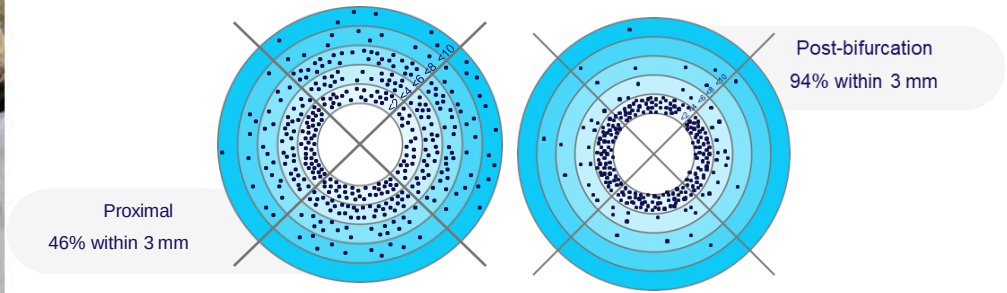
Recommendation	Class[a]	Level[b]
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.[367,368]	III	B

RCT = randomized controlled trial.
[a]Class of recommendation.
[b]Level of evidence.

The procedure was changed to reflect renal nerve anatomy

Renal nerves have a positional bias on radial distance from arterial lumen; distal nerves are closer



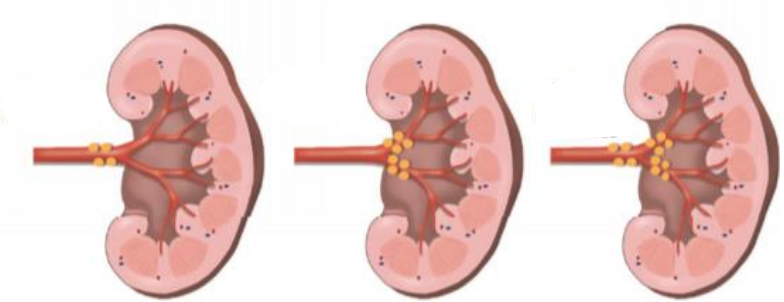


Renal nerve density highest in the post bifurcation region

94% of nerves are located within 3 mm of renal artery lumen post-bifurcation versus 46% in proximal segment[2]

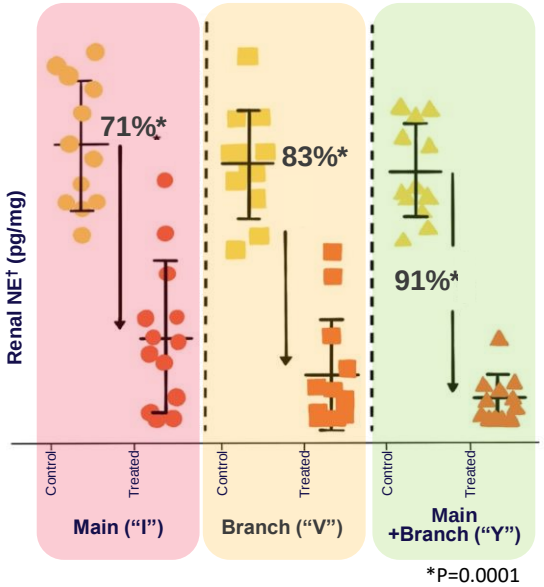
Garcia-Touchard et al. Microdisection of the Human Renal Nervous System. Hypertension. 2020.
Mahfoud, F. Histological examination of renal nerve distribution, density, and function in humans. *EuroIntervention.* 2023

Preclinical study provided rationale for combined branch & main artery treatment



“I”	“V”	“Y”
Main artery only	**Branches only**	**Main artery and branches**

Treating both the branch <u>and</u> main renal artery (Y) resulted in greater nerve destruction and less variability.



*P=0.0001

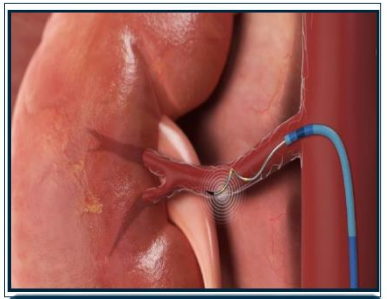
There is increased benefit in ablating nerves in both the main and branch as opposed to main alone.[1]

†NE=Norepinephrine

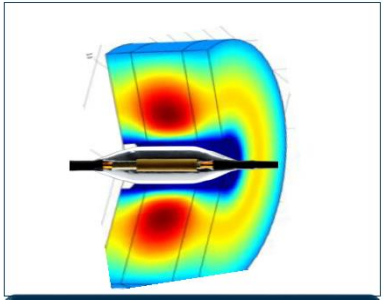
[1] Mahfoud F, et al. *J Am Coll Cardiol.* 2015;66:1766–1775.

Preclinical data may not be representative of clinical performance in human subjects.

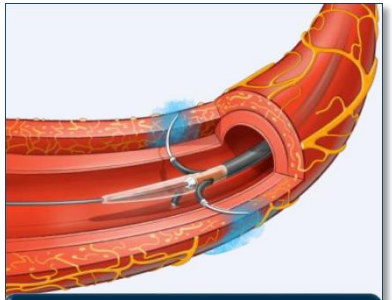
Technologies/techniques for renal denervation (RDN): Second generation devices



Radiofrequency denervation



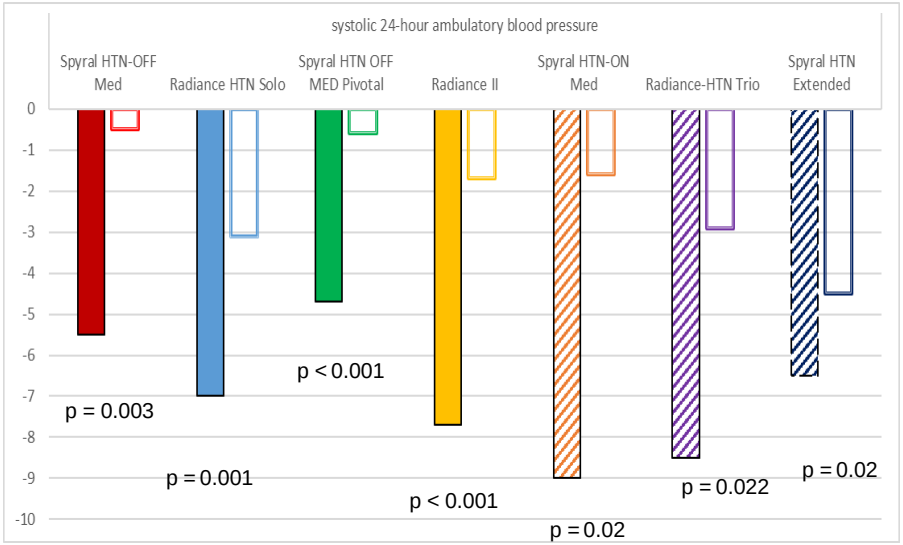
Ultrasound denervation



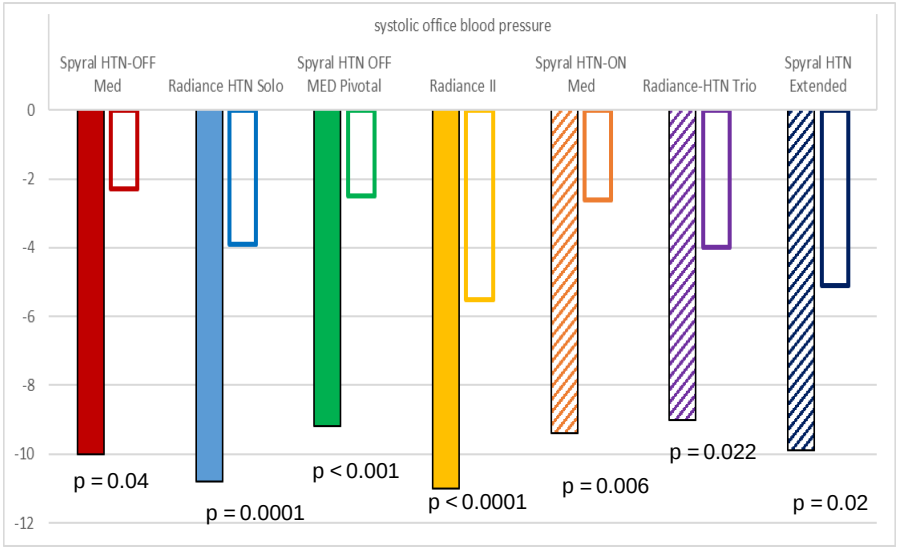
Alcohol mediated denervation

Multiple sham controlled RCT's demonstrated effectiveness of RDN with and without medications

Systolic 24h ABPM (-4.1 mmHg)



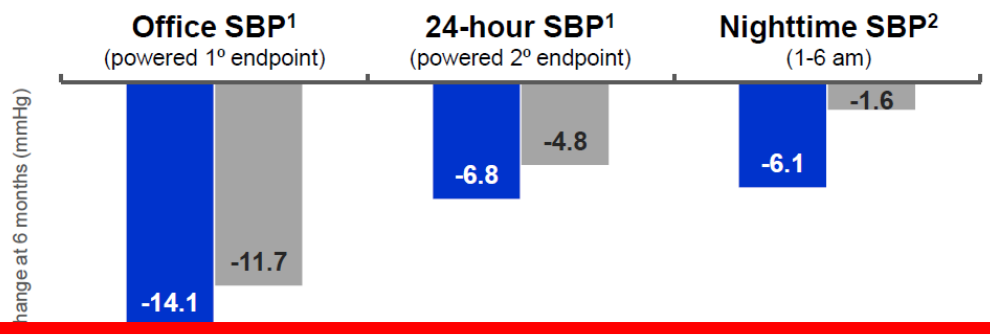
Systolic office BP (-5.7 mmHg)



Schmieder RE, Schneider M. Presented ESH 2023. Meta-analysis of the 5 sham-controlled RCTs

Endpoints at 6 Months

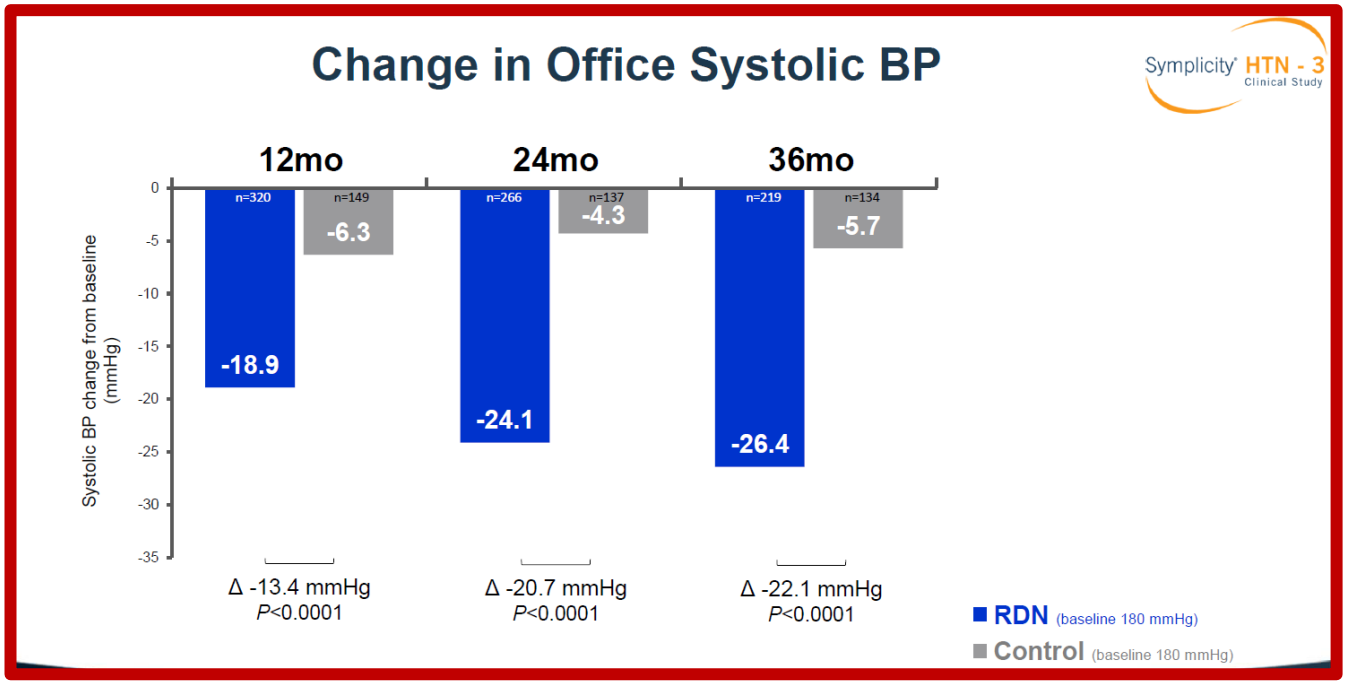
Symplicity HTN - 3 Clinical Study



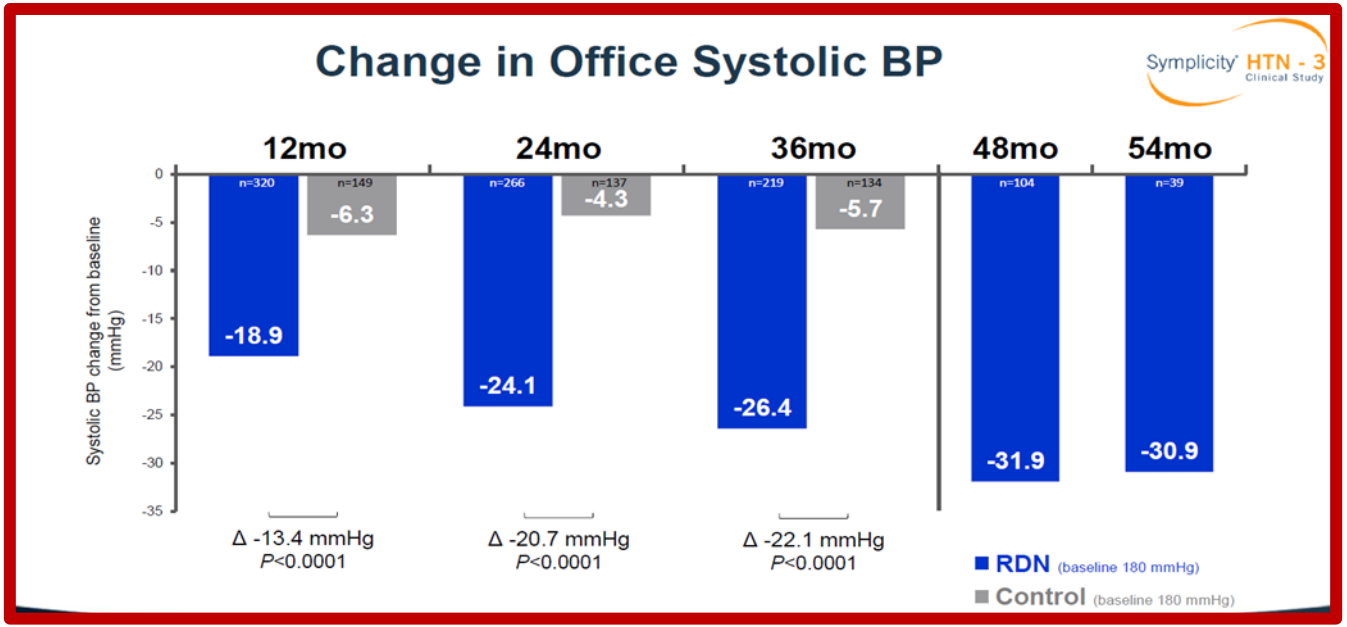
Supplemental Table S6. Safety outcomes in RDN, crossover, and non-crossover patients

% (n)	RDN N=364	Crossover * N=101	Non-Crossover N=70

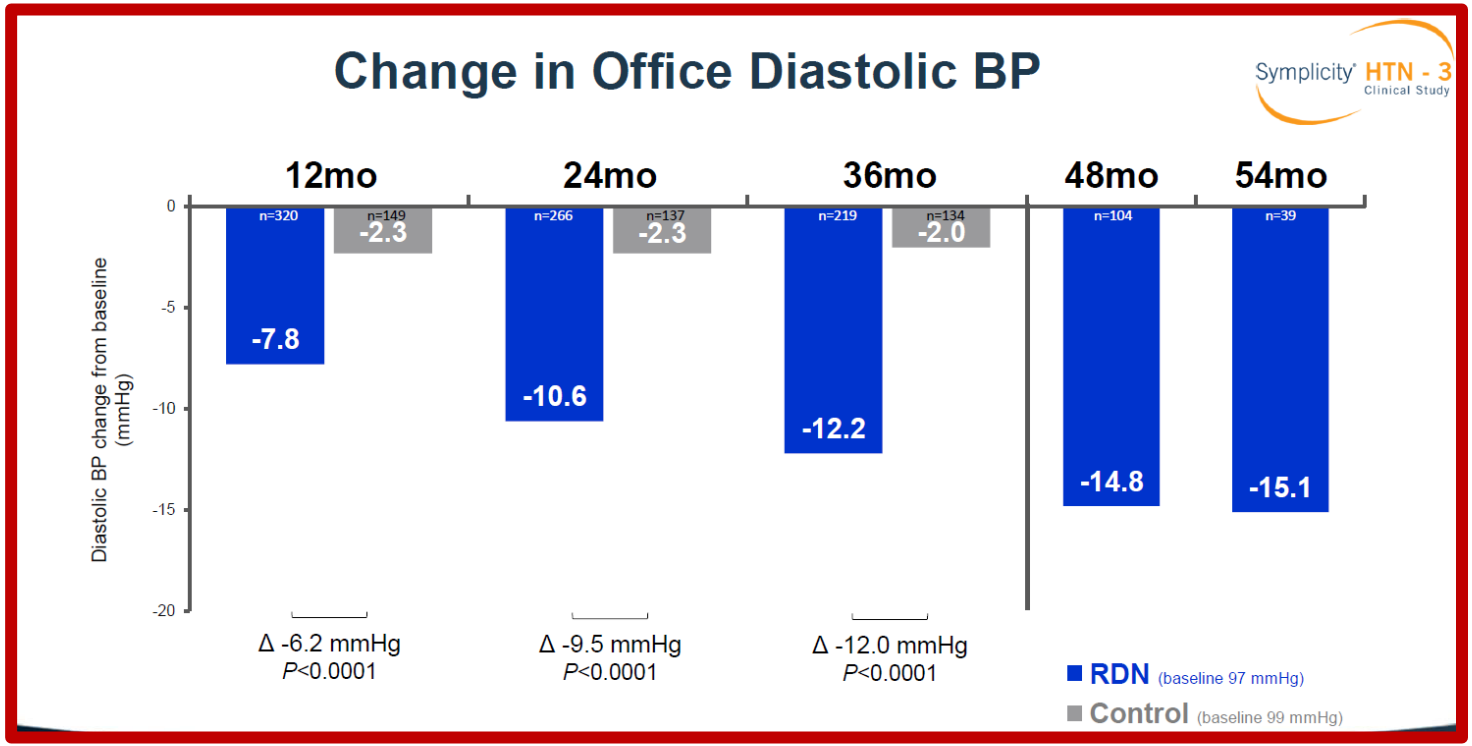
1 Bhatt DL, et al. *N Engl J Med*. 2014;370:1393–1401
2 Kario K, et al. *Hypertension*. 2015;66(6):1130-7



Bhatt DL, et al. Lancet 2022;400:1405-16.



Bhatt DL, et al. Lancet 2022;400:1405-16.

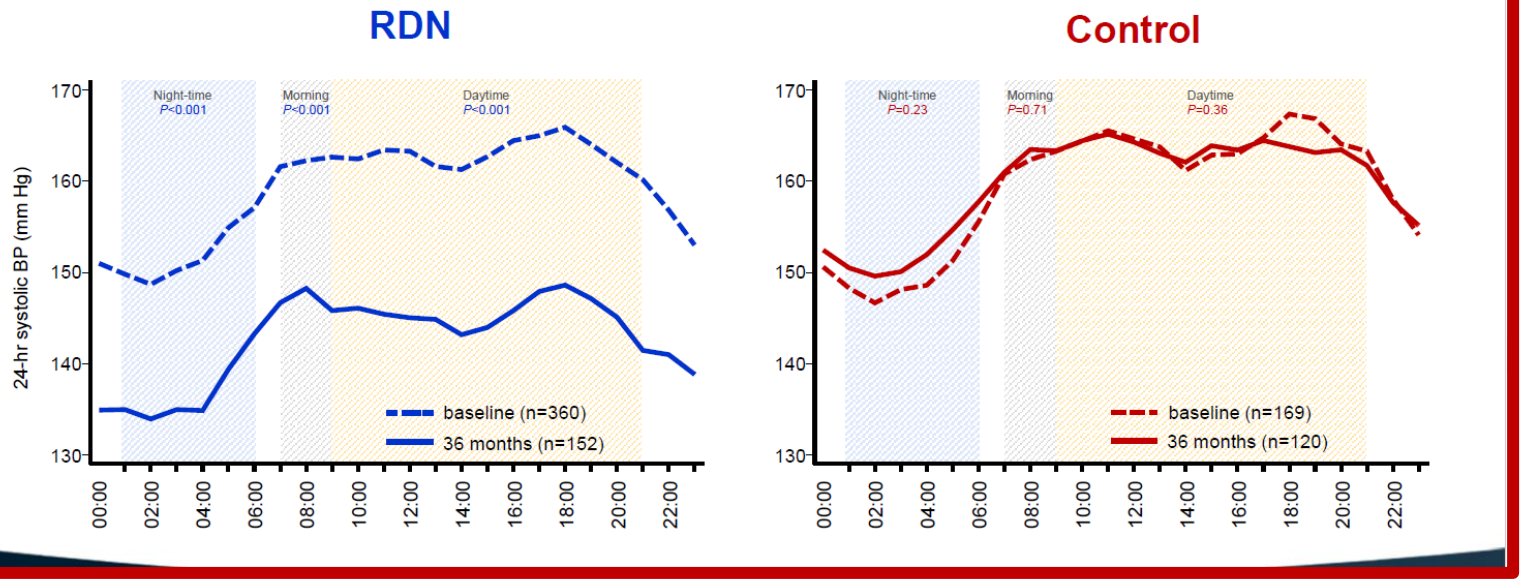


Bhatt DL, et al. Lancet 2022;400:1405-16.

24-Hour Systolic BP

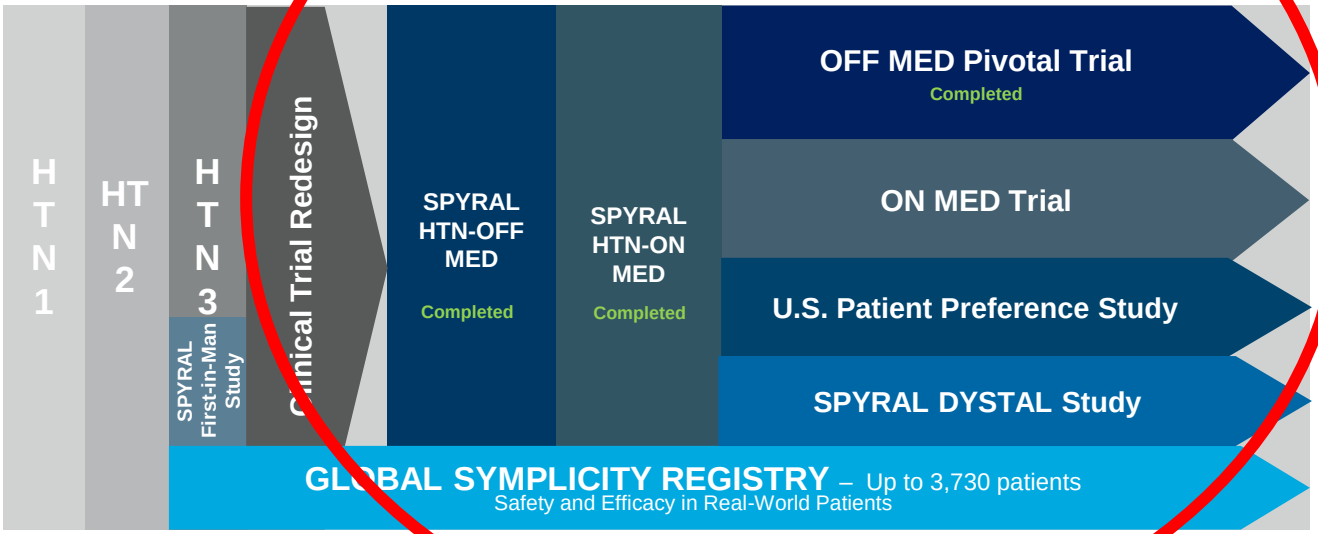
Baseline vs 36 Months

Symplicity HTN - 3 Clinical Study



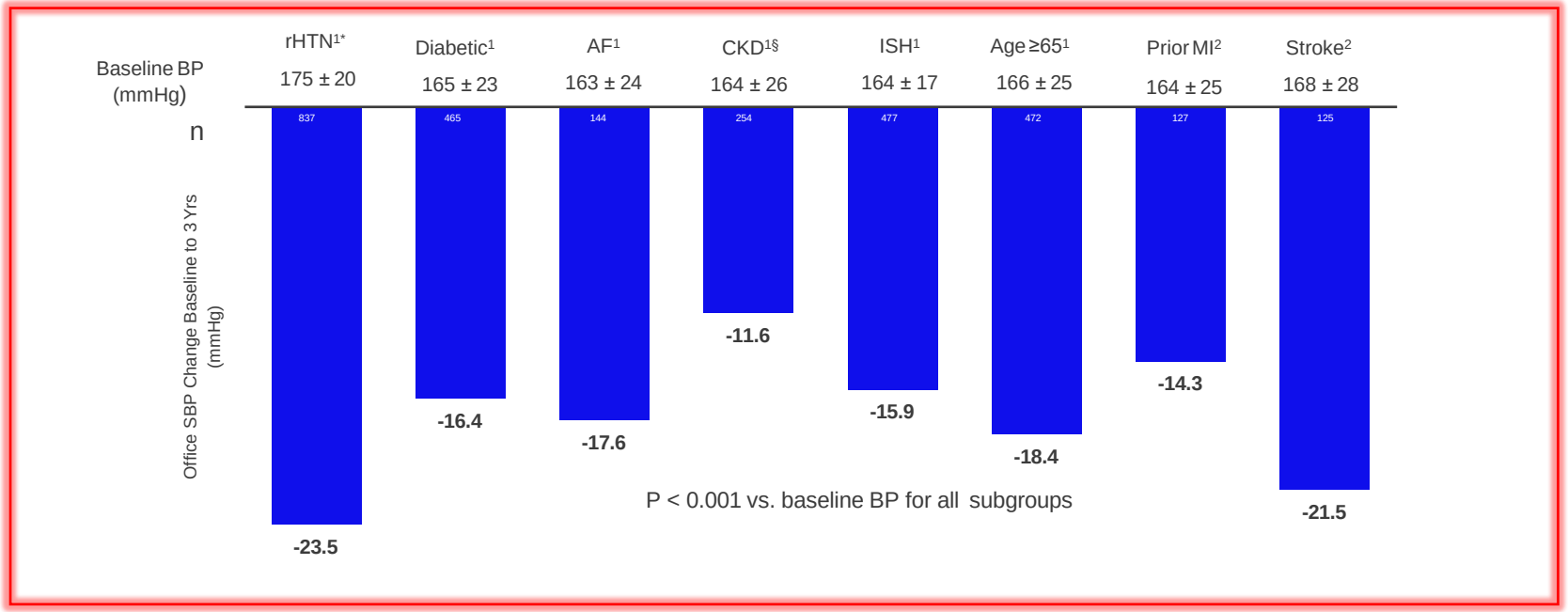
Bhatt DL, et al. Lancet 2022;400:1405-16.

Over 4,500 Patients Studied Across Multiple Trials



Mahfoud et al, EuroPCR 2024

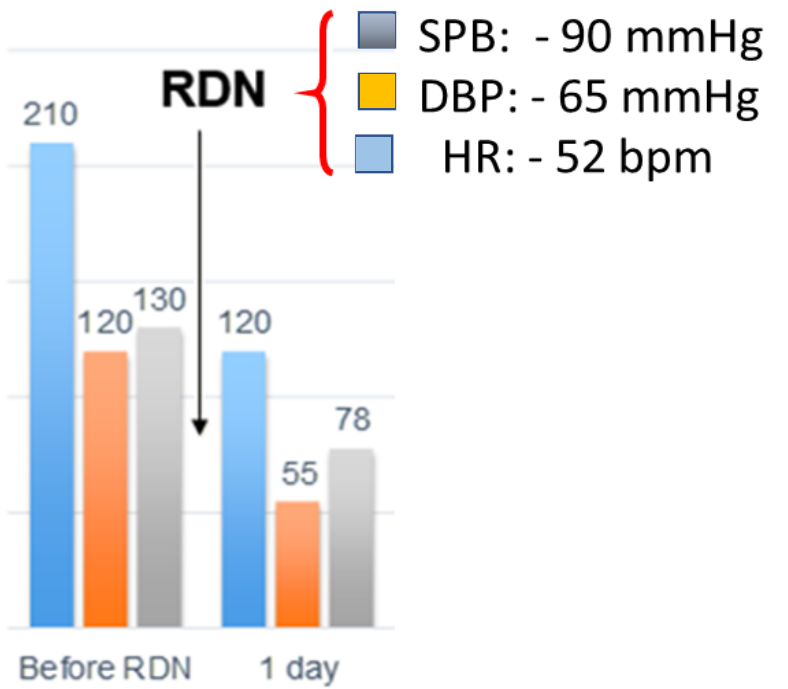
Radiofrequency RDN (Spyral) reduced BP in a variety of patient subgroups at 3 years



1. Mahfoud F, et al. J Am Coll Cardiol. 2020;75:2879-2888.
2. Mahfoud F, et al. ESH 2022.

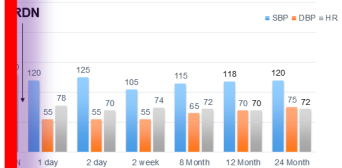
*Resistant hypertension defined as OSBP>150 mmHg, ≥3 anti-hypertensive medications.
§ CKD defined as eGFR <60ml/min/1.73m^2

RDN IN PT WITH AND RESISTANT ON



Hemorrhagic stroke
Glasgow Coma Scale: 9
Norton Scale: 8

Persistent hypertension during hospitalization (BP 210/120 mmHg) despite 6 medications p.o. and urapidil iv



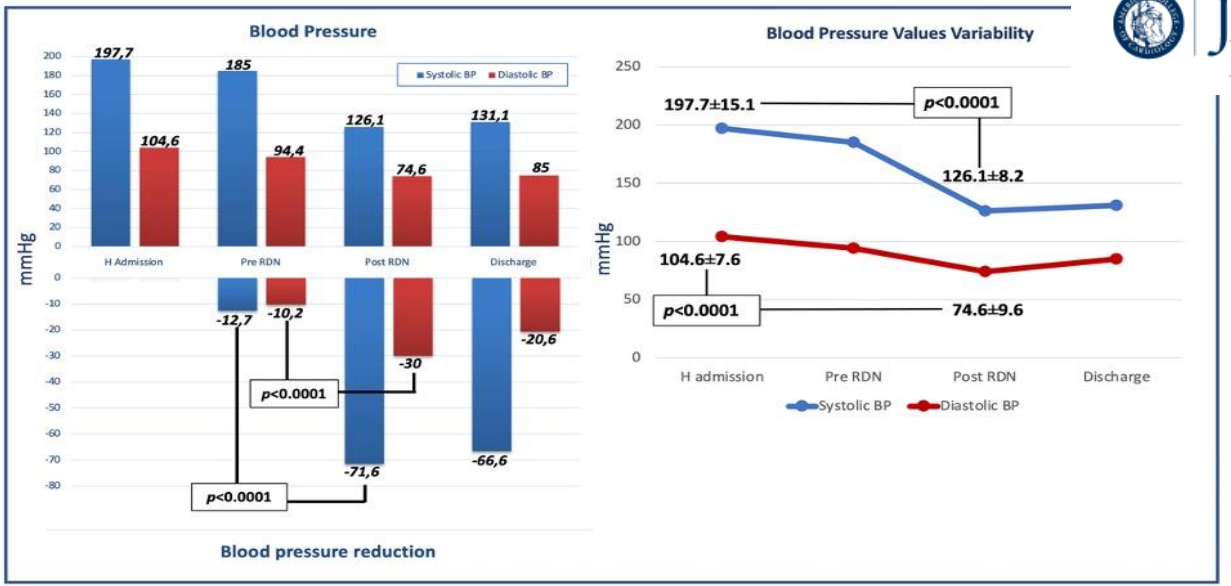
Vers

saci F. et al SAGE Open Med Case Rep. 2019

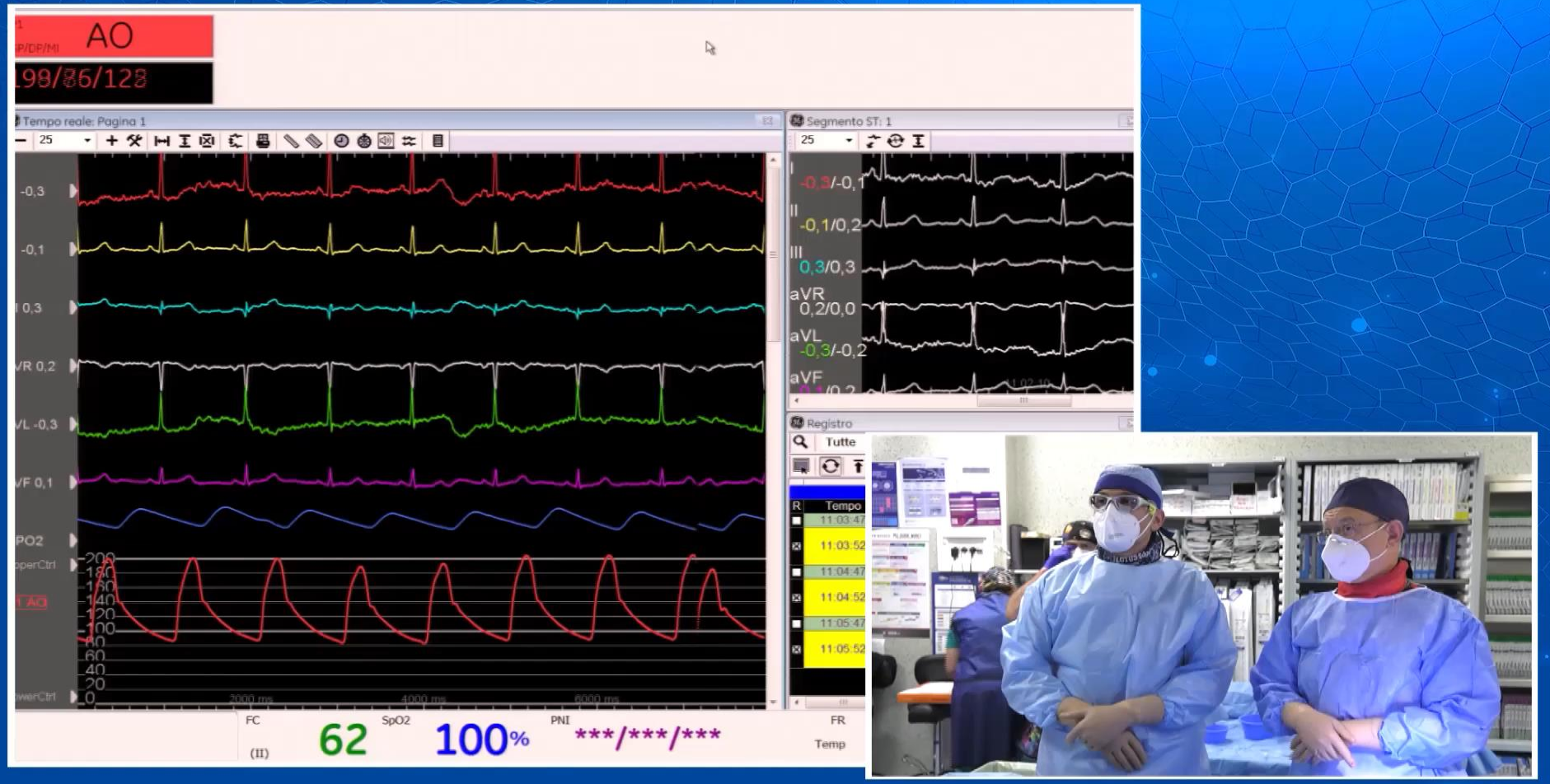
Renal denervation: a novel therapeutic option in the acute phase of hemorrhagic stroke

Blood pressure values trend at different study times

N=10



Versaci F, et al. JACC Adv 2023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100%
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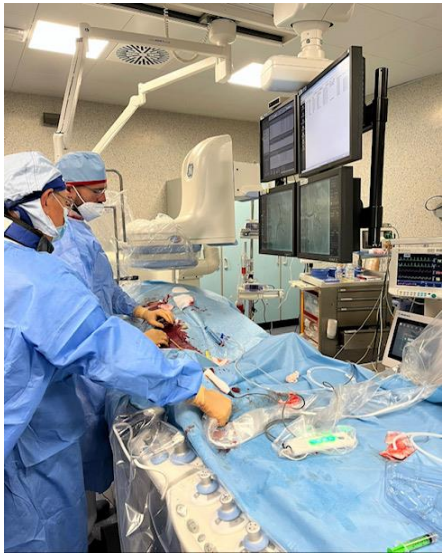
RDN + external ventricular drainage benefit patients with mild ventricular hemorrhage and malignant hypertension



Meta-analysis of 18 reports involving 4,439 patients

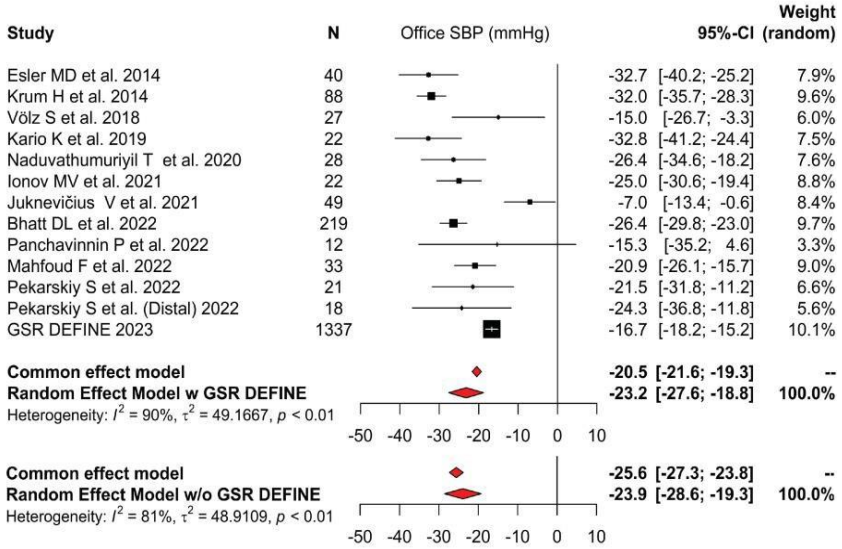
Radiofrequency RDN (Spyral) RDN provided sustained BP reductions at mean follow-up 4.4 years

Screened 220 records, **18 independent reports included**

4,439 patients (12,639 patient-years)

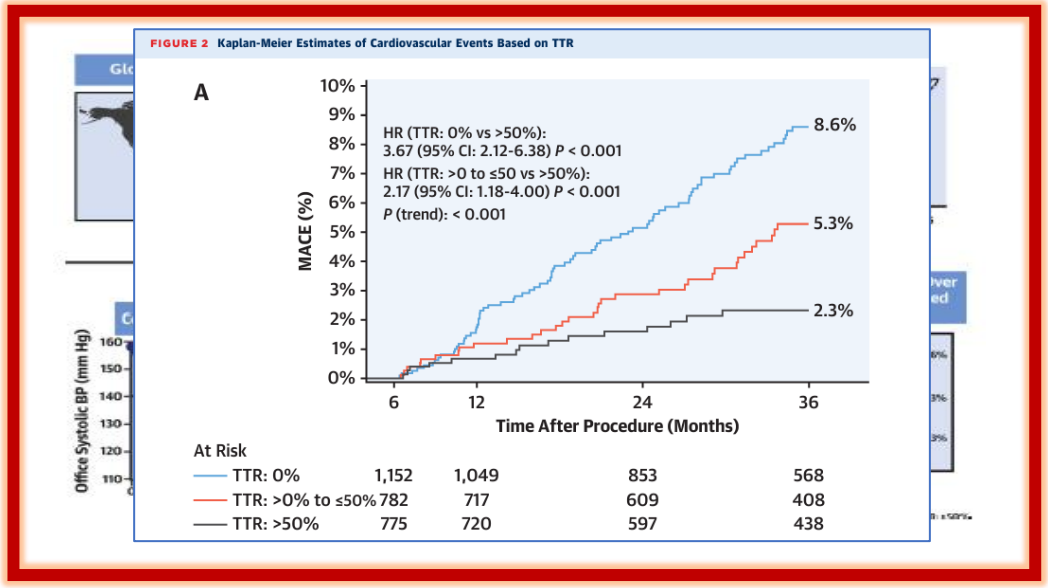
Mean follow up: 4.4 years* (range: 3 - 9.4 years)

Office SBP reduction: -23.2 mmHg (n=1916)
with no escalation in anti-HTN medications



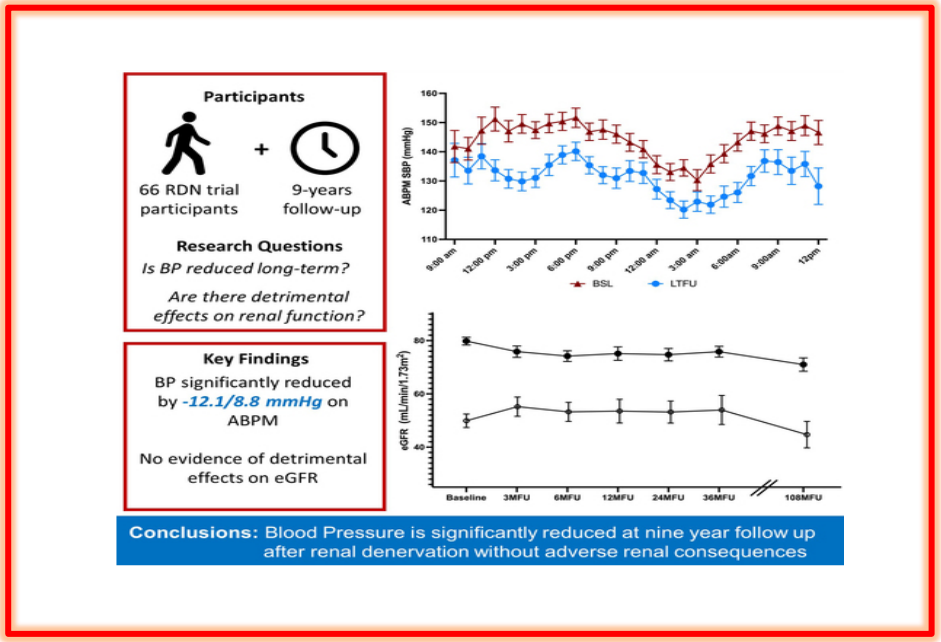
Mahfoud et al. ACC 2024 – EuroPCR 2024

Cardiovascular Risk Reduction After Renal Denervation According to Time in Therapeutic Systolic Blood Pressure Range



Mahfoud F, et al. J Am Coll Cardiol. 2022;80(20):1871–1880.

Catheter-Based Renal Denervation: 9-Year Follow-Up Data on Safety and Blood Pressure Reduction in Patients With Resistant Hypertension



Ashton GS, et al. Hypertension 2023 Apr;80(4):811-819

High-quality RCTs confirmed the BP-lowering safety and efficacy of RDN requiring updated guidance

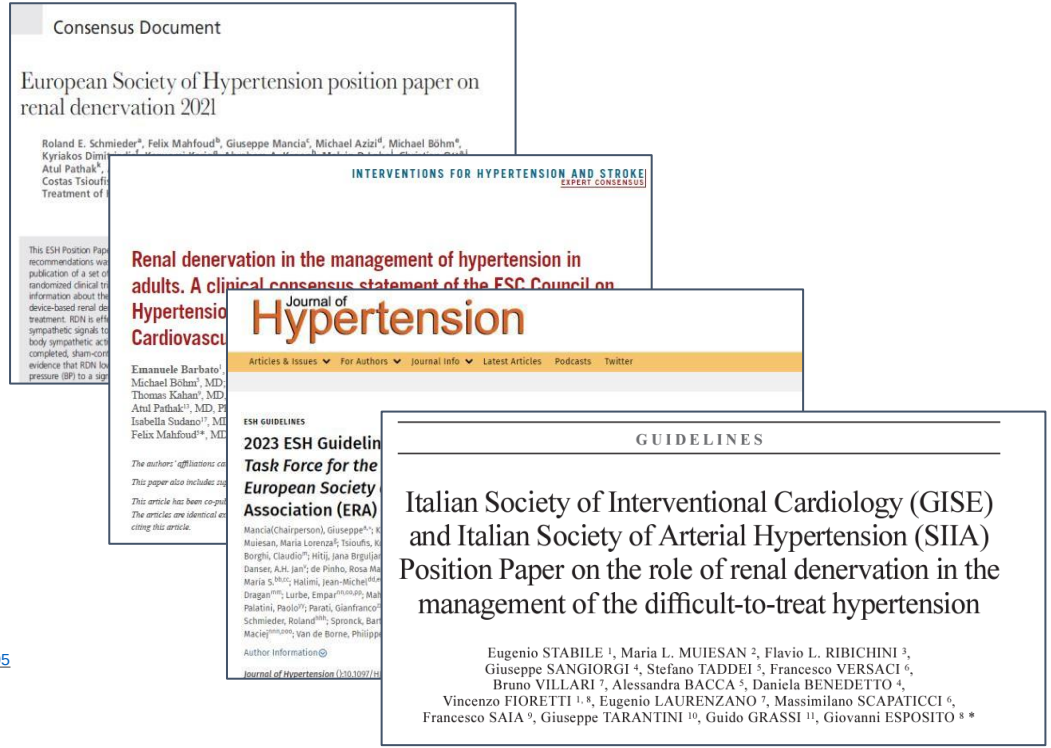
2018 ESC/ESH Guidelines for the Management of Arterial Hypertension[1]

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

©ESC/ESH 2018

RCT = randomized controlled trial.
[a]Class of recommendation.
[b]Level of evidence.



1. Williams B et al, 2018 ESC/ESH Guidelines for hypertension
2. Barbato, et al. European Heart Journal, 15 February 2023, https://doi.org/10.1093/eurheartj/ehad05
3. 4 Kreutz et al. ESH 2023
4. Mancia G. et al. Journal of Hypertension 2023, 41:000–000 DOI:10.1097/HJH.0000000000003480
5. Stabile E. et al. Minerva Cardiol Angiol. 2024 Mar 27. doi: 10.23736/S2724-5683.23.06433-5

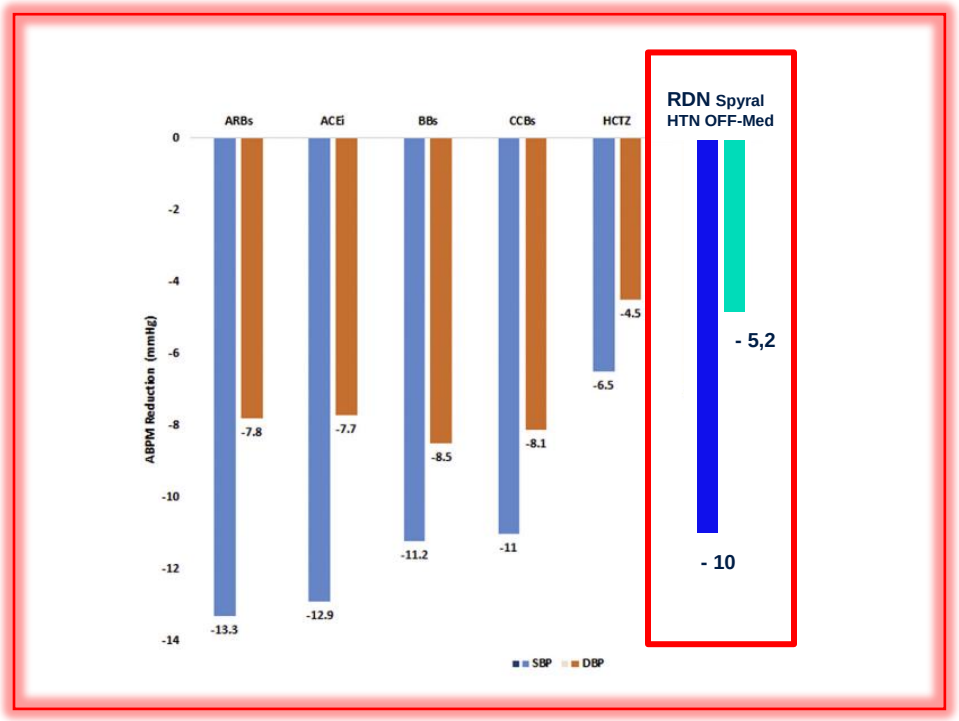
2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Recommendations	Class[a]	Level[b]
To reduce BP, and if performed at a medium-to-high volume centre, catheter-based renal denervation may be considered for resistant hypertension patients who have BP that is uncontrolled despite a three BP-lowering drug combination (including a thiazide or thiazide-like diuretic), and who express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment.[564,566–568,586–590]	IIb	B
To reduce BP, and if performed at a medium-to-high volume centre, catheter-based renal denervation may be considered for patients with both increased CVD risk and uncontrolled hypertension on fewer than three drugs, if they express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment.[564,566–568,586–590]	IIb	A

Recommendations	Class[a]	Level[b]
Due to a lack of adequately powered outcomes trials demonstrating its safety and CVD benefits, renal denervation is not recommended as a first-line BP-lowering intervention for hypertension.	III	C
Renal denervation is not recommended for treating hypertension in patients with moderate-to-severely impaired renal function (eGFR <40 mL/min/1.73 m^2) or secondary causes of hypertension, until further evidence becomes available.	III	C

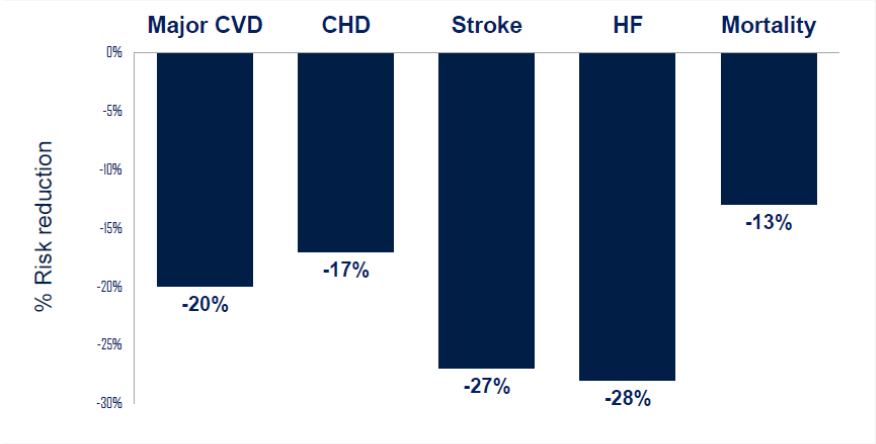
ESC GUIDELINES

McEvoy JW, et al. Eur Heart J. 2024 Oct 7;45(38):3912-4018



Messerli F, et al. J Am Coll Cardiol Intv. 2020 Dec, 13 (24) 2934–2936

RISK REDUCTION FOR A 10 mmHG FALL IN OFFICE SBP



Irrespective of baseline BP or pre-existing conditions

n = 613,815

Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387: 957-67

TAKE HOME MESSAGE

Position Statement on RDN in 2024

- In base ai risultati dei recenti studi clinici controllati effettuati con dispositivi di seconda generazione, la RDN rappresenta un opzione terapeutica per il trattamento dell’ipertensione, assieme a modifiche dello stile di vita ed al trattamento farmacologico.

- La denervazione renale è una strategia terapeutica complementare, non competitiva rispetto alla terapia medica.

- Si raccomanda un percorso strutturato per l'uso clinico di RDN nella pratica quotidiana.

- La discussione multidisciplinare dell'indicazione alla RDN su base personalizzata è essenziale per il successo di un programma di RDN

The NEW ENGLAND JOURNAL of MEDICINE

ANGIOGRAPHIC FOLLOW-UP AFTER PLACEMENT OF A SELF-EXPANDING CORONARY-ARTERY STENT

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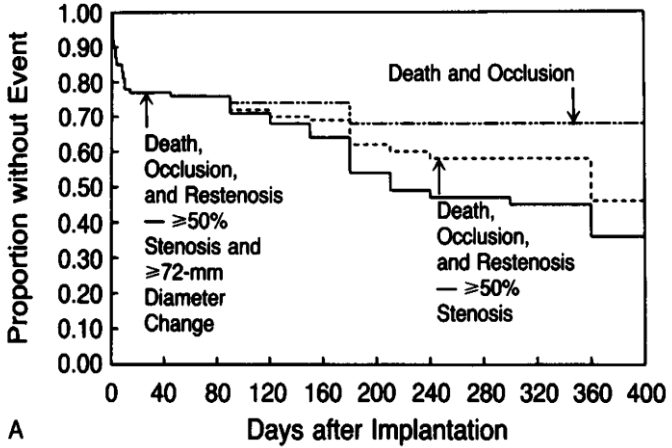
Abstract *Background.* The placement of stents in coronary arteries after coronary angioplasty has been investigated as a way of treating abrupt coronary-artery occlusion related to the angioplasty and of reducing the late intimal hyperplasia responsible for gradual restenosis of the dilated lesion.

Methods. From March 1986 to January 1988, we implanted 117 self-expanding, stainless-steel endovascular stents (Wallstent) in the native coronary arteries (94 stents) or saphenous-vein bypass grafts (23 stents) of 105 patients. Angiograms were obtained immediately before and after placement of the stent and at follow-up at least one month later (unless symptoms required angiography sooner). The mortality after one year was 7.6 percent (8 patients). Follow-up angiograms (after a mean [±SD] of 5.7±4.4 months) were obtained in 95 patients with 105 stents and were analyzed quantitatively by a computer-assisted system of cardiovascular angiographic analysis. The 10 patients without follow-up angiograms included 4 who died.

Results. Complete occlusion occurred in 27 stents in 25 patients (24 percent); 21 occlusions were documented within the first 14 days after implantation. Overall, immediately after placement of the stent there was a significant increase in the minimal luminal diameter and a significant decrease in the percentage of the diameter with stenosis (changing from a mean [±SD] of 1.88±0.43 to 2.48±0.51 mm and from 37±12 to 21±10 percent, respectively; $P<0.0001$). Later, however, there was a significant decrease in the minimal luminal diameter and a significant increase in the stenosis of the segment with the stent (1.68±1.78 mm and 48±34 percent at follow-up). Significant restenosis, as indicated by a reduction of 0.72 mm in the minimal luminal diameter or by an increase in the percentage of stenosis to ≥50 percent, occurred in 32 percent and 14 percent of patent stents, respectively.

Conclusions. Early occlusion remains an important limitation of this coronary-artery stent. Even when the early effects are beneficial, there are frequently late occlusions or restenosis. The place of this form of treatment for coronary artery disease remains to be determined. (N Engl J Med 1991; 324:13-7.)



Renal Sympathetic Nerve Ablation for Uncontrolled Hypertension

59-year-old patient, resistant hypertension, had renal sympathetic nerve activity modulated by catheter-based radiofrequency (RF) ablation

Renal Sympathetic-Nerve Ablation for Uncontrolled Hypertension

TO THE EDITOR: The renal sympathetic nerves have been identified as a major contributor to the complex pathophysiology of hypertension in both experimental models and in humans.[1] Patients with essential hypertension generally have increased efferent sympathetic drive to the kidneys, as evidenced by elevated rates of renal norepinephrine spillover, defined as the amount of transmitter that escapes neuronal uptake and local metabolism and thus "spills over" into the circulation. Hypertension is also characterized by an increased rate of sympathetic-nerve firing, possibly modulated by afferent signaling from renal sensory nerves.[2-4]

A 59-year-old male patient with long-standing essential hypertension that was resistant to pharmacologic treatment with seven different antihypertensive drugs underwent catheter-based radiofrequency ablation to excise renal nerves that carry both efferent sympathetic and afferent sensory fibers. The patient had a history of two transient ischemic attacks and sleep apnea that was untreated because of an inability to tolerate therapy with continuous positive airway pressure. Secondary forms of hypertension and heart failure were excluded. The mean office blood pressure was 161/107 mm Hg, with a heart rate of 76 beats per minute at baseline.

Radiofrequency ablation was applied to both renal arteries without apparent procedural complications. There were no vascular or subsequent biochemical complications, and renal function was unaltered. Renal norepinephrine spillover, as assessed by the radiotracer dilution method[2,4] from both the left and right kidneys, was approximately three times the normal level at baseline (72 and 79 ng per minute, respectively). Bilateral renal-nerve ablation resulted in a marked reduction in renal norepinephrine spillover from both kidneys, with a reduction of 48% from the left kidney and 75% from the right kidney, which demonstrated the effectiveness of the intervention (Fig. 1A). This effect was accompanied by halving of renin activity (from 0.30 to 0.15 μg per liter per hour), an increase in renal plasma flow from 719 to 1126 ml per minute, and a progressive and sustained reduction in systemic blood pressure from 161/107 mm Hg at baseline to 141/90 mm Hg at 30 days to 127/81 mm Hg at 12 months. Whole-body norepinephrine spillover was reduced by 42% (Fig. 1B).

Microneurography at baseline and at 30 days and 12 months showed a gradual reduction in muscle sympathetic-nerve activity to normal levels (56, 41, and 19 bursts per minute, respectively) (Fig. 1C). We also observed an improvement in cardiac baroreflex sensitivity after renal denervation (from 7.8 to 11.7 msec per millimeter of mercury). Cardiovascular magnetic resonance

Schlaich MP, et al. New Engl J Med. 2009;361:932-934.

Changes in Underlying Physiology Consistent With RDN

New Engl J Med Case Study

	Baseline	1 Month	Δ
Office BP (mm Hg)	161/107	141/90	(127/81 at 12 M)
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%
Left ventricular mass (g/m^2)	78.8	73.1	-7%

Schlaich MP, et al. New Engl J Med. 2009;361:932-934

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

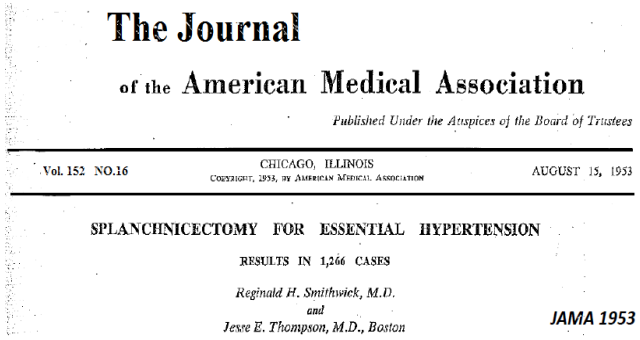
THE BRITISH JOURNAL OF SURGERY

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

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

SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

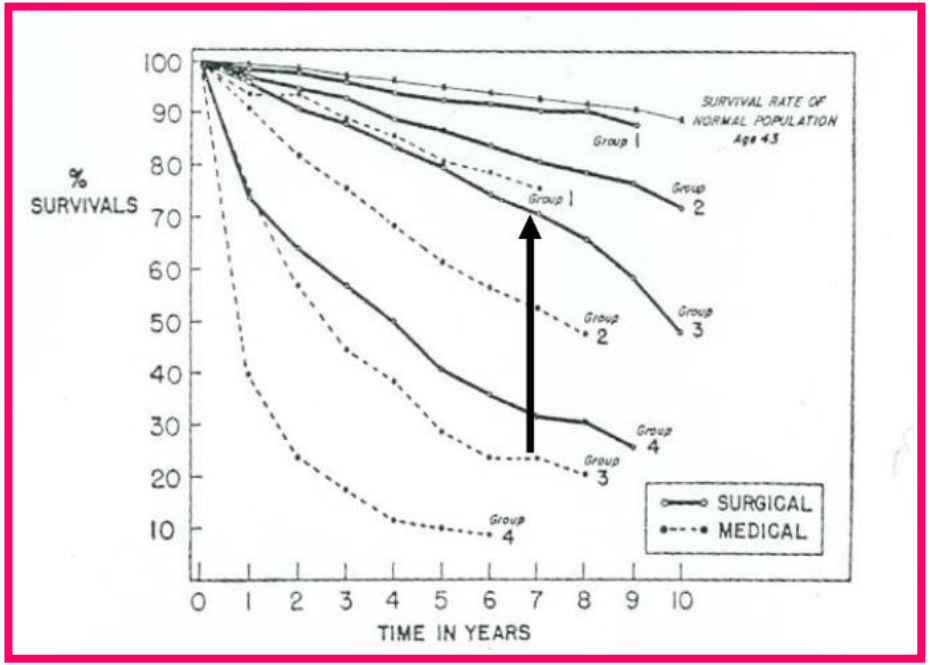
RESULTS IN 1,266 CASES

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

JAMA 1953

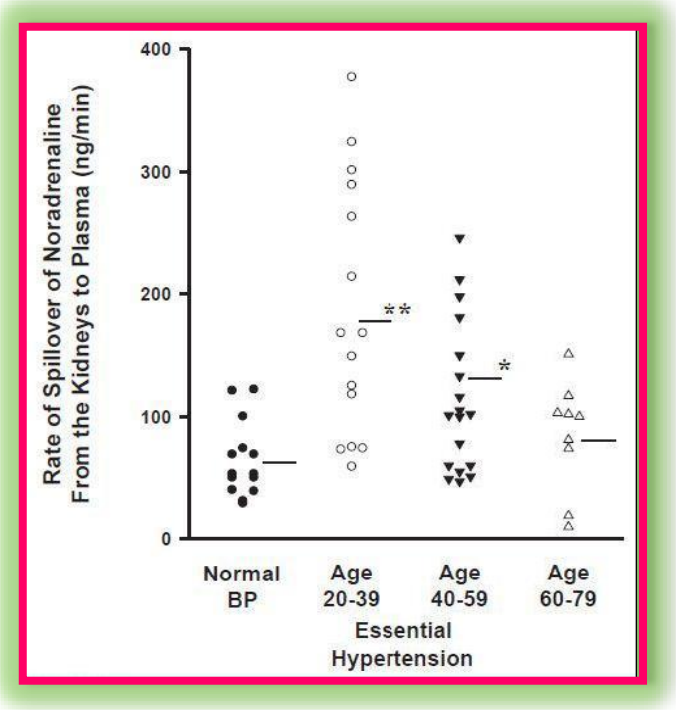
Effective, but significant morbidity

Sympathectomy in Hypertension:
Effects on Survival



Smithwick,R JAMA 1953

Renal Sympathetic Activation in Patients with Hypertension



Esler et M al. Clin Exp Hyper 1984

CLASSIFICATION OF HYPERTENSION STAGES ACCORDING TO BLOOD PRESSURE LEVELS, PRESENCE OF CARDIOVASCULAR RISK FACTORS, HYPERTENSION-MEDIATED ORGAN DAMAGE, OR COMORBIDITIES

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

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

ESC/ESH GUIDELINES

RDN guidelines and consensus published in multiple countries

2018 - 2020

European Society of Cardiology

European Society of Hypertension

Italian Society of Arterial Hypertension (SIIA)

Asia Consortium (ARDeC)

European Clinical Consensus Conference

Russian Medical Society of Cardiology

Brazil Society of Arterial Hypertension

Israeli Society of Hypertension

2021

European Society of Hypertension

International Society of Hypertension

South African HTN Society SA Society of CV Intervention

Spanish Society of HTN Spanish Society of Cardiology

Society for Cardiovascular Angiography and Intervention / National Kidney Foundation

2022

Malaysian Renal Nerve Denervation Working Group (My RDN)

Danish Society of Cardiology †

Taiwan Society of Cardiology†

Netherlands Expert Consortium

2023

European Society of Cardiology and EAPCI

European Society of Hypertension (ESH) Guidelines†

SCAI position statement

Thai Hypertension Society

Italian Society of Cardiology/ Interventional Cardiology Joint Consensus Statement

Irish Consensus Statement

2024 Pending

European Society of Cardiology†

AHA Position Statement**

Expert Consensus Document**

Asia Consortium** (ARDeC)

Philippines Society**

Hypertension Australia**

CHL (China Hypertension League)† Austrian Consensus Statement**

High-quality RCTs confirmed the BP-lowering safety and efficacy of RDN requiring updated guidance

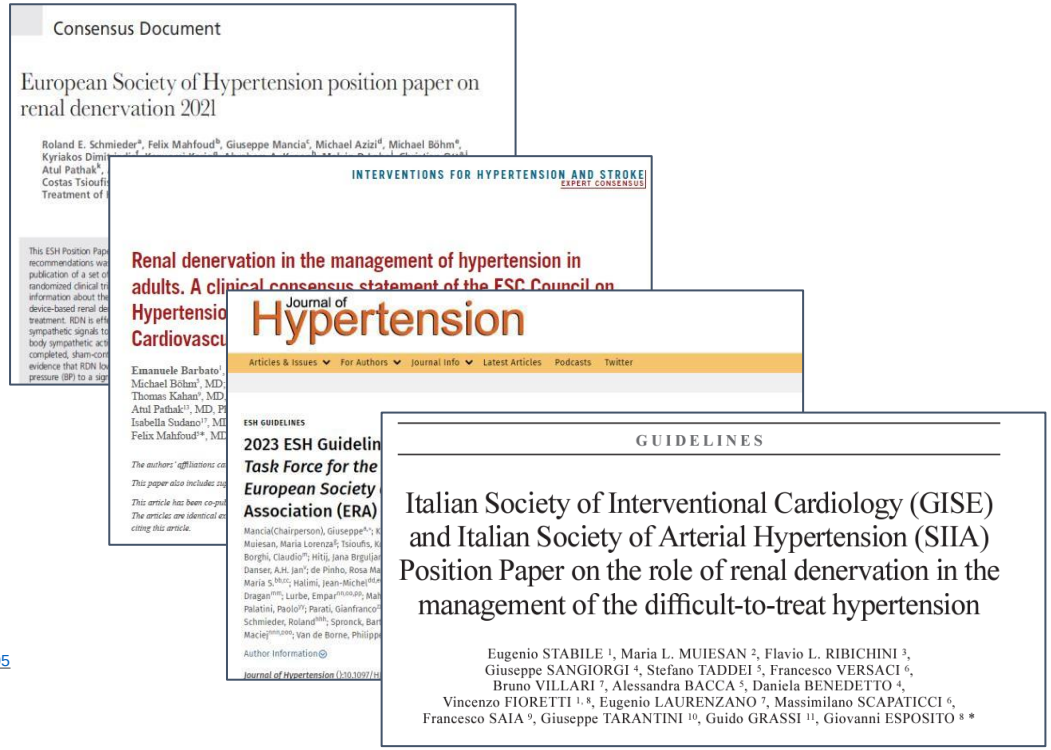
2018 ESC/ESH Guidelines for the Management of Arterial Hypertension[1]

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

©ESC/ESH 2018

RCT = randomized controlled trial.
[a]Class of recommendation.
[b]Level of evidence.



1. Williams B et al, 2018 ESC/ESH Guidelines for hypertension
2. Barbato, et al. European Heart Journal, 15 February 2023, https://doi.org/10.1093/eurheartj/ehad05
3. 4 Kreutz et al. ESH 2023
4. Mancia G. et al. Journal of Hypertension 2023, 41:000–000 DOI:10.1097/HJH.0000000000003480
5. Stabile E. et al. Minerva Cardiol Angiol. 2024 Mar 27. doi: 10.23736/S2724-5683.23.06433-5

European Society of Hypertension (ESH) 2023 guidelines

Recommendations and statements	Class of recommendation	Level of evidence
• RDN can be considered as a treatment option in patients with an eGFR >40 ml/min/1.73m^2 who have **uncontrolled BP** despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
• RDN can be considered as an additional treatment option in patients with **resistant hypertension** if eGFR is >40 ml/min/1.73m^2		
• Selection of patients to whom RDN is offered should be done **in a shared decision-making** process after objectives and complete patient's information	I	C
• Renal denervation should be performed in **experienced centers to guarantee appropriate selection of eligible patients** and completeness of the denervation procedure		

Mancia G. et al. Journal of Hypertension 2023

Two possible clinical profiles of patients candidates to RDN

1 **Resistant** hypertensive patients

Main features:

- Uncontrolled office and 24h BP
- In treatment with an association RAS-blocker / CCB / Diur at maximally tolerated doses
- No secondary hypertension
- Eligible renal artery anatomy

Additional features:

- Adverse effects with spironolactone
- Poor drug adherence despite extensive counseling
- Preferentially systo-diastolic hypertension
- (But isolated systolic hypertension not controindicated!)
- No extensive vascular damage
- High/very high lifetime cardiovascular risk
- Patient preferences

Evidence from Symplicity trials; GSR; DENERHTN; Prague-15; Azizi M et al, Circulation 2016; Mahfoud F et al Eur Heart J 2017, GSR ACC2019

2 **Difficult-to-treat** hypertensive patients

Main features:

- Grade 1-2 hypertensive patients
- Untreated or with uncontrolled systodiastolic office and 24h BP with 1-2 drugs
- Systo-diastolic hypertension
- No secondary hypertension
- Eligible renal artery anatomy

Additional features:

- Multiple intolerance to bp-lowering drugs / adverse effects
- Poor drug adherence despite extensive counseling
- 24h- heart rate >73.5 bpm
- Parossistic/persistent atrial fibrillation
- High / very high lifetime cardiovascular risk
- Patient preferences

Evidence from Spyral OFF-med, ON-med, Radiance solo; Bohm et al,Eur Heart J. 2019; Atti V et al. J C Electrophysiol 2019 SIIA Position Paper, High Blood Pressure &Cardiovascular Prevention 2020

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–107
https://doi.org/10.1093/eurheartj/ehae178

ESC GUIDELINES

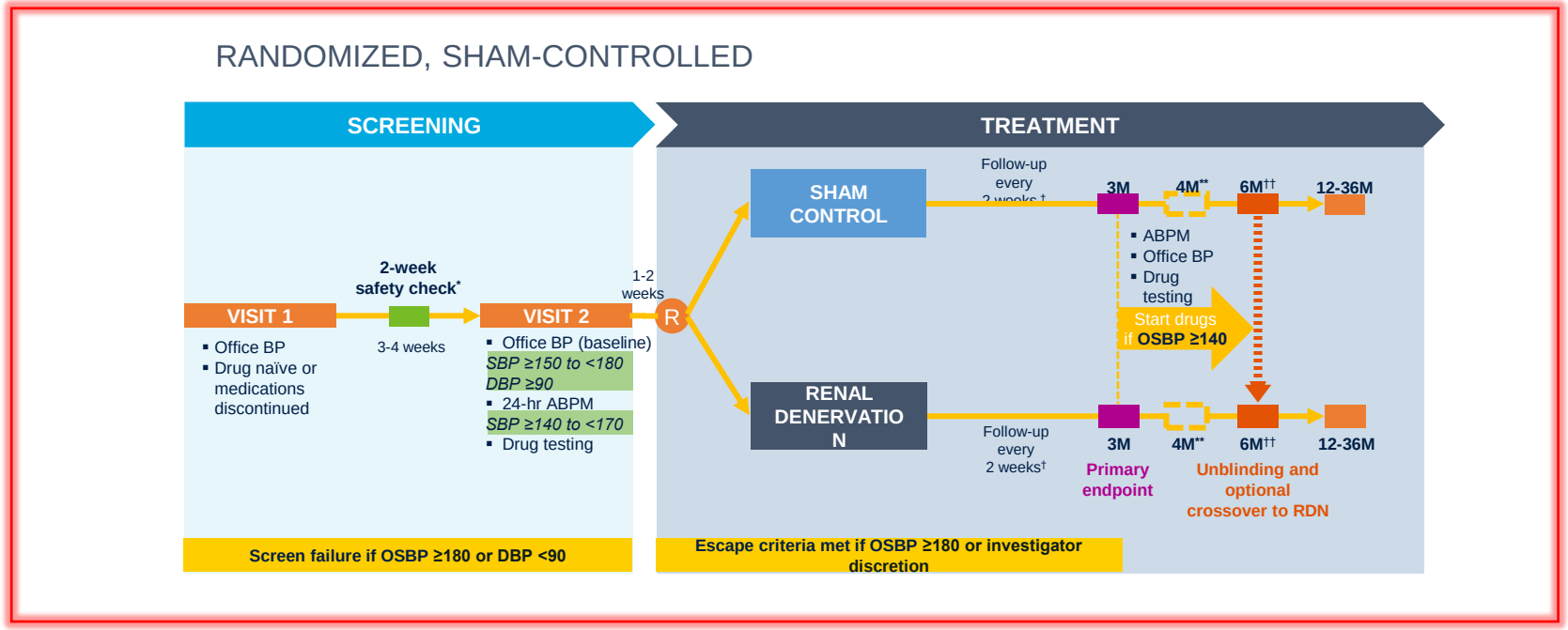
2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Recommendation Table 32 — Recommendations for acutely managing blood pressure in patients with intracerebral haemorrhage or acute ischaemic stroke

Recommendations	Class[a]	Level[b]
For patients with ischaemic stroke or TIA and an indication for BP lowering, it is recommended that BP-lowering therapy be commenced before hospital discharge.[819,820,823]	I	B
In patients with acute ischaemic stroke, early BP lowering with BP-lowering therapy should be considered in the first 24 h in the following settings:		
• In patients who are eligible for re-perfusion therapy with intravenous thrombolysis or mechanical thrombectomy, BP should be carefully lowered and maintained at <180/105 mmHg for at least the first 24 h after treatment.[956–960]	IIa	B
• In patients with ischaemic stroke not receiving re-perfusion treatment and BP of ≥220/110 mmHg, BP should be carefully lowered by approximately 15% during the first 24 h after stroke onset.[956–960]	IIa	C
In patients with intracerebral haemorrhage, immediate BP lowering (within 6 h of symptom onset) should be considered to a systolic target 140–160 mmHg to prevent haematoma expansion and improve functional outcome.[948,949]	IIa	A
In patients with intracerebral haemorrhage presenting with systolic BP ≥220 mmHg, acute reduction in systolic BP >70 mmHg from initial levels within 1 h of commencing treatment is not recommended.[950,951,960–963]	III	B

BP, blood pressure; TIA, transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.

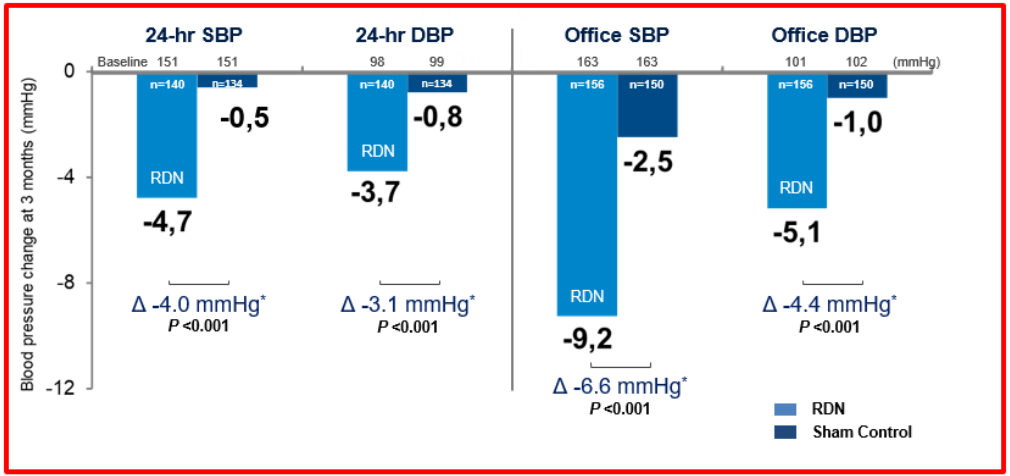
PROOF OF CONCEPT STUDIES IN HYPERTENSION: SPYRAL HTN-OFF MED PIVOTAL TRIAL



Townsend RR, et al. *Lancet*. 2017;390:2160–2170.

PROOF OF CONCEPT STUDIES IN HYPERTENSION:
SPYRAL HTN-OFF MED PIVOTAL TRIAL

BLOOD PRESSURE CHANGE FROM BASELINE AT 3 MONTHS



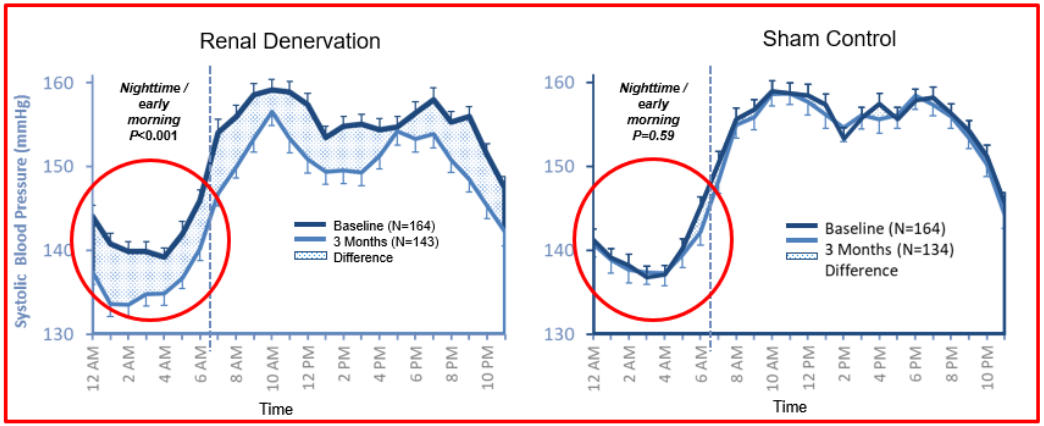
Rdn showed significant reductions in all bp measures

Townsend RR, et al. *Lancet*. 2017;390:2160–2170.

SPYRAL HTN-OFF MED PIVOTAL TRIAL

Rdn demonstrated an “always on” effect on 24-hour Bp lowering[1]

24-HOUR SYSTOLIC ABPM TREND AT 3 MONTHS



The nighttime / early morning period is a “high-risk zone” associated with increased risk for stroke and cardiovascular events[2,3]

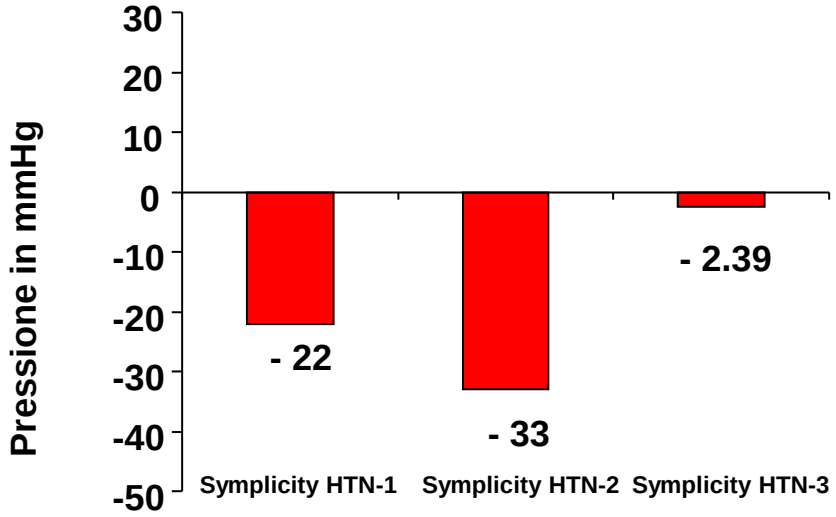
1. Böhm et al. The Lancet, 2020.
2. Amodeo C, Blood Pressure Monit, 2014
3. Boggia J, The Lancet, 2007

Save the date

INFARTO E STROKE: OGNI MINUTO CONTA

ROMA
Hotel Holiday Inn
Parco del Medici
24-25 Ottobre 2024

6M-FU: RDN vs Gruppo di Controllo
Riduzione della PA Sistolica



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Lessons in Uncertainty and Humility — Clinical Trials Involving Hypertension

Marc A. Pfeffer, M.D., Ph.D., and John J.V. McMurray, M.D.

Pfeffer and McMurray, New Engl J Med 2016

Table 1. Major Outcome of Trials Assessing the Risks and Benefits of Treating Elevated Blood Pressure.*

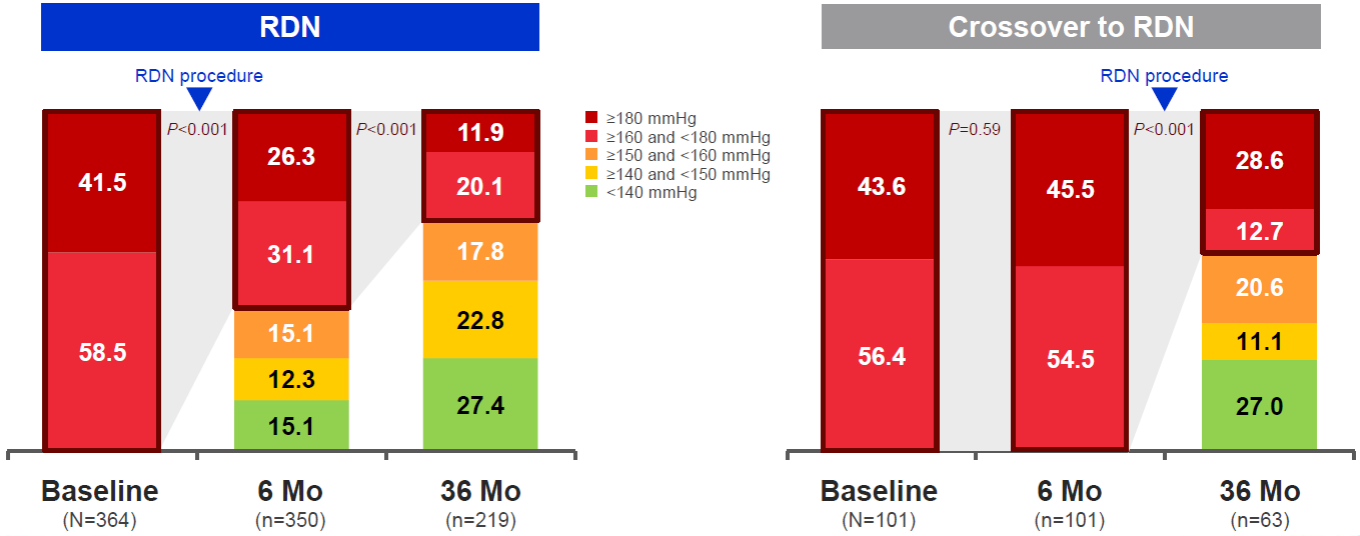
HDFP (1979)[14] Duration: 1974–1979 Participants: 10,940	Diastolic pressure 90 to >115 mm Hg	Stepped care vs. referred care	Stepped care: 159/101 Referred care: 159/101	Decrease of 17% in all-cause mortality (P<0.01)	No	All patients could be treated
MRC (1985)[17] Duration: 1977–1985 Participants: 17,354	Diastolic pressure 90–109 mm Hg, systolic pressure <200 mm Hg	Thiazide or propanolol vs. placebo	*Men* Thiazide: 158/98 Propanolol: 158/98 Placebo: 158/98 *Women* Thiazide: 165/98 Propanolol: 165/98 Placebo: 165/98	Decrease of 46% in stroke (P<0.01) and 19% in cardiovascular events (P<0.05)	Yes	Previous data considered insufficient for general recommendations; active drug initially recommended for patients with systolic pressure ≥210 mm Hg or diastolic pressure ≥115 mm Hg; reduced during trial to ≥200 mm Hg and ≥110 mm Hg, respectively
Syst-Eur (1997)[20] Duration: 1989–1997 Participants: 4695	Diastolic pressure <95 mm Hg with systolic pressure 160–219 mm Hg; age ≥60 yr	Antihypertensive treatment vs. placebo	Treatment: 174/86 Placebo: 174/86	Decrease of 42% in stroke (P=0.003)	Yes	Eligibility requirements similar to SHEP and STOP; active treatment for systolic pressure >219 mm Hg or diastolic pressure >99 mm Hg; during trial, ethics committee lowered eligible systolic pressure to 200 mm Hg
HOT trial (1998)[21] Duration: 1992–1997 Participants: 18,790	Diastolic pressure 100–115 mm Hg	Different intensities of antihypertensive treatment intended to target diastolic blood pressures of <90, ≤85, or ≤80 mm Hg	Participants in each of three treatment groups: 170/105	No significant difference in rate of cardiovascular death, myocardial infarction, or stroke across all three groups; however, fewer clinical events in patients with diabetes in subgroup targeting lower diastolic pressure	No	Therapy started with calcium-channel blocker, with ACE inhibitor, beta-blocker, diuretic, or any combination thereof added; three levels of reduction of diastolic pressure targeted
ALLHAT (2000)[22] Duration: 1994–1999 Participants: 24,335	Systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg and one or more risk factors for coronary heart disease; age ≥55 yr	Chlorthalidone vs. doxazosin	Chlorthalidone: 145/83 Doxazosin: 145/84	No significant difference in primary outcome of death from coronary heart disease or nonfatal myocardial infarction; trial terminated prematurely when rate of heart failure with doxazosin increased 104% vs. chlorthalidone (P<0.001)	No	Intended to control blood pressure and address potential differences between agents

Pfeffer and McMurray, New Engl J Med 2016

Office Systolic BP Distribution

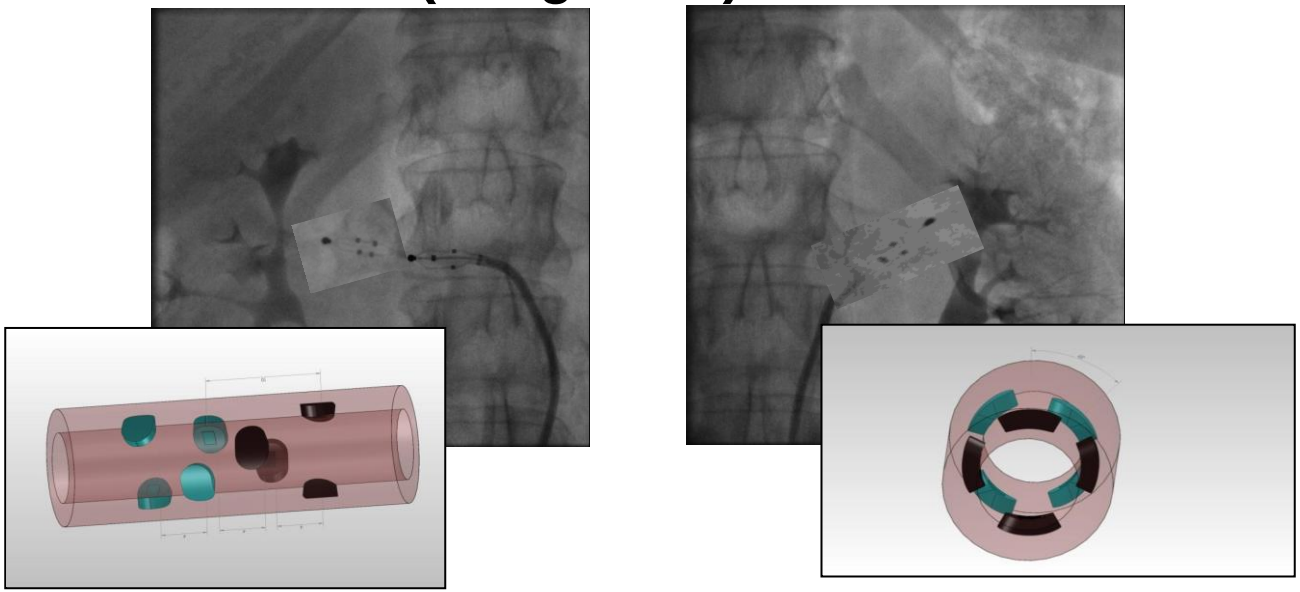
(% Patients)

Symplicity HTN - 3 Clinical Study



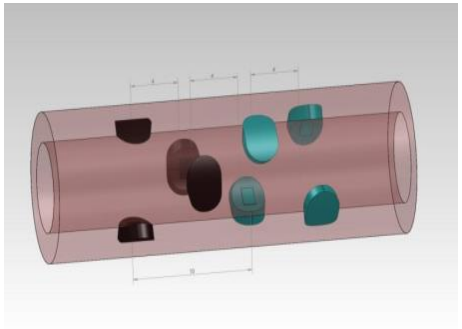
Bhatt DL, et al. Lancet 2022;400:1405-16.

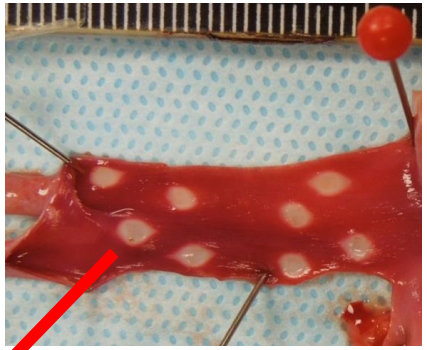
RDN
(EnlighHTN)

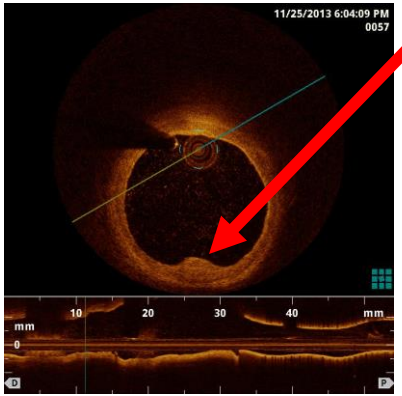


F.Versaci, et al. Int J Cardiol, May 2014

RDN (EnlighHTN)

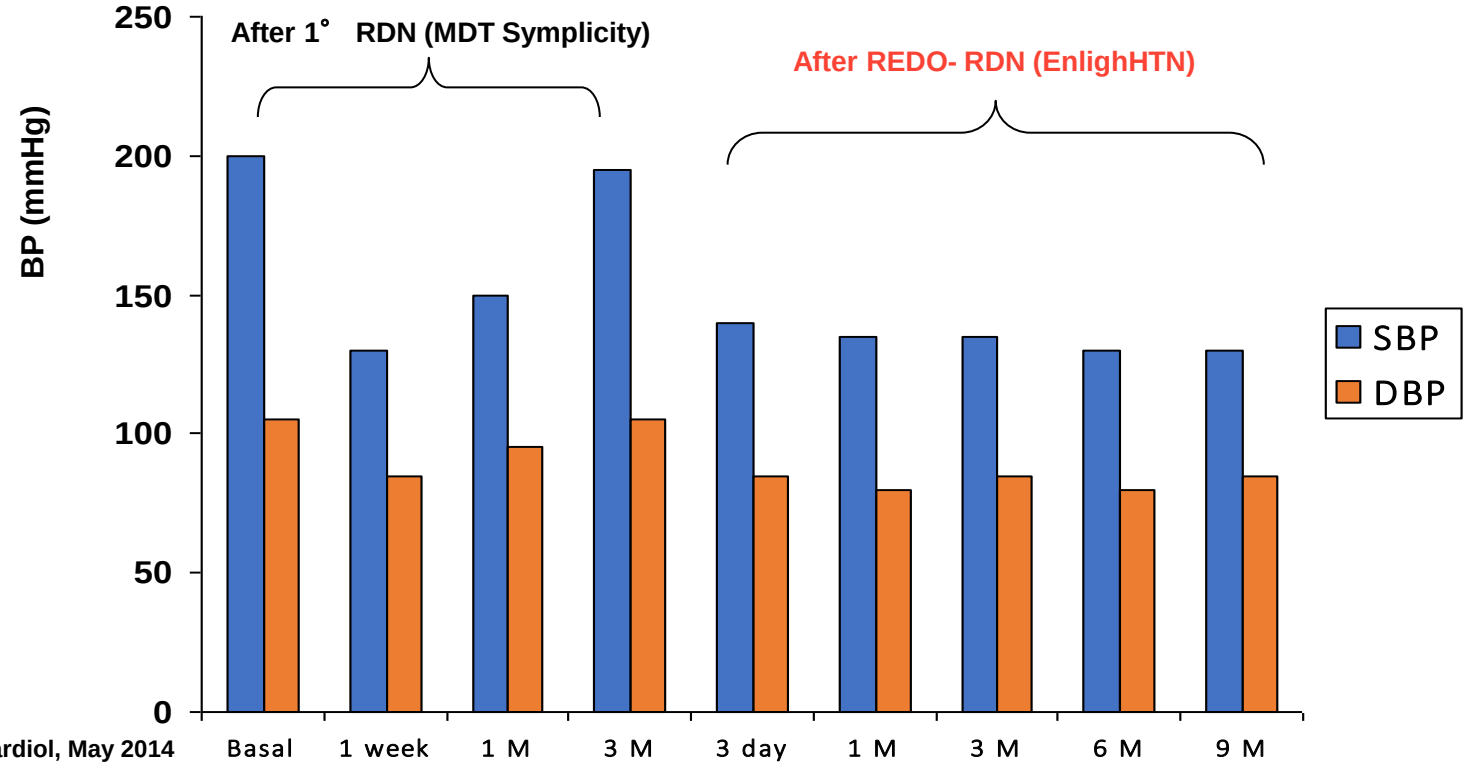






F. Versaci, et al. Int J Cardiol, May 2014

Redo of RDN: a case of effective treatment with a second generation of device in a patient with recurrent resistant hypertension after primary treatment success.



F.Versaci, et al. Int J Cardiol, May 2014

Boston Scientific Vessix Renal Denervation System

- Balloon-based technology (sizes 4 – 7 mm)
- Low pressure non-compliant balloon (3 atm/304 kPa)
- Helical pattern of RF electrodes for uniform treatment
- 30 second treatment time with up to 8 RF electrodes activated simultaneously
- Electrodes that are unapposed to vessel wall are automatically deactivated
- Bipolar energy delivery, using energy of ~1W
- Temperature control algorithm ensures energy deliver at precisely 68°C
- One button operation
- CE marked and TGA approved

Vascular response after percutaneous sympathectomy: not all devices are equal.

Symplicity vs Vessix (n:20)
ABPM 1 month

	Blood pressure	ABPM pre-procedure	ABPM 1 month post-procedure
Symplicity	Systolic BP 24h	138,44 ± 16	138,14 ± 8,88
	Diastolic BP 24h	73,89 ± 5,71	72,71 ± 6,7
	Systolic BP «awake»	141,11 ± 16,45	140 ± 8,02
	Diastolic BP «awake»	76,67 ± 6,24	74,43 ± 6,85
	Systolic BP «asleep»	129,44 ± 17,71	131,29 ± 14,67
	Diastolic BP «asleep»	64,78 ± 5,67	66 ± 8,72
Vessix	Systolic BP 24h	143,29 ± 21,28	135,33 ± 8,31
	Diastolic BP 24h	76 ± 9,8	70,33 ± 6,62
	Systolic BP «awake»	144,86 ± 21,28	139 ± 8,22
	Diastolic BP «awake»	77,14 ± 9,75	73,67 ± 7,66
	Systolic BP «asleep»	139,57 ± 26,37	123,5 ± 10,01
	Diastolic BP «asleep»	74,14 ± 13,94	60 ± 5,21

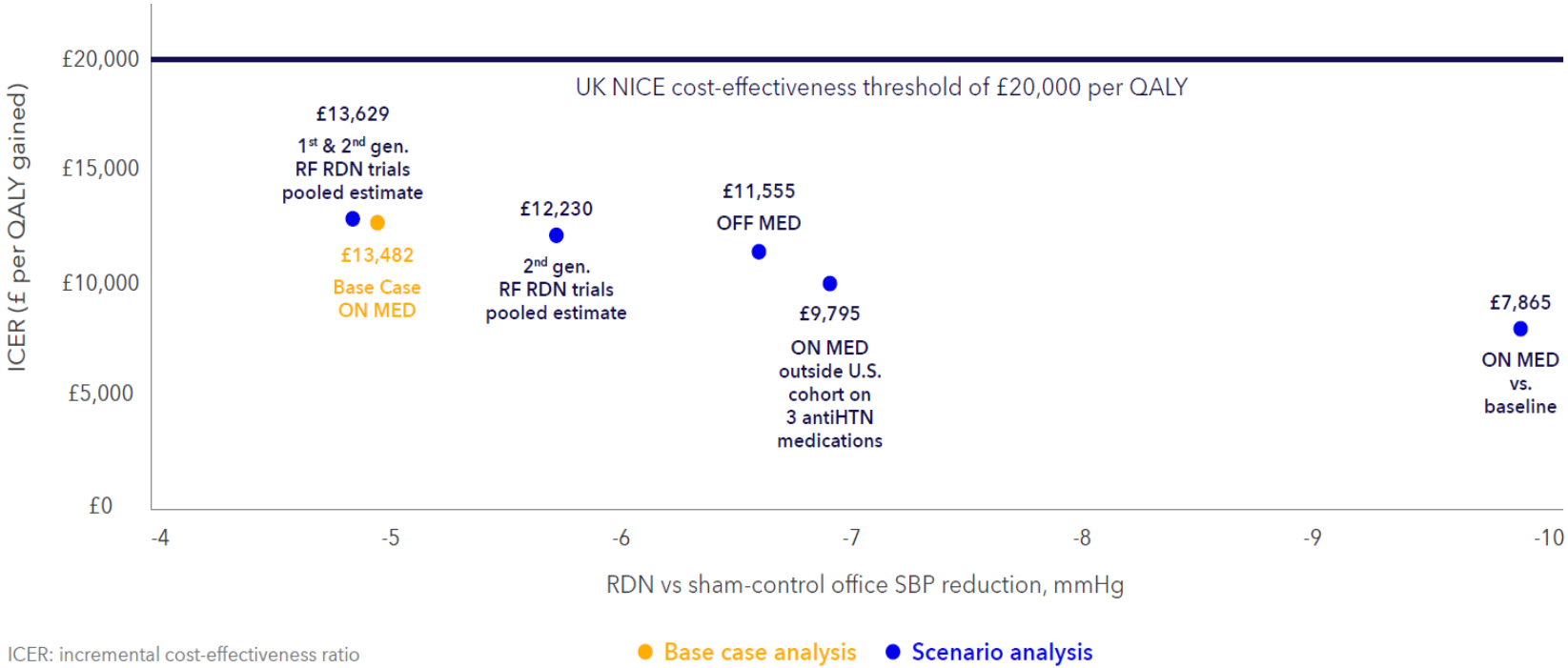
Versaci et al., JACC 2015

Audience Q&A

Prof Alta Schutte

Is it cost effective?

RF RDN was shown to be cost-effective in uncontrolled hypertension

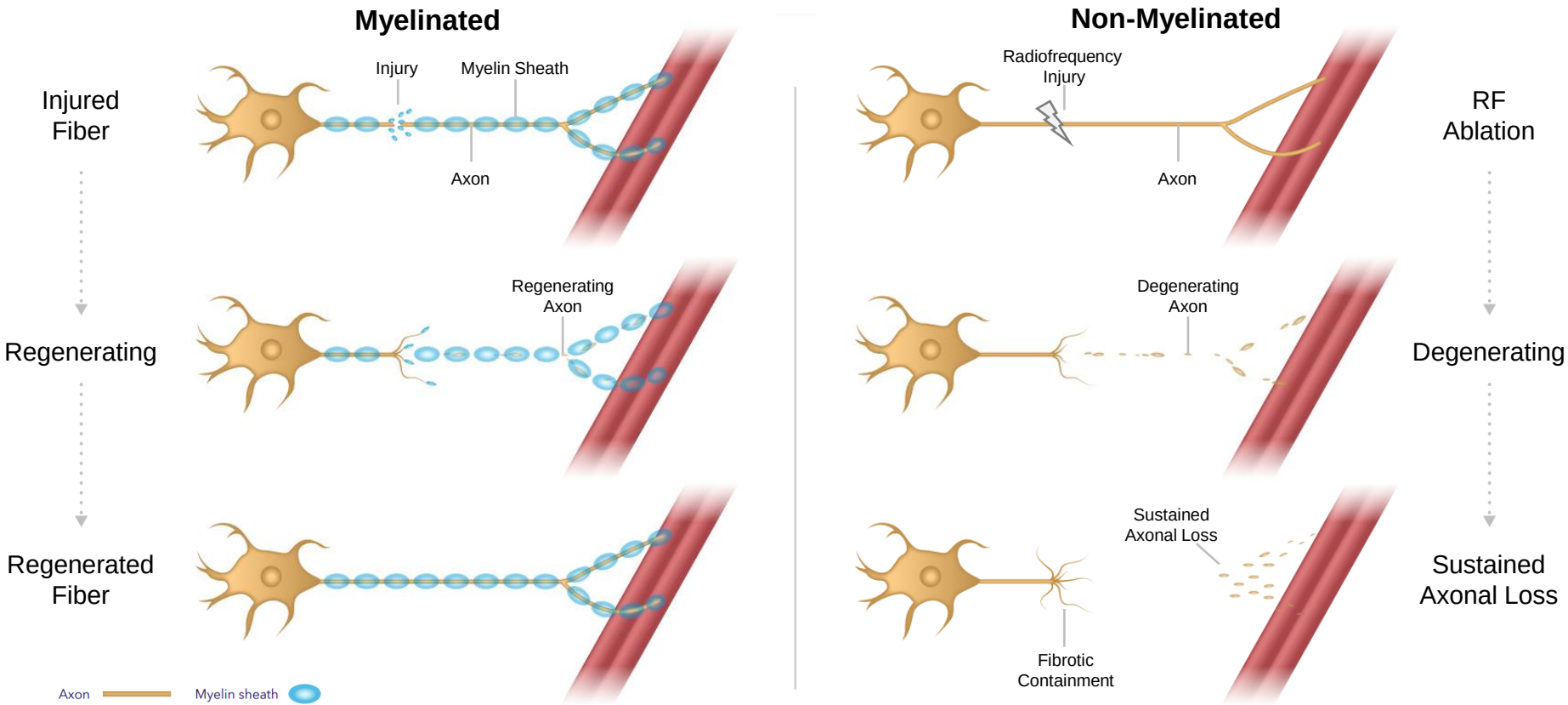


ICER: incremental cost-effectiveness ratio

Sharp et al. European Heart Journal - Quality of Care and Clinical Outcomes (2024) 0, 1–11 https://doi.org/10.1093/ehjqcco/qcae001

Do the nerves regrow after RDN?

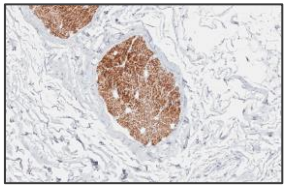
Lack of myelination may be the key to RF RDN durability



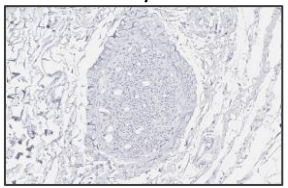
Unrecoverable Sympathetic Nerve Activity After RF RDN

Permanent axonal destruction and sustained reductions in renal norepinephrine in a porcine model

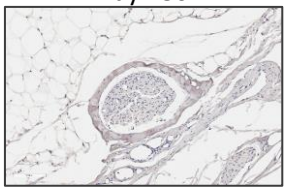
Pre-RDN



Day 7

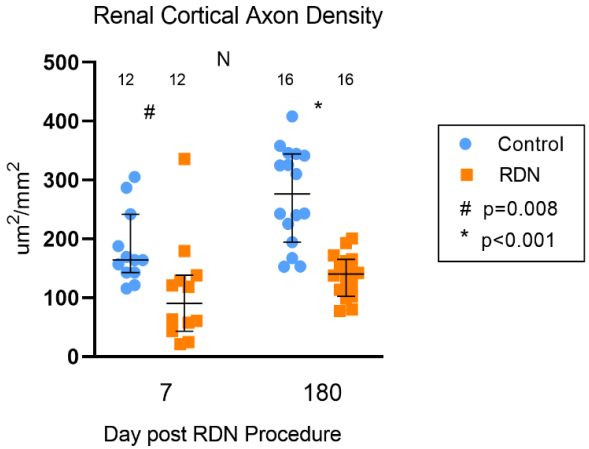


Day 180

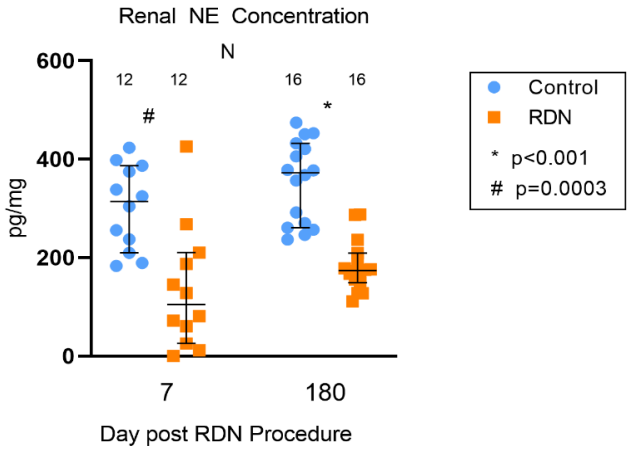


Brown staining = viable axons

Morphological Assessment



Physiological Assessment



Sharp A, et al. *J Hypertension*. 2022;40(10),2068-2075.

Are there any predictors of response?

Many predictors of RDN response have been proposed but no single attribute has emerged

INCREASED SYMPATHETIC ACTIVITY

Response Predictor	Reference
Younger age	▪ Azizi M, et al. *Lancet*. 2018;391:2335-234. ▪ Fengler K, et al. *J Hypertens*. 2018;36:1578-1584.
Higher baseline heart rate	▪ Böhm M, et al. *Eur Heart J*. 2019;40:743-751. ▪ Böhm M, et al. *J Am Coll Cardiol*. 2021;78(10):1028-1038.
Higher baroreceptor sensitivity	▪ Zuern C, et al. *J Am Coll Cardiol*. 2013;62:2124–30.
Worse renal function	▪ Vink E, et al. *J Hypertens*. 2014;32:2045-53.
Plasma biomarkers	▪ Mahfoud F, et al; *J Am Coll Cardiol*. 2021;77:2909-19. ▪ Fisher N, et al. Journal of Hypertension 2022;40:221–228. ▪ Dörr O, et al. *Hypertension*. 2014;63:984-990. ▪ Dörr O, et al. *J Am Coll Cardiol*. 2015;65:1151-3.
Lower BMI	▪ Id D, et al. *Catheter Cardiovasc Interv*. 2016;87:E30-8.
Sleep Apnea	▪ Kario K, et al. *Circ J*. 2016;80(6):1404-12.
Nighttime BP	▪ Gosse P, et al. *Hypertension*. 2017;69(3):494-500. ▪ Gosse P, et al. *Hypertension*. 2021;77(2):529-536.
Orthostatic Hypertension	▪ Saxena M, et al. *J Hum Hypertens*. 2022 Jul;36(7):629-639. ▪ Kario K. AHA 2019.
RAAS activity	▪ Lin S, et al. Rev Cardiovasc Med. 2022;23(2):65.

LOWER ARTERIAL STIFFNESS

Response Predictor	Reference
Aortic Calcification	▪ Courand P, et al. *J Am Heart Assoc*. 2017;6(10):e007062.
Aortic Distensibility	▪ Stoiber L, et al. *Clin Res Cardiol*. 2018;107(8):642-652.
Pulse wave velocity	▪ Zeijen V, et al. *J Hypertens*. 2023 Jan 20. ▪ Fengler K, et al. *EuroIntervention*. 2022. EIJ-D-21-01036 ▪ Fengler K, et al. *J Am Heart Assoc*. 2017;6(5):e005879. ▪ Davies J. EuroPCR 2016.
Central Pulse Pressure	▪ Ott C , et al. *EuroIntervention*. 2015;11:110-6.
Augmentation Index	▪ Schlaich M, et al. *J Hypertens*. 2013,31:1893–1900. ▪ Weber T, et al. *Hypertension*. 2022;79:1506-1514.

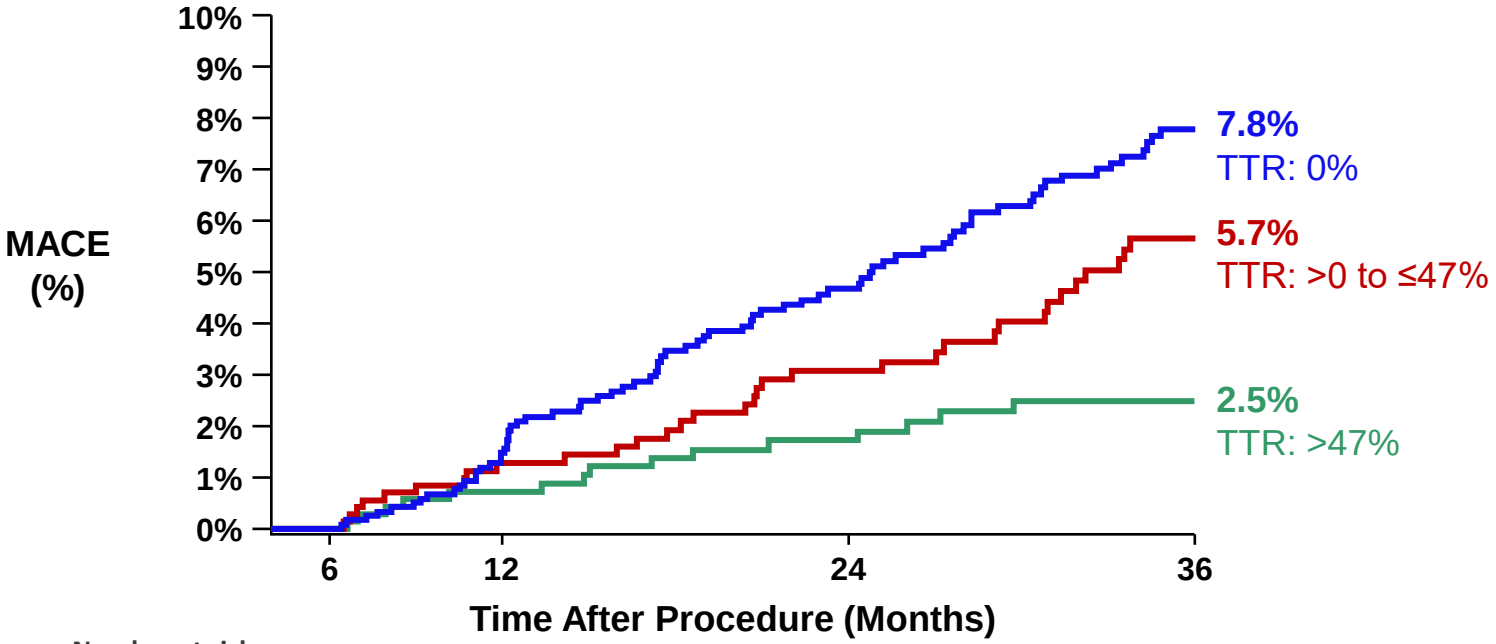
No single attribute with sufficient sensitivity and specificity **has been identified to predict response** at the patient level

Research into a multi-parameter model ongoing

Can we reduce CV events following RDN?
Will we have an outcomes study?

Increased TTR corresponds with a significant decrease in MACE

GSR DEFINE outcomes

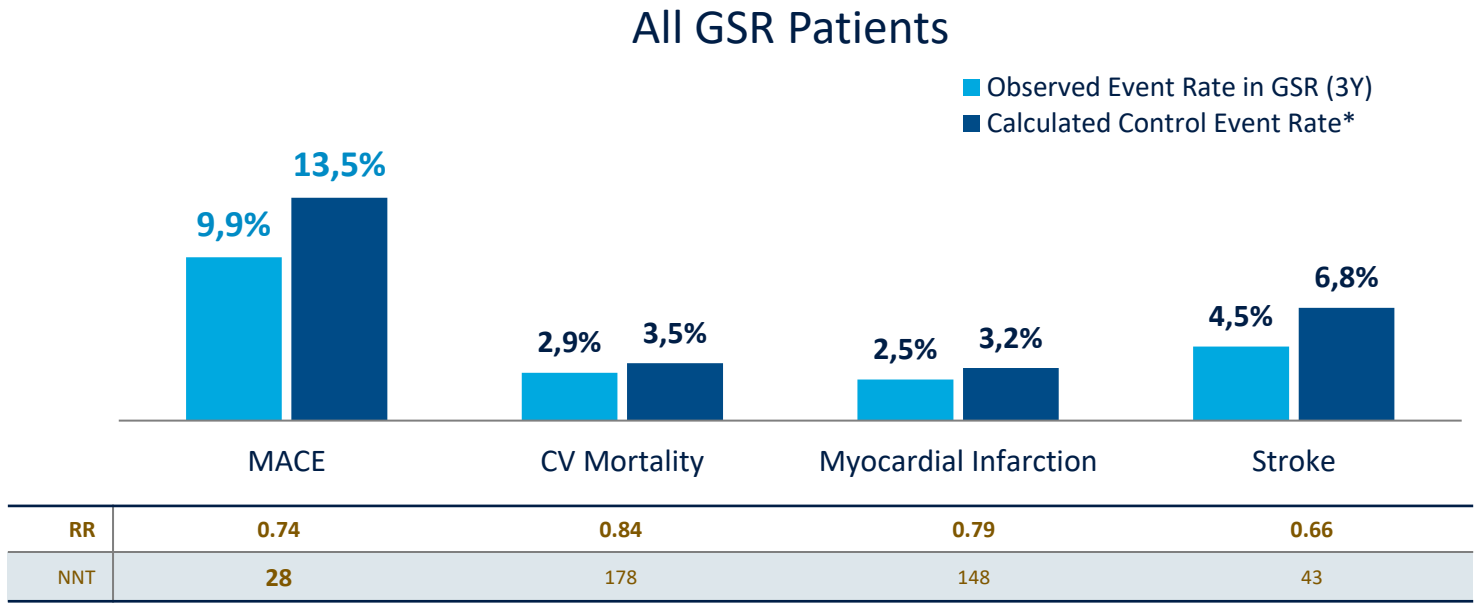


Number at risk				
TTR: 0%	1223	1120	914	614
TTR: >0 to ≤47%	730	668	567	384
TTR: >47%	719	668	555	402

Mahfoud et al. JACC Vol. 80, No. 20, Nov. 2022: 1871-1880

RDN associated with 26% relative risk reduction in MACE over 3 yrs[1]

Observed event rates for GSR patients vs. calculated control*



RR	**0.74**	**0.84**	**0.79**	**0.66**
NNT	**28**	178	148	43

*Analysis applied a previously published CV risk regression meta-analysis[2] to estimate the event rates of a modeled control group using the assumption the baseline blood pressure and anti-hypertensive drug prescription regimen remained unchanged for patients enrolled in GSR

1 Adopted from Schmieder RE, et al. Eur Heart J Qual Care Clin Outcomes. 2022 Sep 4:qcac056. doi: 10.1093/ehjqcco/qcac056.
2 Thomopoulos C, et al. J Hypertension. 2014;32:2285-2295

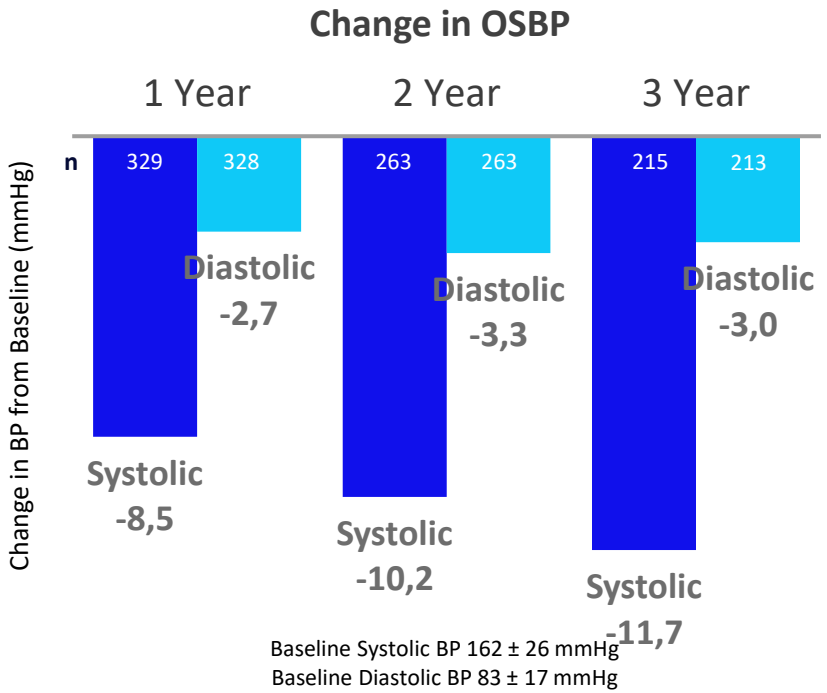
MACE: major adverse cardiovascular events, calculated as composite of CV death, MI, and stroke
RR: relative risk; calculated from modeled control
NNT: number needed to treat; calculated from modeled control

How can you tell if the procedure has been successful?
Will we have a procedural success marker?

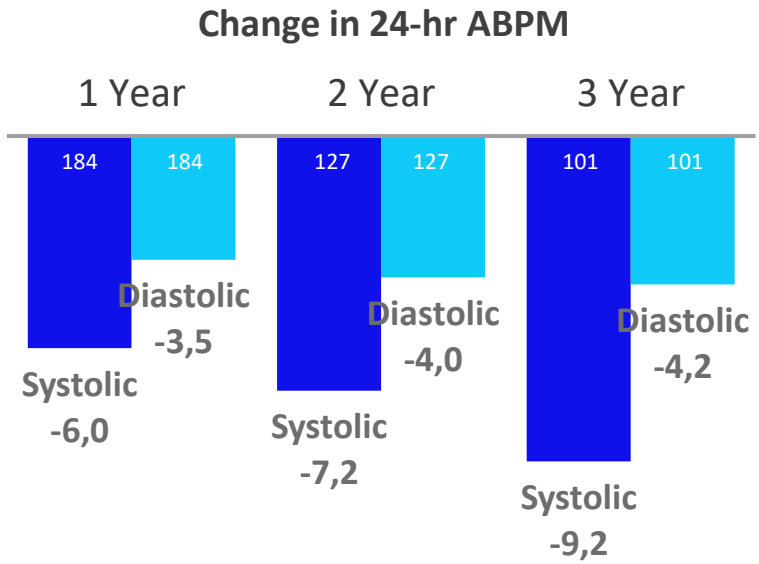
Can RDN be used in CKD patients?

BP reductions observed in CKD patients following RDN in GSR

Global SYMPLICITY Registry results out to 3 years



Baseline Systolic BP 162 ± 26 mmHg
Baseline Diastolic BP 83 ± 17 mmHg



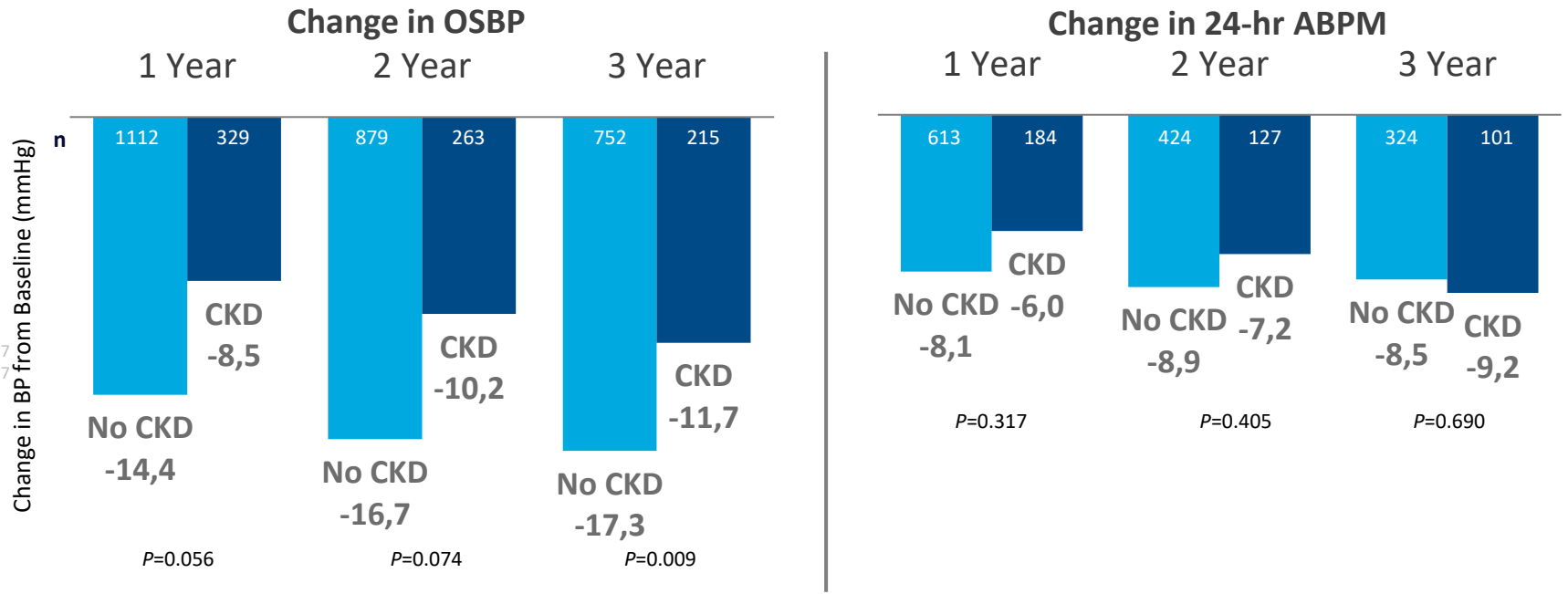
Baseline Systolic BP 154 ± 19 mmHg
Baseline Diastolic BP 82 ± 14 mmHg

CKD defined as baseline eGFR<60 ml/min/1.73m^2

Ott C, et al. *Nephrol Dial Transplant*. 2022;37(2):304-310.

Renal denervation in patients with vs without CKD*

Results from the Global SYMPLICITY Registry with follow-up data to 3 years



Ott C, et al. *Nephrol Dial Transplant*. 2022;37(2):304-310.
*CKD defined as baseline eGFR<60 ml/min/1.73m^2

RDN in CKD patients in GSR

Global SYMPLICITY Registry: safety at 3 years

%	Without CKD (n=1087)	With CKD (n=338)	P-value
MAE*	8.0	18.6	<0.001
All-cause death	4.1	9.2	<0.001
CV death	2.4	5.3	0.007
Myocardial Infarction	2.5	3.6	0.294
Stroke	3.6	6.2	0.036
New onset ESRD	0.3	5.9	<0.001

CKD defined as baseline eGFR<60 ml/min/1.73m^2

*MAE: death, new onset end-stage renal disease, significant embolic event resulting in end-organ damage, renal artery re-intervention due to perforation or dissection, vascular complications, hospitalisation for hypertensive crisis / hypertensive emergency or new renal artery stenosis > 70%

Ott C, et al. *Nephrol Dial Transplant*. 2022;37(2):304-310.

RDN in CKD vs non-CKD patients in an independent study

Verona experience: patient baseline characteristics

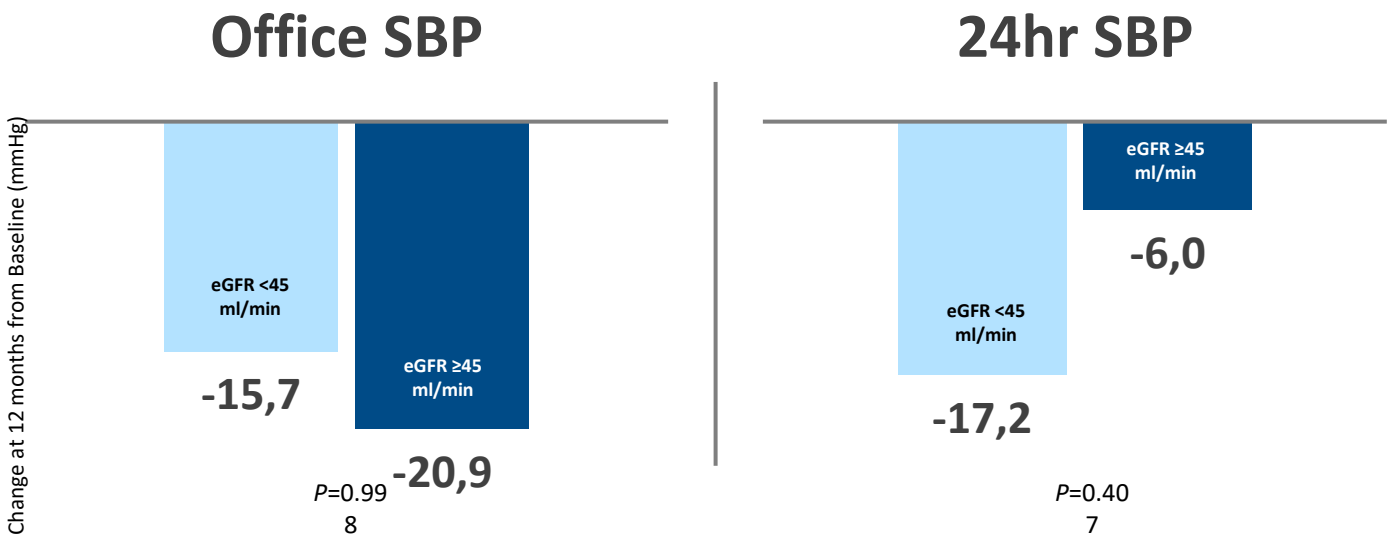
Mean ± SD or % (n)	eGFR <45 ml/min N=27	eGFR ≥45 ml/min N=45	P
BASELINE PATIENT CHARACTERISTICS			
Age (years)	58.5 ± 17.0	59.8 ± 14.0	0.79
Male	81.5% (22)	66.7% (30)	0.17
eGFR (ml/min)	26.7 ± 12.9	77.2 ± 20.0	<0.001
CKD	100% (27)	35.5% (16)	<0.001
Stage V	25.9% (7)	-	-
Diabetes, type 2	51.9% (14)	37.8% (17)	0.50
ISH	48.1% (13)	55.6% (25)	0.36
CAD	18.5% (5)	28.9% (13)	0.39
Antihypertensive medications	5.5 ± 0.9	5.1 ± 1.2	0.31

Mean ± SD or % (n)	eGFR <45 ml/min N=27	eGFR ≥45 ml/min N=45	P
BASELINE BLOOD PRESSURE			
Office SBP (mmHg)	160.6 ± 22.1	157.6 ± 24.5	0.61
24-hr SBP (mmHg)	157.4 ± 16.8	148.3 ± 19.2	0.10

Ribichini F. EuroPCR 2022.
Marin F, et al. *J Nephrol*. 2021;34(5):1445-1455.

BP reductions in CKD vs non-CKD patients in independent study

Verona experience: similar efficacy at 12 months

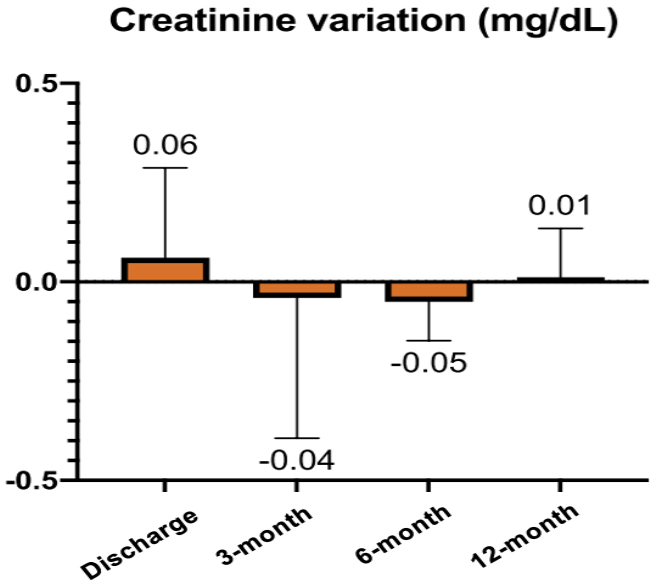


Ribichini F. EuroPCR 2022.

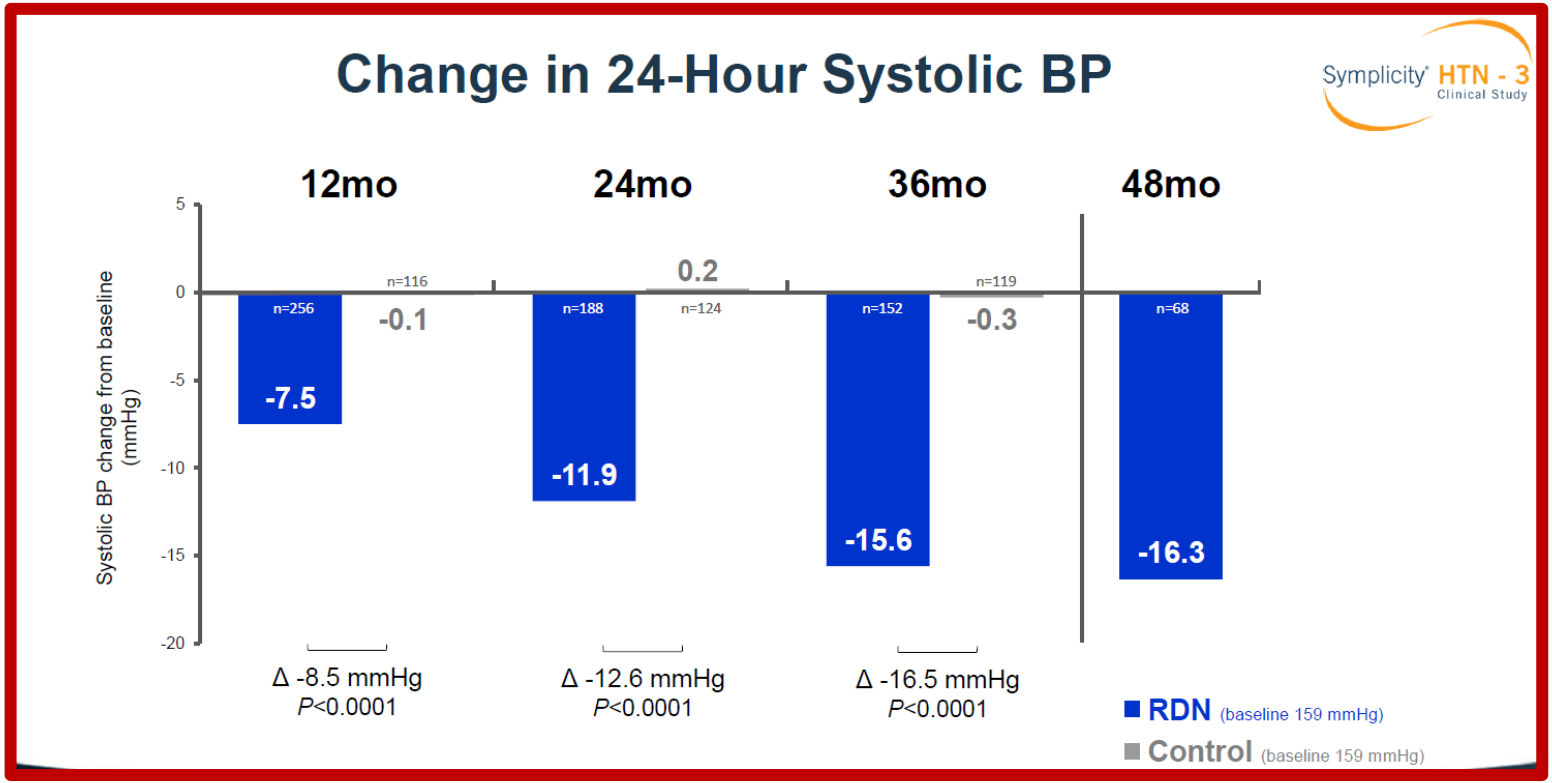
BP reductions in CKD vs non-CKD patients in independent study

Verona Renal Denervation Study at 12 months

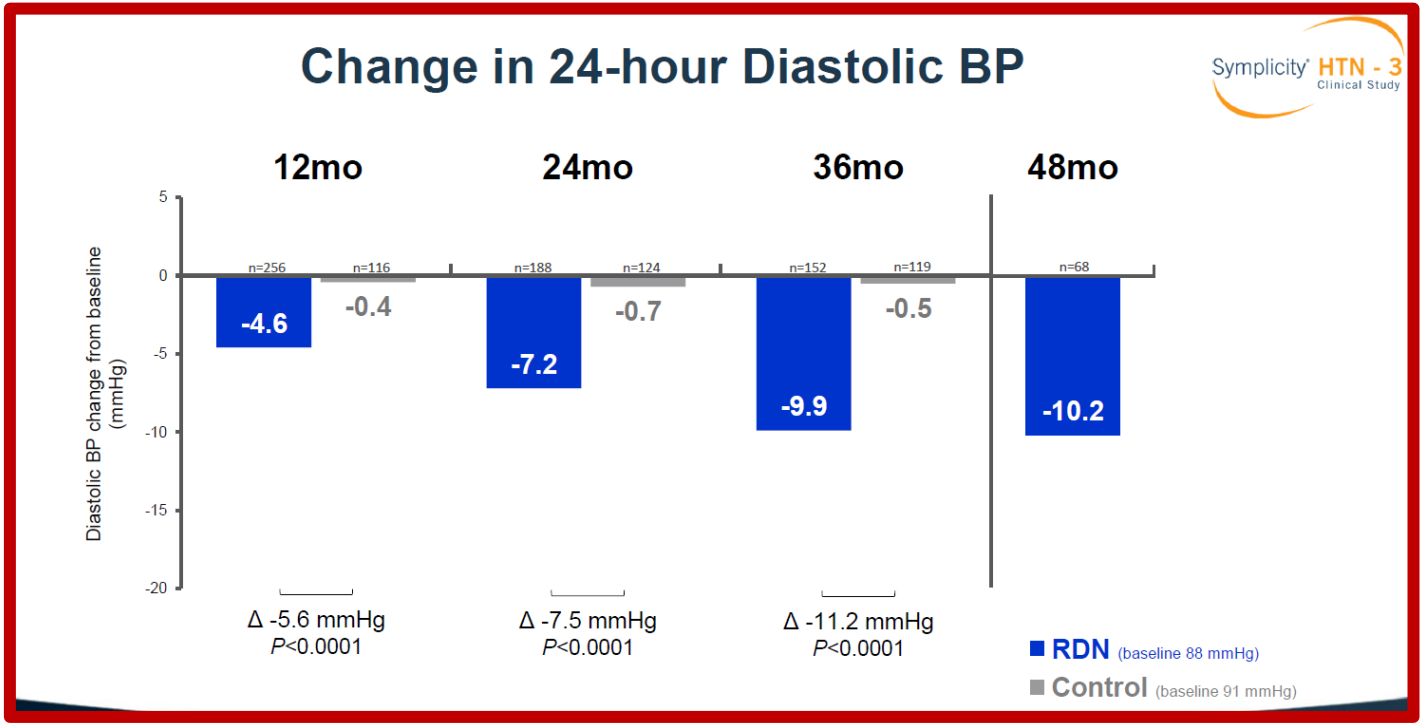
% (n)	Overall N=72	eGFR <45 ml/min N=27	eGFR ≥45 ml/min N=45	P
Major complication and MACE	0	0	0	-
Minor complication	8.3% (6)	14.8% (4)	4.4% (2)	0.12
Transient increment of creatinine	5.5% (4)	11.1% (3)	2.2% (1)	**0.003**
Femoral Pseudoaneurysm	2.7% (2)	3.7% (1)	2.2% (1)	0.999



Ribichini F. EuroPCR 2022.



Bhatt DL, et al. Lancet 2022;400:1405-16.



Bhatt DL, et al. Lancet 2022;400:1405-16.

PROGRAMMA SCIENTIFICO

14:45 Registrazione dei partecipanti

15:00 **Apertura dei Lavori**
Francesco Versaci

I SESSIONE
MISURE EFFICACI PER LA GESTIONE DELL'IPERTENSIONE NON CONTROLLATA
Moderatori:
Emanuele Barbato
Eugenio Stabile

15:10 **La ragionevole terapia farmacologica antipertensiva: le nuove linee guida**
Giuliano Tocci

15:25 **Strategie di approccio al trattamento dell'ipertensione. L'aderenza terapeutica e la terapia combinata**
Giovambattista Desideri

15:40 **La storia clinica della denervazione renale fino alle nuove linee guida**
Francesco Versaci

15:55 **Denervazione renale: il punto di vista del Nefrologo**
Sandro Feriozzi

16:10 **Discussione**

16:30 **Coffee Break**

II SESSIONE
DALLA TEORIA ALLA PRATICA CLINICA: L'ESPERIENZA REGIONALE SULLA DENERVAZIONE RENALE
Moderatori:
Andrea Berni
Achille Gaspardone
Sebastiano Sciarretta

Discussants:
Angelo D'Urso - Cristian Di Russo - Michael Donahue - Benedetta Giannico - Luigi Iuliano - Anna Paola Mitterhofer - Raffaele Papa - Igino Proietti - Francesco Rotolo - Andrea Spampinato - Gaetano Tanzilli

17:00 **Il protocollo per lo screening del paziente candidato alla denervazione renale**
Mauro Pennacchi

17:10 **Aspetti procedurali del trattamento: il nuovo razionale clinico**
Fabrizio Tomai

17:20 **Ablazione delle arterie renali con radiofrequenza e ultrasuoni: due tecnologie per un obiettivo comune**
Iginio Colaiori

17:30 **Modello "Pisano" del trattamento dell'ipertensione resistente**
Alessandra Bacca

17:40 **Discussione**

17:50 **Sicurezza ed efficacia a lungo termine**
Carlo Penzo

18:00 **Stenosi dell'arteria renale: PTA o denervazione? Protocollo empirico per un corretto planning**
Domenico Tavella

18:10 **L'esperienza nei pazienti con eventi cerebrali dovuti ad ipertensione non controllata**
Massimiliano Scappaticci

18:20 **Denervazione renale e nuove frontiere: fibrillazione atriale e scompenso cardiaco**
Cristiano Miotti

18:30 **Discussione**

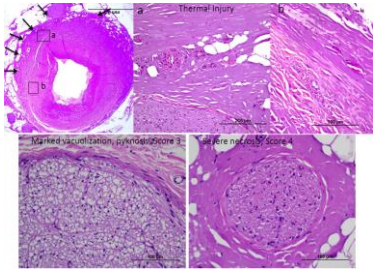
18:50 **Tavola Rotonda: Come approcciare il territorio per efficientare il processo di riferimento del paziente iperteso:**
Giuseppe Biondi Zoccai
Giovambattista Desideri
Carlo Penzo
Fabrizio Tomai
Francesco Versaci

19.10 **Take home message e chiusura lavori**
Francesco Versaci

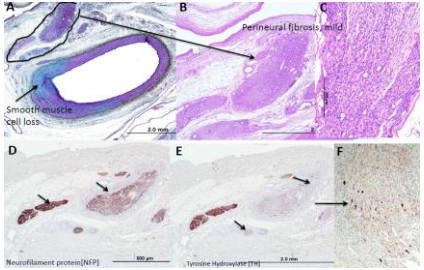
19.15 **Questionario ECM**

Histology after Renal denervation

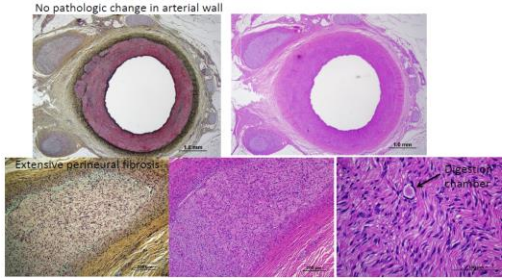
4 Hours after RDN

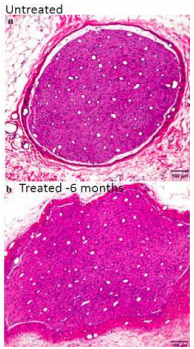


14 days after RDN



6 Months after RDN

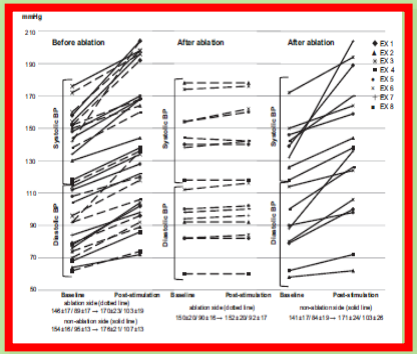




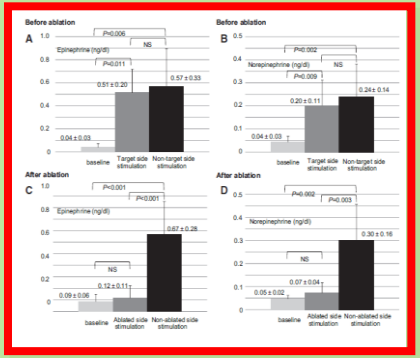
Courtesy of R. Virmani

Blood Pressure and Autonomic Responses to Electrical Stimulation of the Renal Arterial Nerves Before and After Ablation of the Renal Artery

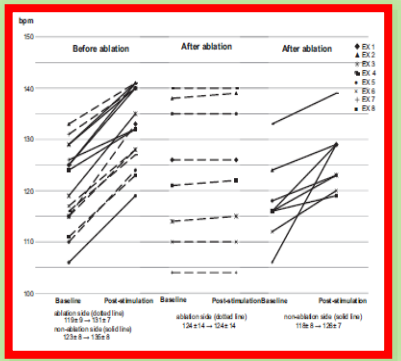
Blood Pressure Responses



Serum Cathecolamine Analysis

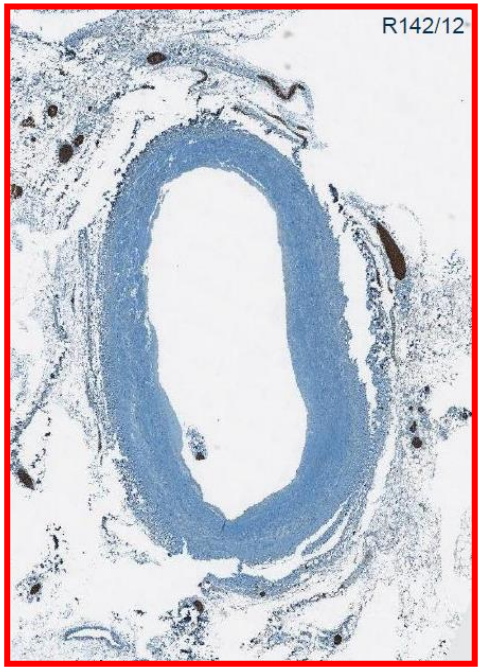


Heart Rate Response

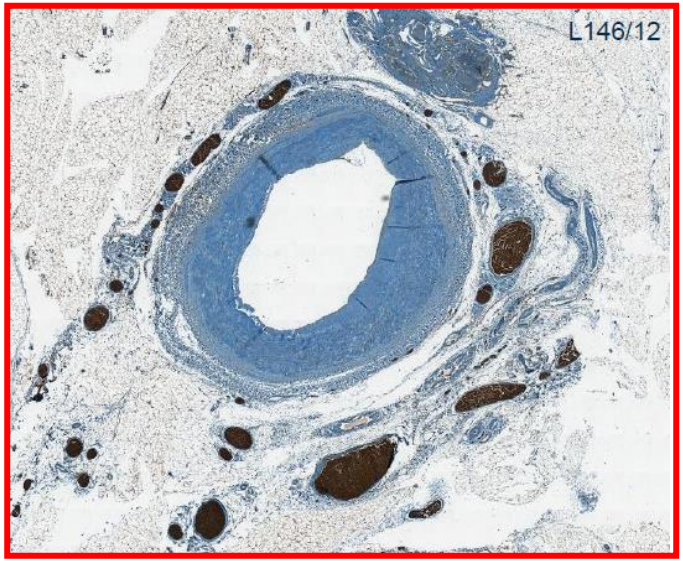


Chinushi M et al. Hypertension. 2013; 61:450-456

Case Example

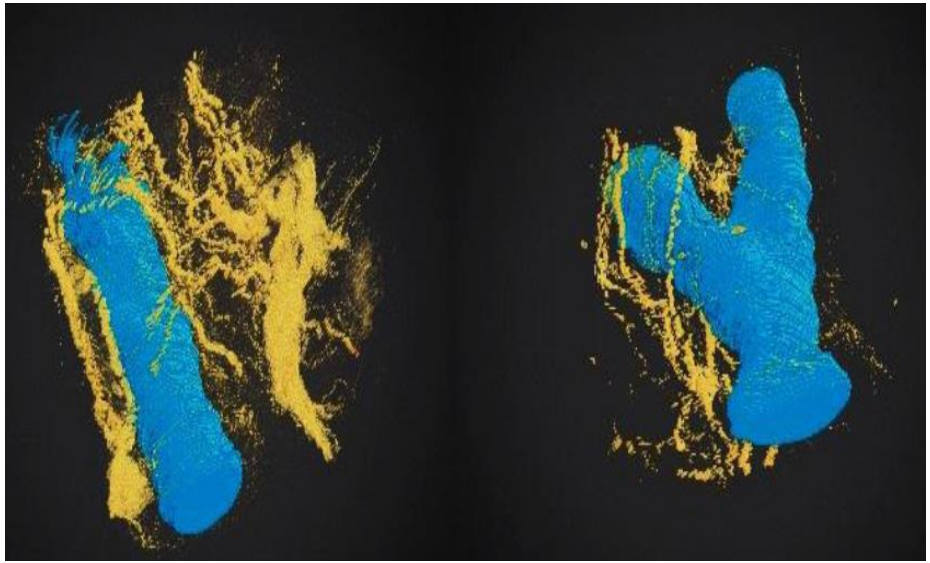


Normotensive



Hypertensive

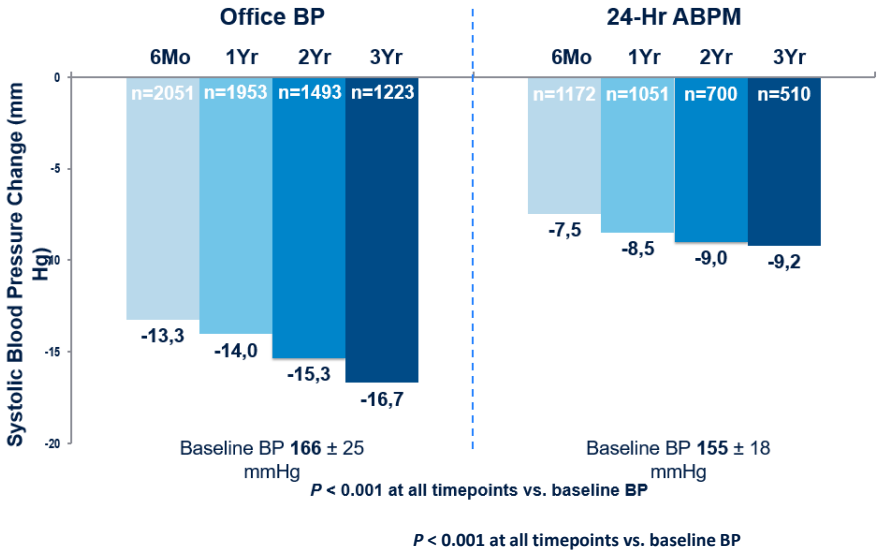
Three Dimensional Nerve Reconstruction in Hypertensive vs. Normotensive Pts



Hypertensive **Normotensive**

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

BP CHANGE IN HIGH-RISK PATIENTS WAS SIMILAR TO OVERALL COHORT

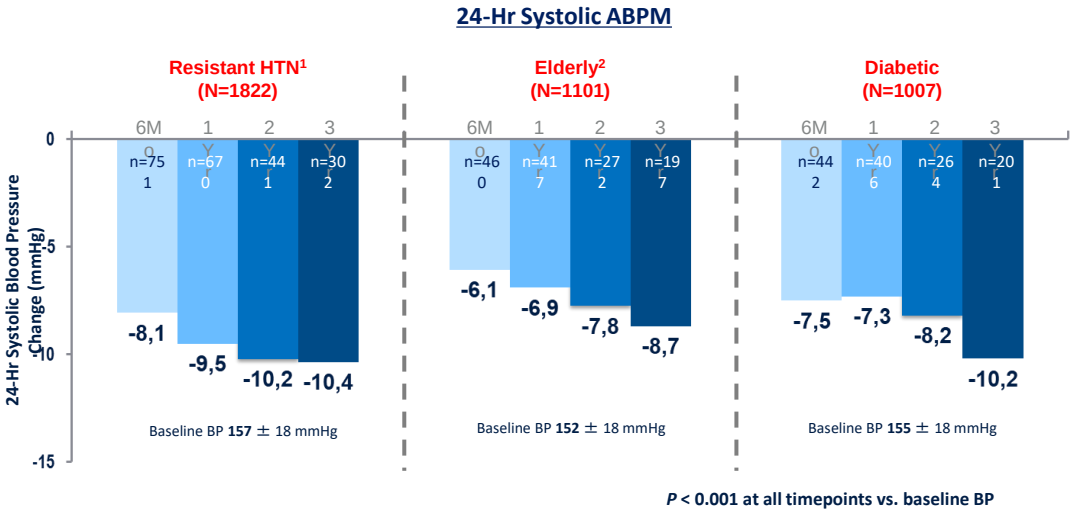


P < 0.001 at all timepoints vs. baseline BP

Mahfoud et al. EuroPCR 2022

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

BP CHANGE IN HIGH-RISK PATIENTS WAS SIMILAR TO OVERALL COHORT



Mahfoud et al. EuroPCR 2022

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

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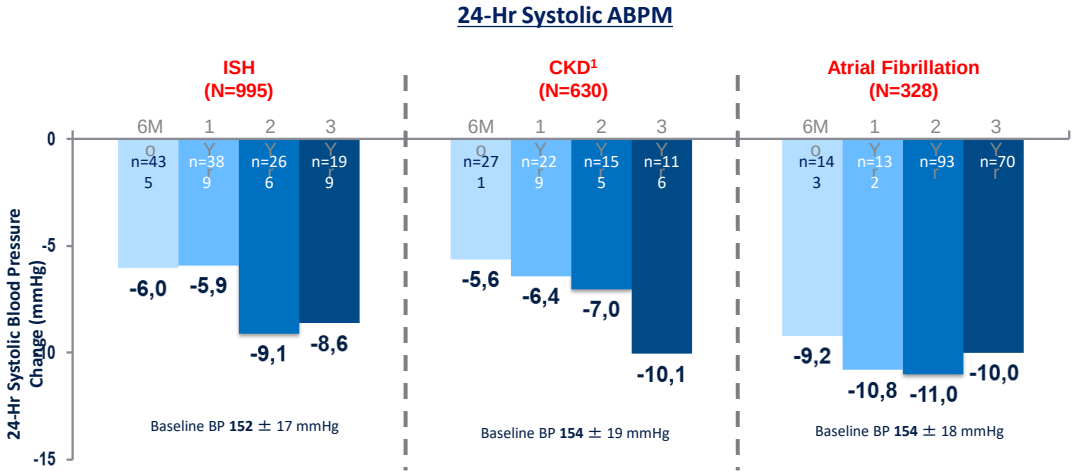
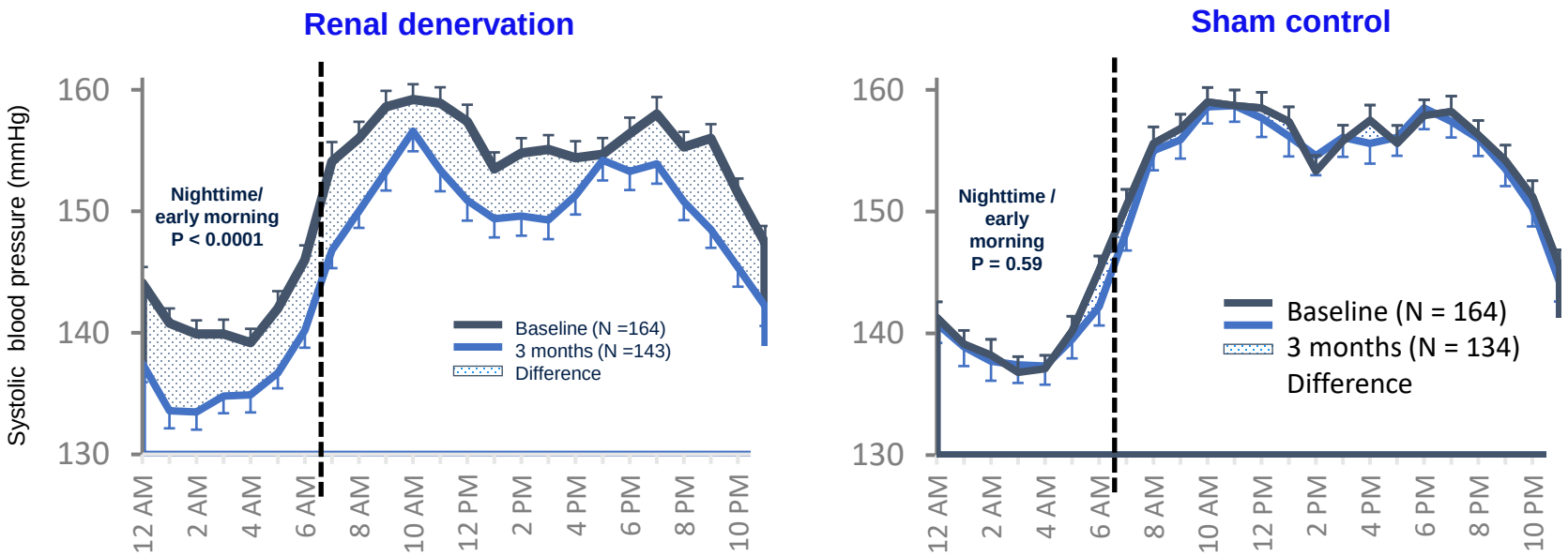


P < 0.001 at all timepoints vs. baseline BP

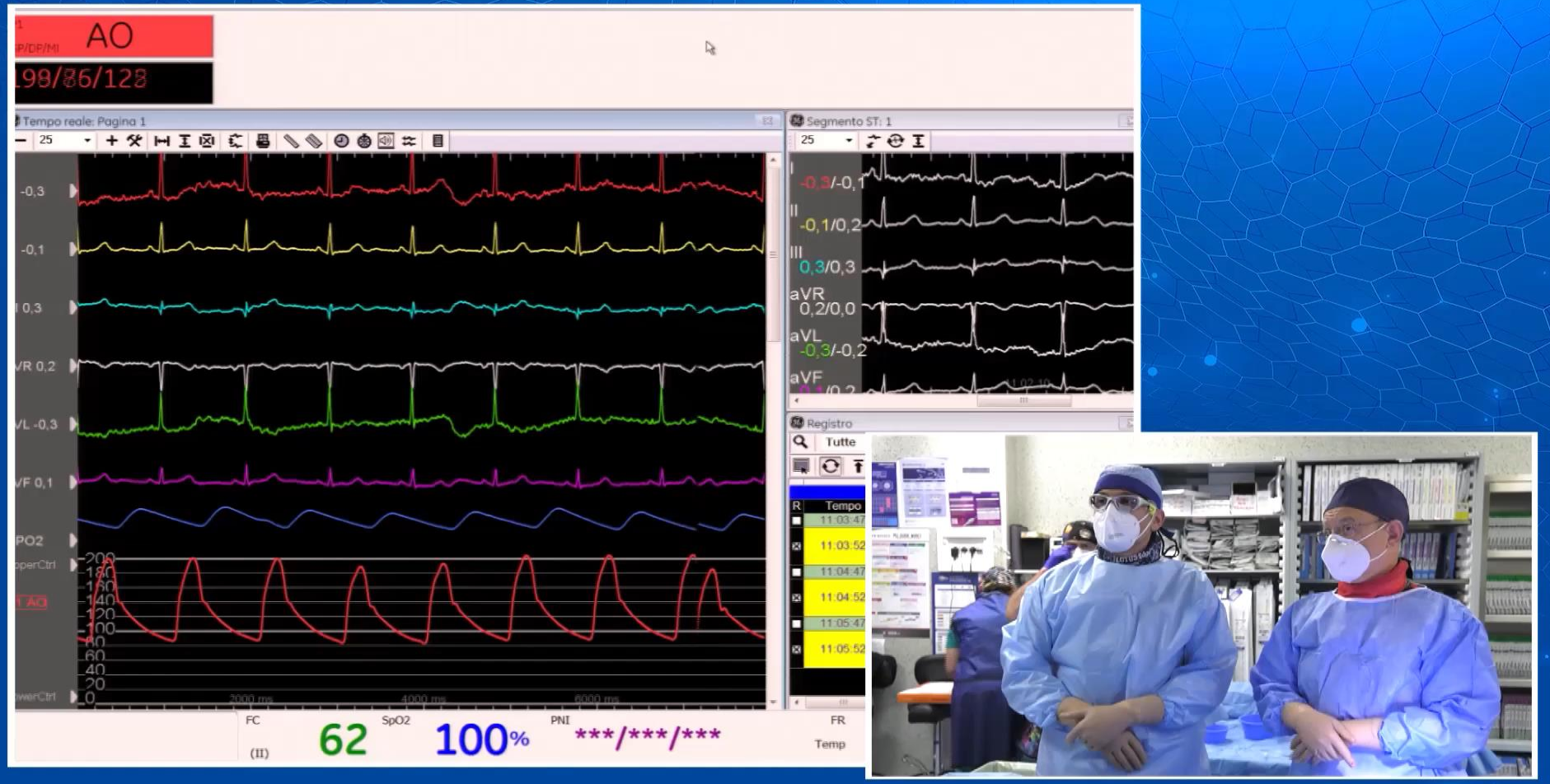
Mahfoud et al. EuroPCR 2022

RDN demonstrated an “always on” effect on 24-hour BP lowering[1]



The nighttime/early morning period is a “high-risk zone” associated with increased risk for stroke and cardiovascular events[2,3]

1. Bohm M, et al. *Lancet*. 2020;395:1444-1451
2. Amodeo C. *Blood Press Monit.* 2014;19:199-202
3. Boggia J, et al. *Lancet*. 2007;370:1219-1229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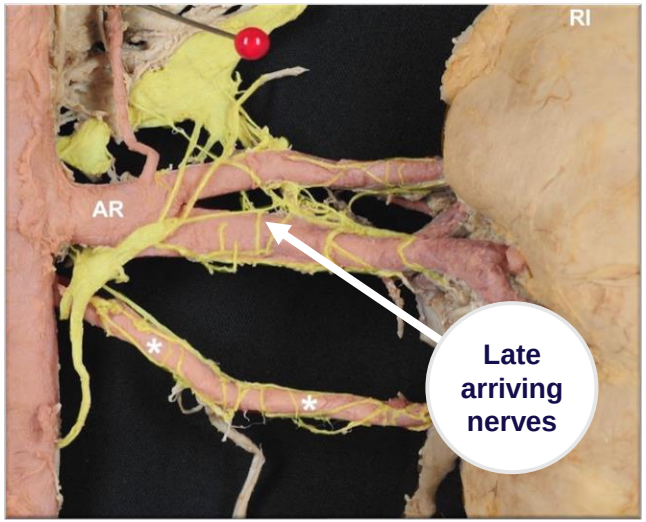
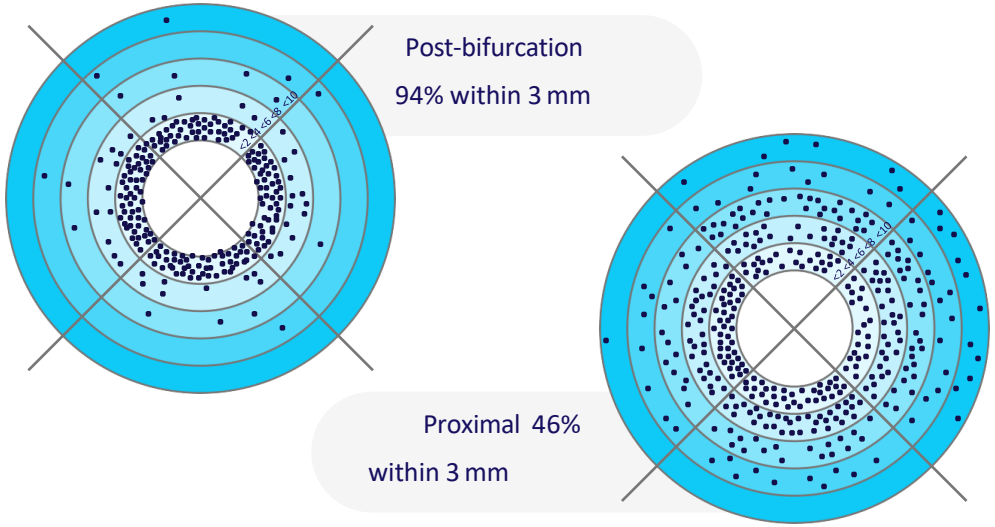
The Symplicity Spyral™ procedure reflects renal nerve anatomy



Nerve may not completely converge until beyond the main bifurcation

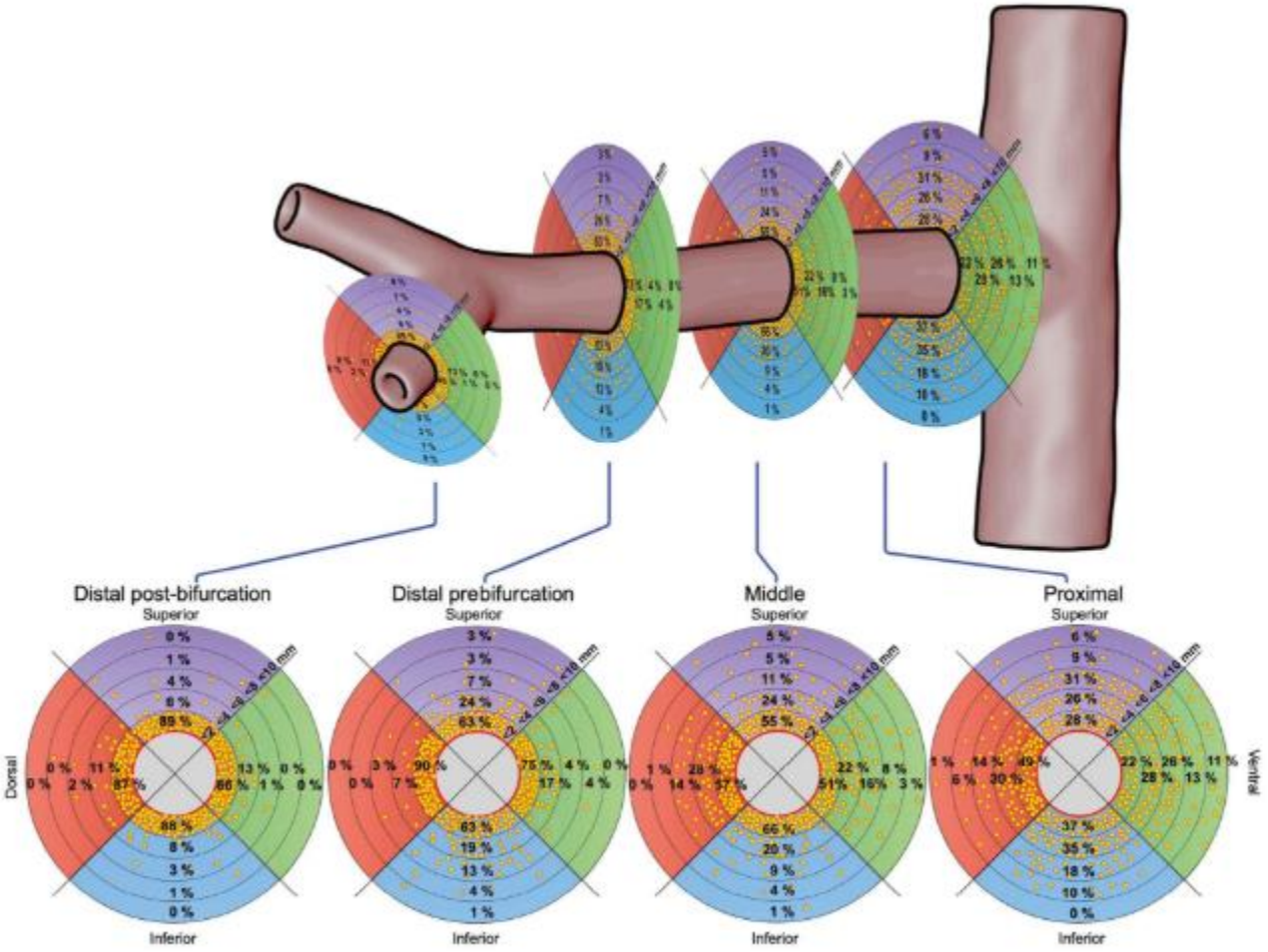
63% of kidneys had renal nerves that joined distal to the main renal artery bifurcation[1]



Renal nerve density highest in the post bifurcation region

94% of nerves are located within 3 mm of renal artery lumen post-bifurcation versus 46% in proximal segment[2]

[1] Garcia-Touchard et al. Microdisection of the Human Renal Nervous System. Hypertension. 2020.
[2] Mahfoud, F. Histological examination of renal nerve distribution, density, and function in humans. *EuroIntervention.* 2023.



The plots show the percentage of nerves in regions within <2, <4, <6, <8, and <10 mm from the renal arteries' lumen.

Rateo dose

mGy/min 0

Geometria

20 cm

Medtronic RF RDN results in clinically meaningful, safe, and sustained BP reductions

- **Meta-analysis of 18 reports involving 4,439 patients**

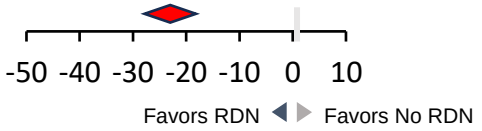
Screened 220 records, **18 independent reports**

4,439 patients* (12,639 patient-years)

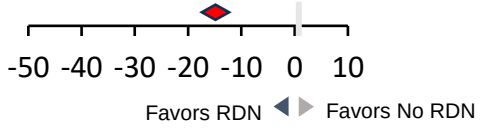
Mean follow up: 4.4 years (range: 3 - 9.4 years)

Random effects model:

Long-term office SBP reductions
-23.2 mmHg
[95% CI: -27.6 to -18.8; p <0.001]
(n=1916)



Long-term 24-hr ambulatory SBP reductions
-14.0 mmHg
[95% CI: -17.4 to -10.7; p <0.001]
(n=912)

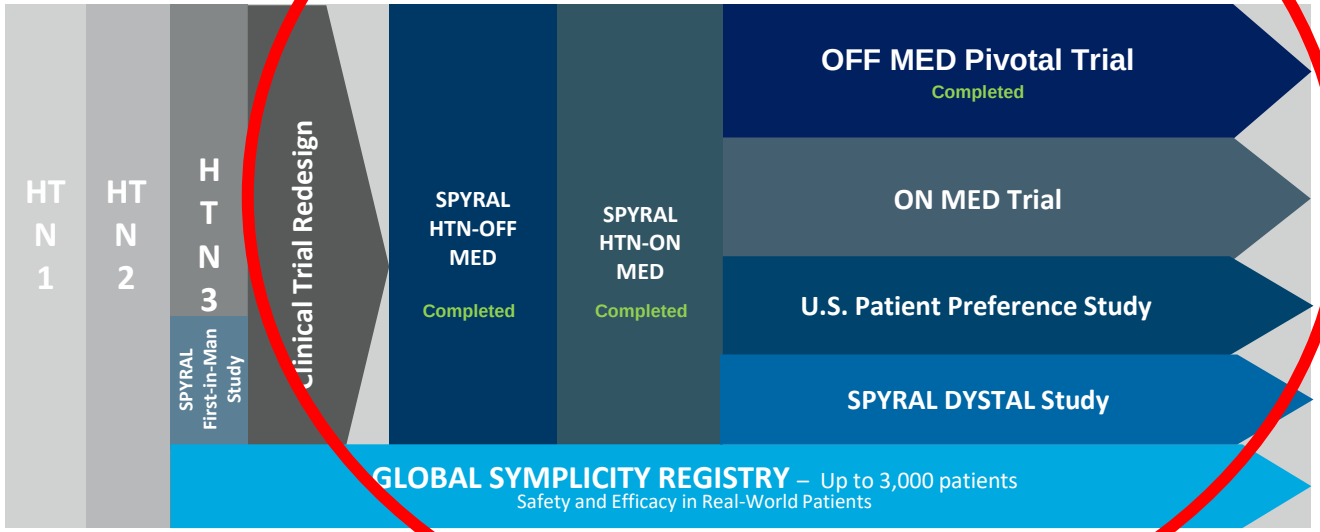


No escalation in anti-HTN meds through follow-up

Mahfoud et al. ACC 2024.

*Over 2000 of the 4,439 contributed to long-term data analysis of 3 years and beyond

OVER 4,000 PATIENTS STUDIED ACROSS MULTIPLE TRIALS



Mahfoud et al, EuroPCR 2022

SIIA position paper on the role of renal denervation in the management of the difficult-to-treat hypertensive patient

Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

Bruno RM [1], Taddei S [1], Borghi C [2], Colivicchi F [3], Desideri G [4], Grassi G [5], Mazza A [6], Muiesan ML [7],Parati G [8], Pontremoli R [9],Trimarco B [10], Volpe M [11], Ferri C [4]

[1] University of Pisa, Pisa, [2] University of Bologna, Bologna, [3] Ospedale San Filippo Neri, Roma, [4] University of L'Aquila, L'Aquila,, [5] University of Milano-Bicocca, Milano, [6] AUSL Rovigo, Rovigo, Italy, [7] University of Brescia, Brescia, [8] Istituto Auxologico Italiano ,IRCCS & Department of Medicine and Surgery, University of Milano Bicocca, Milano, [9] University of Genova, Genova, [10] University of Napoli, Napoli, [11] University of Rome "La Sapienza", Roma

Two possible clinical profiles of patients candidates to RDN

1 **Resistant** hypertensive patients

Main features:

- Uncontrolled office and 24h BP
- In treatment with an association RAS-blocker / CCB / Diur at maximally tolerated doses
- No secondary hypertension
- Eligible renal artery anatomy

Additional features:

- Adverse effects with spironolactone
- Poor drug adherence despite extensive counseling
- Preferentially systo-diastolic hypertension
- (But isolated systolic hypertension not controindicated!)
- No extensive vascular damage
- High/very high lifetime cardiovascular risk
- Patient preferences

Evidence from Symplicity trials; GSR; DENERHTN; Prague-15; Azizi M et al, Circulation 2016; Mahfoud F et al Eur Heart J 2017, GSR ACC2019

2 **Difficult-to-treat** hypertensive patients

Main features:

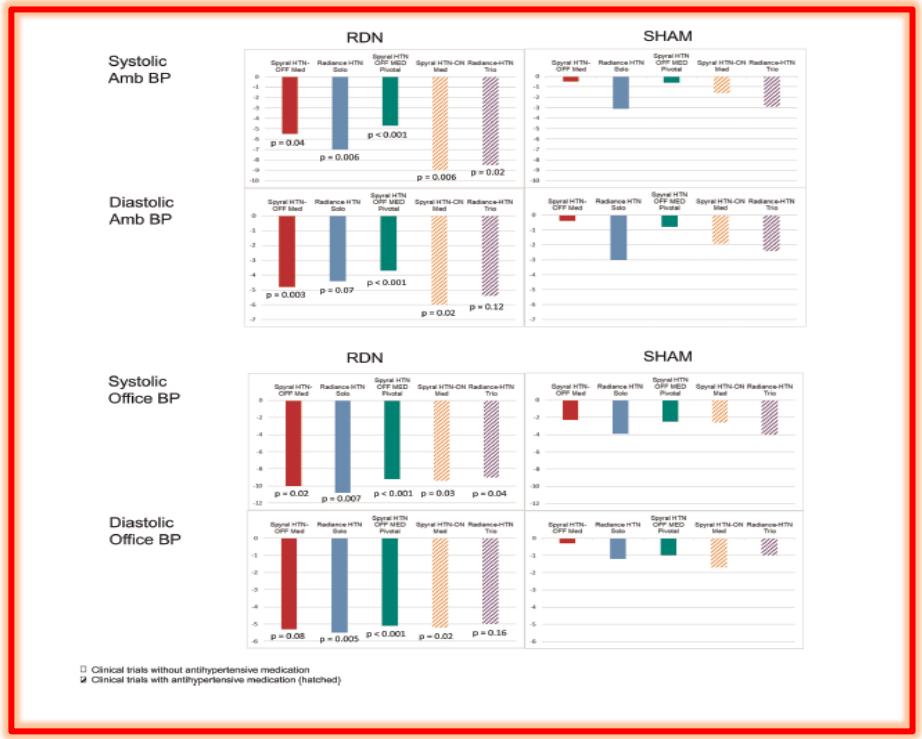
- Grade 1-2 hypertensive patients
- Untreated or with uncontrolled systodiastolic office and 24h BP with 1-2 drugs
- Systo-diastolic hypertension
- No secondary hypertension
- Eligible renal artery anatomy

Additional features:

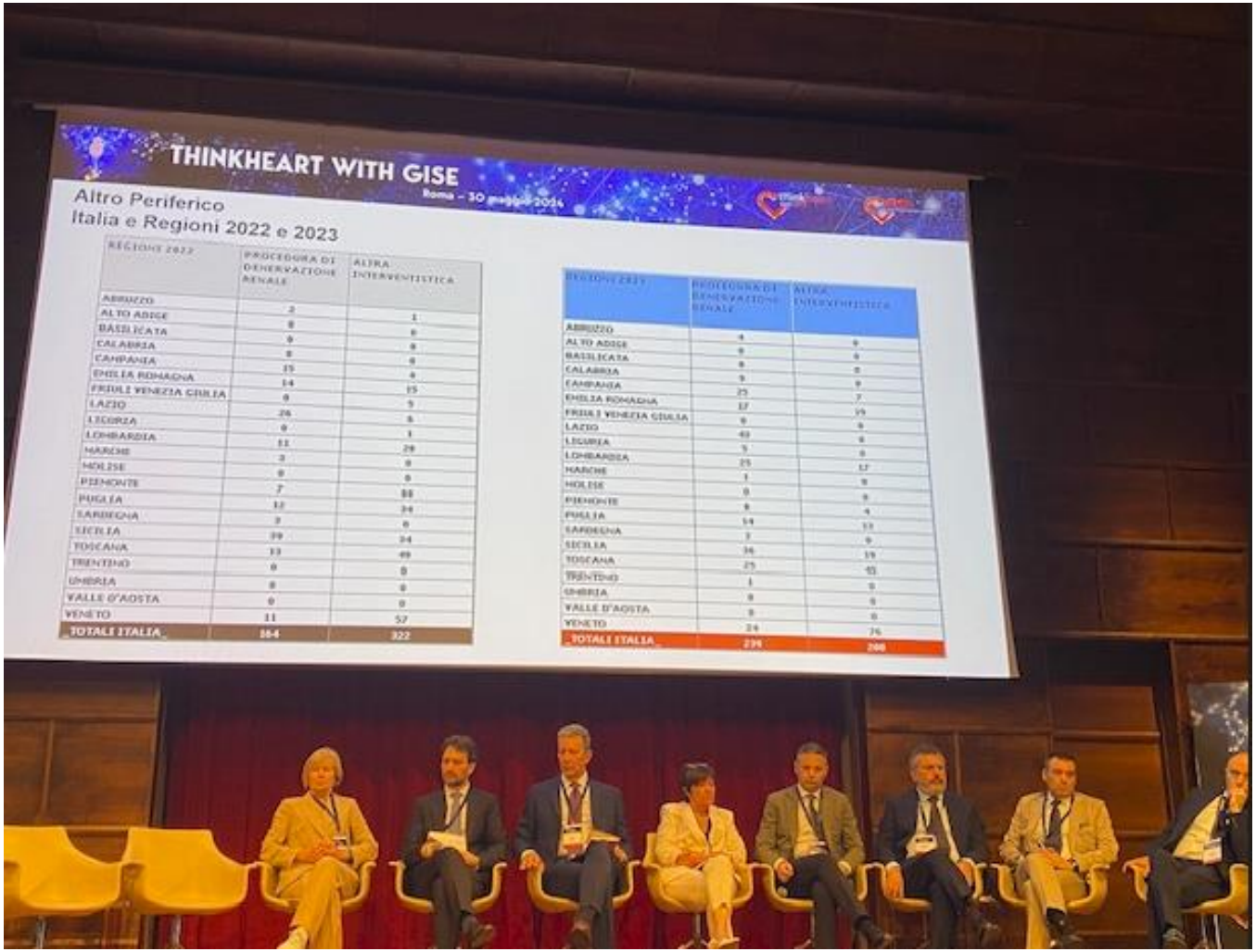
- Multiple intolerance to bp-lowering drugs / adverse effects
- Poor drug adherence despite extensive counseling
- 24h- heart rate >73.5 bpm
- Parossistic/persistent atrial fibrillation
- High / very high lifetime cardiovascular risk
- Patient preferences

Evidence from Spyral OFF-med, ON-med, Radiance solo; Bohm et al,Eur Heart J. 2019; Atti V et al. J C Electrophysiol 2019
SIIA Position Paper, High Blood Pressure &Cardiovascular Prevention 2020

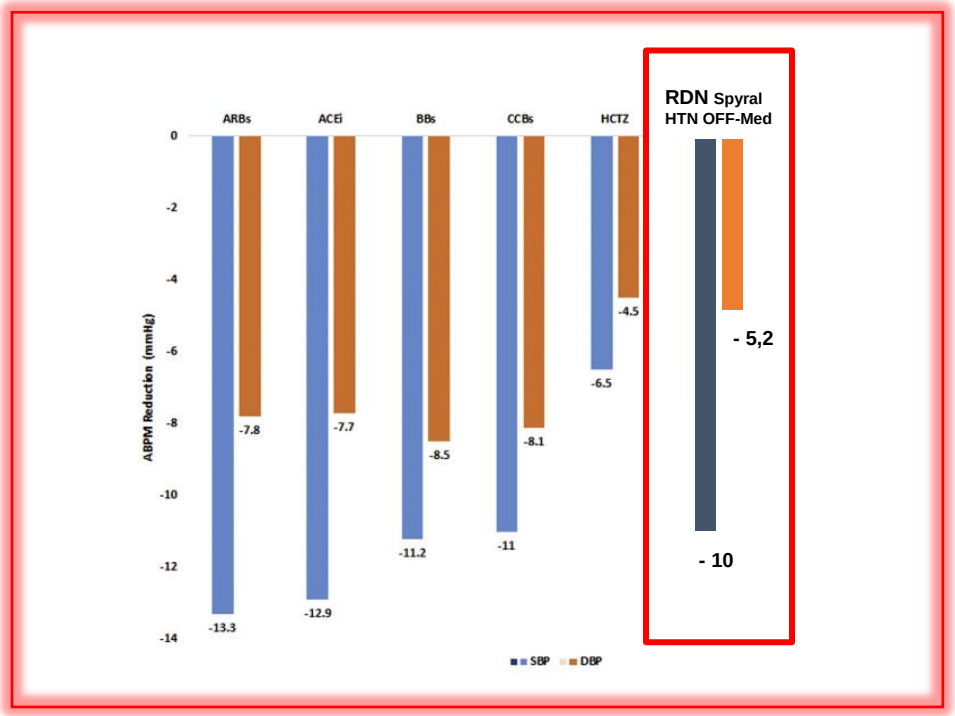
Change in 24-h ambulatory and office BP after RDN observed in 5 sham-controlled randomized clinical trials of second generation



Schmieder et al. J Hypertens. 2021 Sept 1;39(9):1733-1741

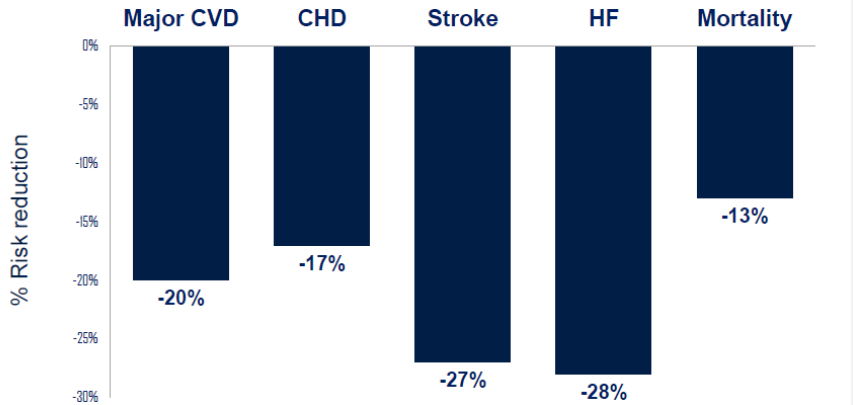

THINKHEART WITH GISE
Roma – 30 maggio 2024
Altro Periferico
Italia e Regioni 2022 e 2023
REGIONI 2022
PROCEDURA DI DENERVAZIONE RENALE
ALTRA INTERVENTISTICA
ABRUZZO 2 1
ALTO ADIGE 0 0
BASILICATA 0 0
CALABRIA 0 0
CAMPANIA 8 0
EMILIA ROMAGNA 15 4
FRIULI VENEZIA GIULIA 14 15
LAZIO 0 5
LIGURIA 26 5
LOMBARDIA 0 1
MARCHE 11 29
MOLISE 3 0
PIEMONTE 0 0
PUGLIA 7 88
SARDEGNA 12 24
SICILIA 3 0
TOSCANA 39 24
TRENTINO 13 49
UMBRIA 0 0
VALLE D'AOSTA 0 0
VENETO 0 0
TOTALE ITALIA 11 57
354 322
REGIONI 2023
PROCEDURA DI DENERVAZIONE RENALE
ALTRA INTERVENTISTICA
ABRUZZO 4 0
ALTO ADIGE 0 0
BASILICATA 0 0
CALABRIA 0 0
CAMPANIA 0 0
EMILIA ROMAGNA 25 7
FRIULI VENEZIA GIULIA 17 19
LAZIO 0 0
LIGURIA 40 0
LOMBARDIA 5 0
MARCHE 25 17
MOLISE 1 0
PIEMONTE 0 0
PUGLIA 0 4
SARDEGNA 14 13
SICILIA 7 0
TOSCANA 36 19
TRENTINO 25 43
UMBRIA 1 0
VALLE D'AOSTA 0 0
VENETO 0 0
TOTALE ITALIA 24 24
239 200

Antihypertensive Efficacy of RDN Compared to Antihypertensive Drugs



Messerli F, et al. J Am Coll Cardiol Intv. 2020 Dec, 13 (24) 2934–2936

RISK REDUCTION FOR A 10 mmHG FALL IN OFFICE SBP



Irrespective of baseline BP or pre-existing conditions

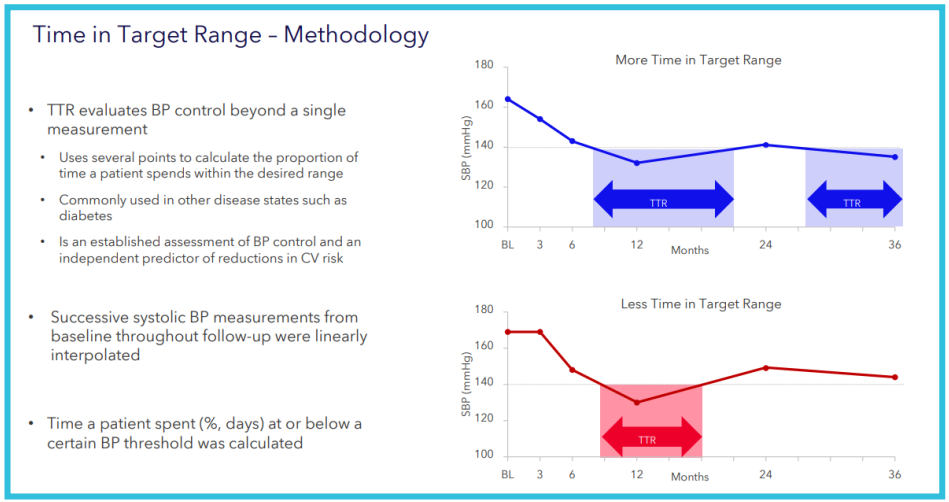
n = 613,815

Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387: 957-67

Renal Denervation Increased Time in Target Range (TTR)

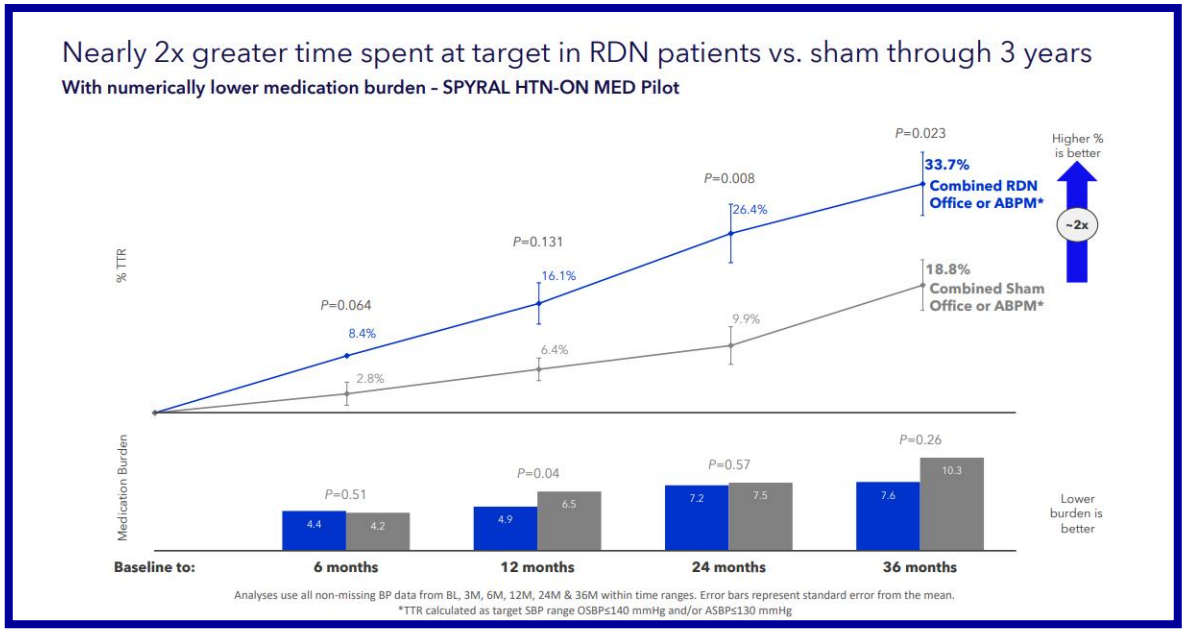
Renal Denervation increases long-term time in target blood pressure range compared with sham control: ON MED pilot data

Blood pressure and MACE reductions after renal denervation: 3-year GSR result



Mahfoud et al. EuroPCR 2022

Renal Denervation Increased Time in Target Range (TTR)



Kandzari, et al. EuroPCR 2022.

TAKE HOME MESSAGE (1)

European Society of Hypertension: Position Statement on RDN in 2021

- In base ai risultati dei recenti studi clinici controllati effettuati con dispositivi di seconda generazione, la RDN rappresenta un opzione terapeutica per il trattamento dell'ipertensione, assieme a modifiche dello stile di vita ed al trattamento farmacologico.

- La denervazione renale è una strategia terapeutica alternativa o additiva, non competitiva.

- Si raccomanda un percorso strutturato per l'uso clinico di RDN nella pratica quotidiana.

TAKE HOME MESSAGE (2)

European Society of Hypertension: Position Statement on RDN in 2021

La prospettiva e le preferenze dei pazienti, nonché lo stadio della malattia ipertensiva, comprese le comorbidità, dovrebbero portare a una strategia di trattamento individualizzata in un processo decisionale condiviso, che includa attentamente le varie opzioni di trattamento, inclusa la denervazione renale.

The NEW ENGLAND JOURNAL of MEDICINE

ANGIOGRAPHIC FOLLOW-UP AFTER PLACEMENT OF A SELF-EXPANDING CORONARY-ARTERY STENT

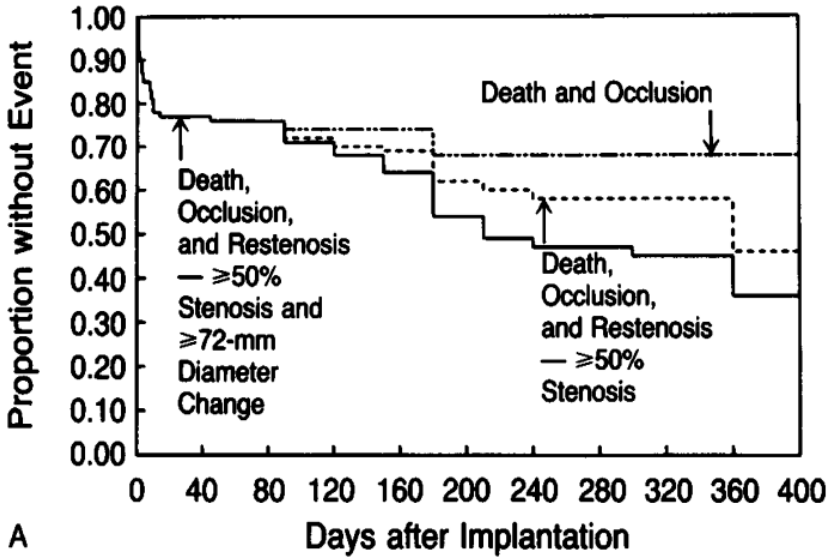
PATRICK W. SERRUYS, M.D., BRADLEY H. STRAUSS, M.D., KEVIN J. BEATT, M.B., B.S., MICHEL E. BERTRAND, M.D., JACQUES PUEL, M.D., ANTHONY F. RICKARDS, M.B., B.S., BERNHARD MEIER, M.D., JEAN-JACQUES GOY, M.D., PIERRE VOGT, M.D., LUKAS KAPPENBERGER, M.D., AND ULRICH SIGWART, M.D.

Abstract *Background.* The placement of stents in coronary arteries after coronary angioplasty has been investigated as a way of treating abrupt coronary-artery occlusion related to the angioplasty and of reducing the late intimal hyperplasia responsible for gradual restenosis of the dilated lesion.

Methods. From March 1986 to January 1988, we implanted 117 self-expanding, stainless-steel endovascular stents (Wallstent) in the native coronary arteries (94 stents) or saphenous-vein bypass grafts (23 stents) of 105 patients. Angiograms were obtained immediately before and after placement of the stent and at follow-up at least one month later (unless symptoms required angiography sooner). The mortality after one year was 7.6 percent (8 patients). Follow-up angiograms (after a mean [±SD] of 5.7±4.4 months) were obtained in 95 patients with 105 stents and were analyzed quantitatively by a computer-assisted system of cardiovascular angiographic analysis. The 10 patients without follow-up angiograms included 4 who died.

Results. Complete occlusion occurred in 27 stents in 25 patients (24 percent); 21 occlusions were documented within the first 14 days after implantation. Overall, immediately after placement of the stent there was a significant increase in the minimal luminal diameter and a significant decrease in the percentage of the diameter with stenosis (changing from a mean [±SD] of 1.88±0.43 to 2.48±0.51 mm and from 37±12 to 21±10 percent, respectively; $P<0.0001$). Later, however, there was a significant decrease in the minimal luminal diameter and a significant increase in the stenosis of the segment with the stent (1.68±1.78 mm and 48±34 percent at follow-up). Significant restenosis, as indicated by a reduction of 0.72 mm in the minimal luminal diameter or by an increase in the percentage of stenosis to ≥50 percent, occurred in 32 percent and 14 percent of patent stents, respectively.

Conclusions. Early occlusion remains an important limitation of this coronary-artery stent. Even when the early effects are beneficial, there are frequently late occlusions or restenosis. The place of this form of treatment for coronary artery disease remains to be determined. (N Engl J Med 1991; 324:13-7.)



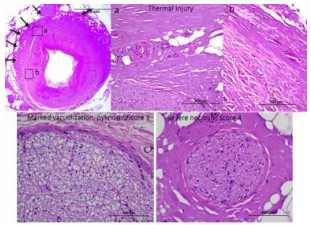
HTN3: Guppo Sham 5.2±1.4 farmaci al giorno a dosaggio pieno

… è eticamente corretto prevedere «a vita» una terapia con 5 o più farmaci a dosaggi così elevati da essere difficilmente gestibile per la presenza di effetti collaterali…

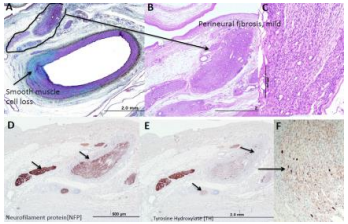
Renal Nerve Anatomy Allows a Catheter-Based Approach

Histology after Renal denervation

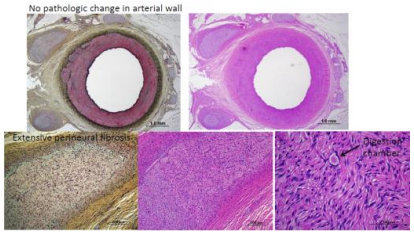
4 Hours after RDN

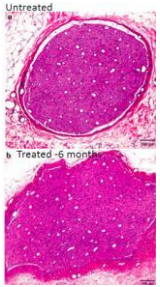


14 days after RDN



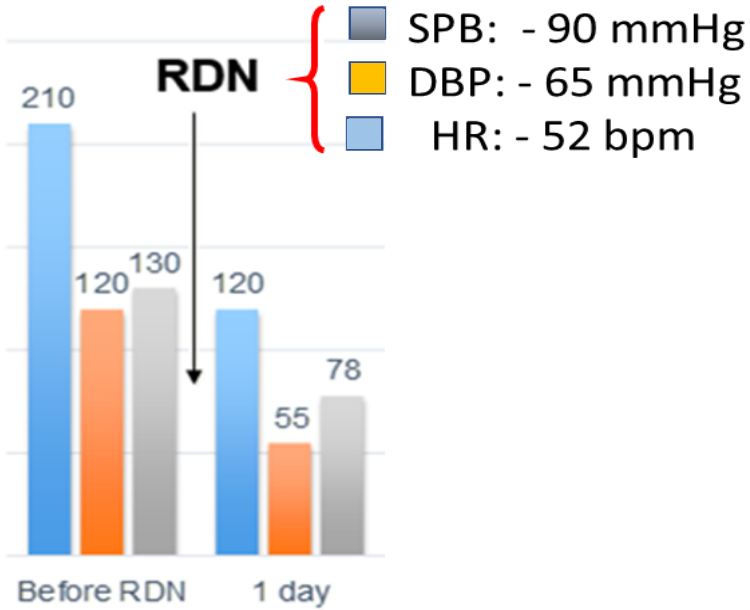
6 Months after RDN





Courtesy of R. Virmani

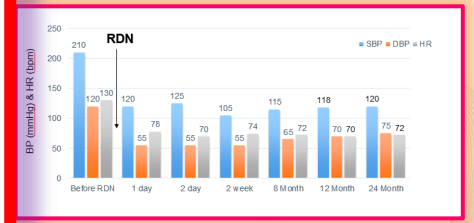
ITH RDN IN PT WITH KE AND RESISTANT ENSION



sion despite:
g twice daily
wice daily
g twice daily
g twice daily

Hemorrhagic stroke
Glasgow Coma Scale: 9
Norton Scale: 8

Persistent hypertension during hospitalization (BP 210/120 mmHg) despite 6 medications p.o. and urapidil iv

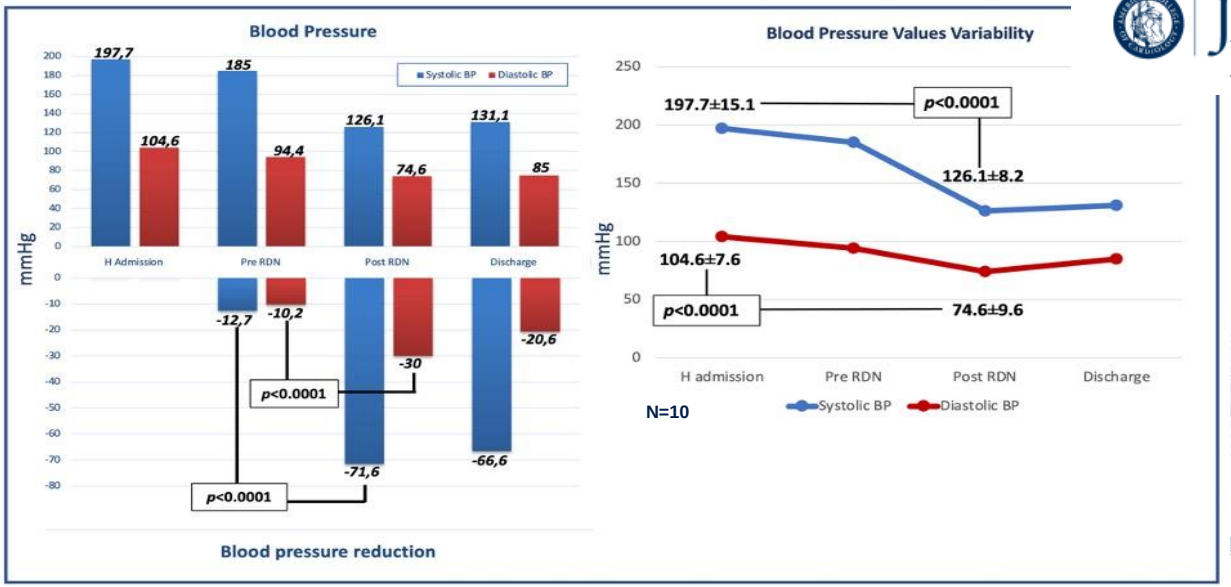


Versaci F et al. Int J. Neurol Neurother 2015

Versaci F. et al SAGE Open Med Case Rep. 2019

Renal denervation: a novel therapeutic option in the acute phase of hemorrhagic stroke

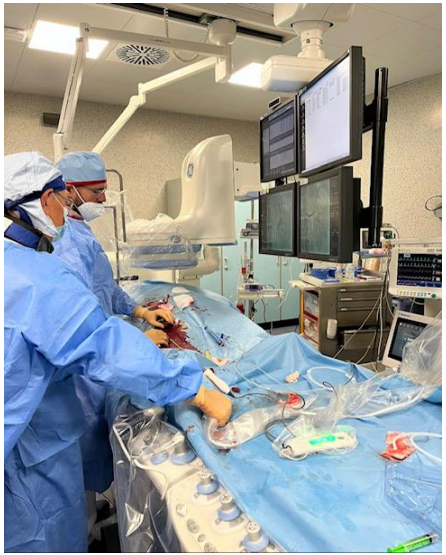
Blood pressure values trend at different study times



JACC Journals

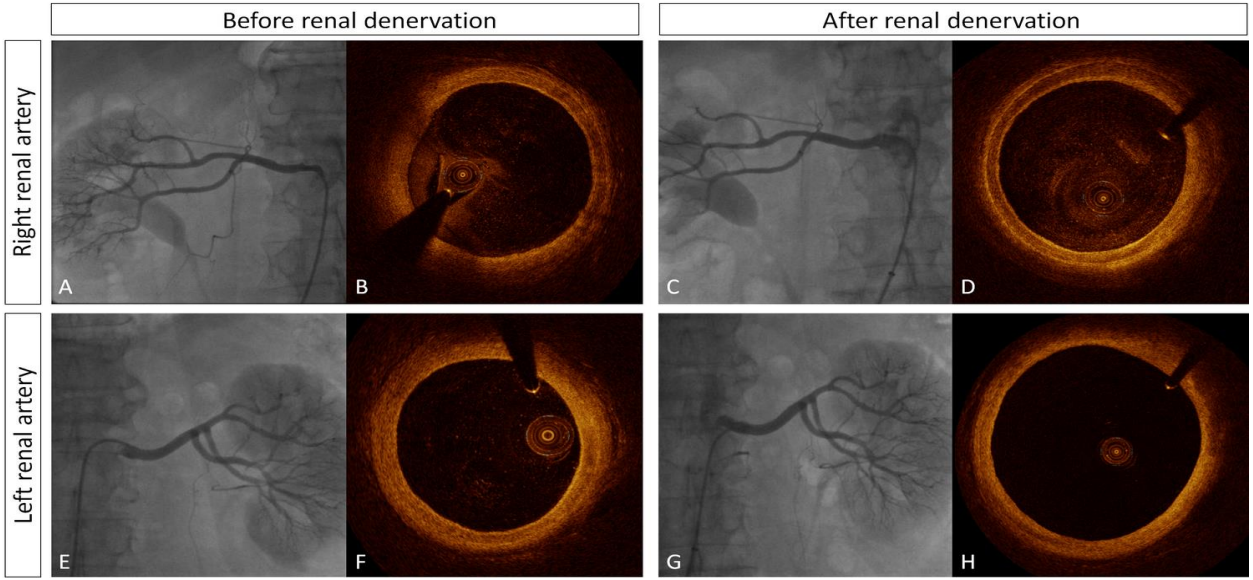
Versaci F, et al. JACC Adv 2023

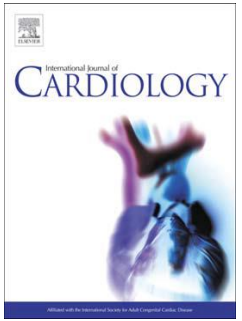
RDN + external ventricular drainage benefit patients with mild ventricular hemorrhage and malignant hypertension



Vascular response after percutaneous sympathectomy: not all devices are equal.

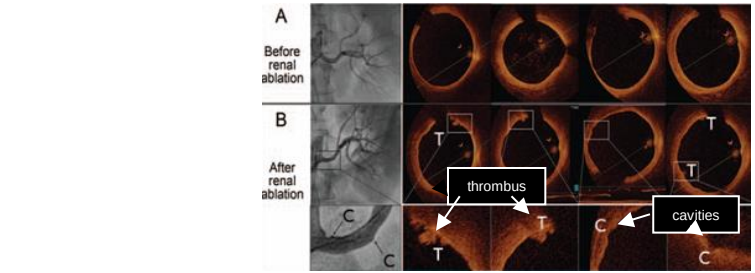
OCT evaluation of 14 renal arteries

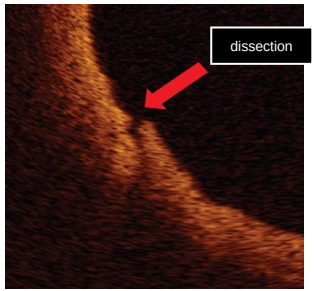


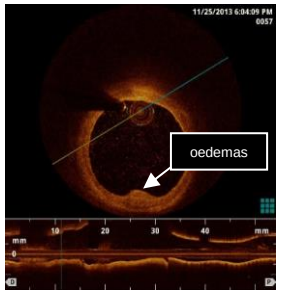


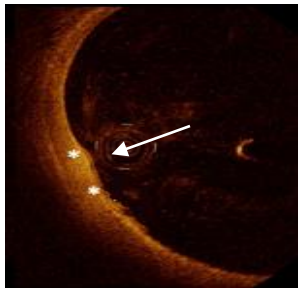
F.Versaci et al. , Int J Cardiol, April 2014

Optical Coherence Tomography: Findings in Renal Denervation









Cook S, Eur Heart J. 2012 Dec.

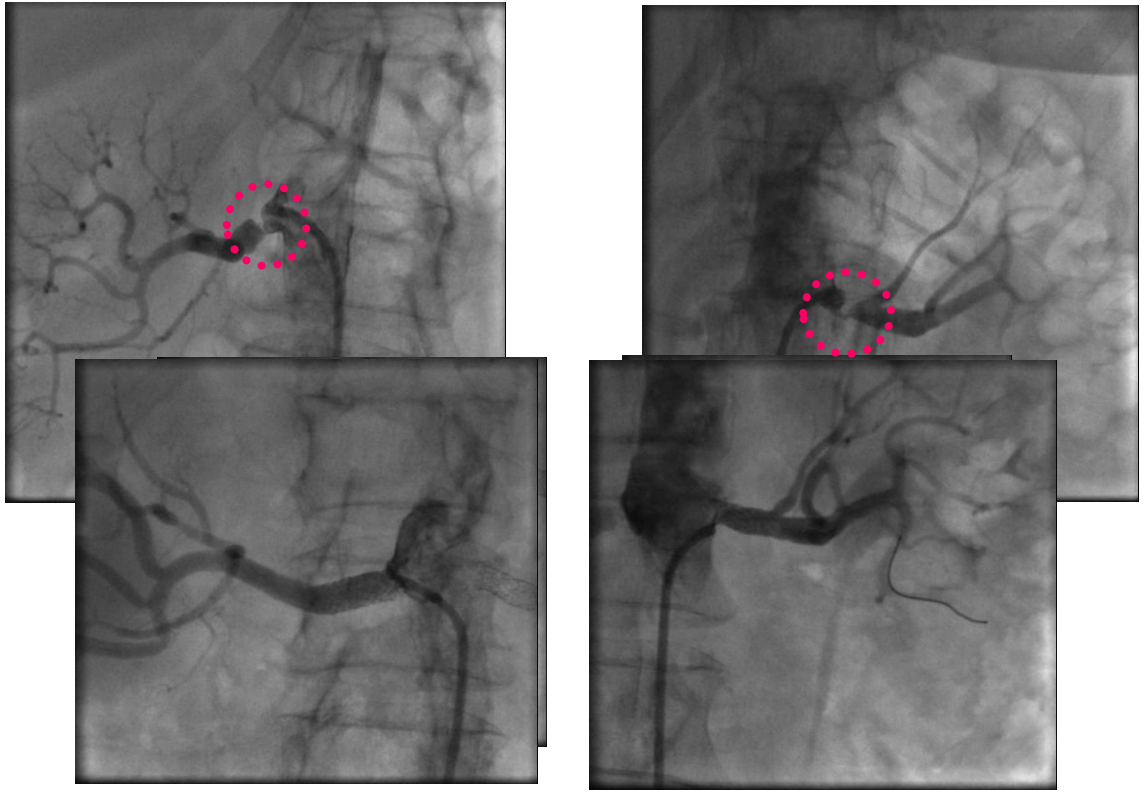
Ierna S, et al. Int J Cardiol. 2013 May
Versaci F, et al. JEVT 2014

RDN: from theory to daily practice

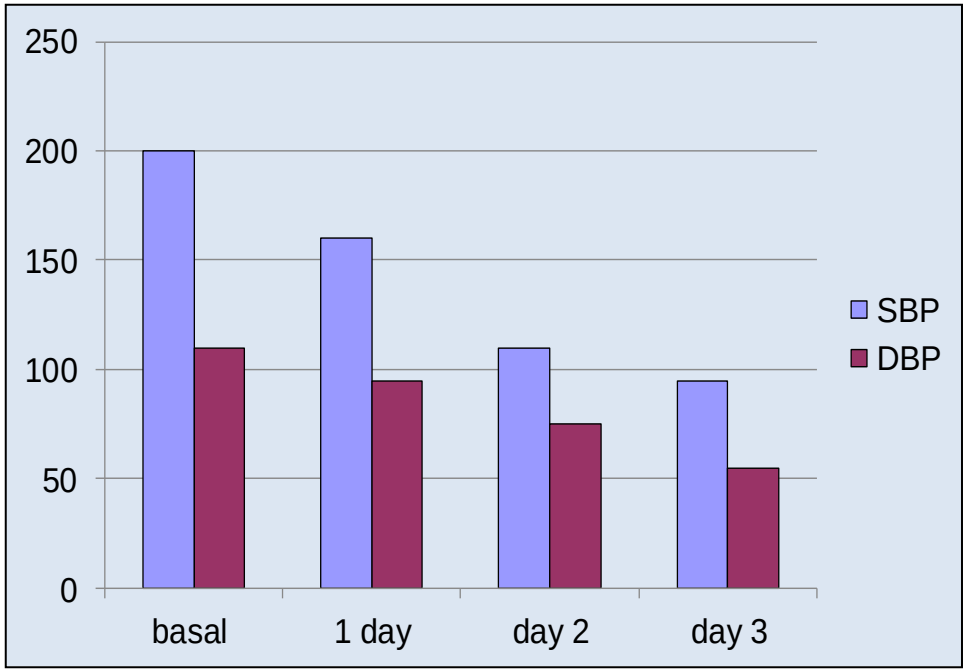
(Case:5)

- 65 year old woman,
- CV risk factors: family history, hypercholesterolemia – Hypertension
- «true» refractory HTN
  - β-blocker
  - α-blocker
  - ACE
  - Vasodilator
  - 2 diuretics
  - Direct Renin Inhibitor

RDN: from theory to daily practice



RDN: from theory to daily practice



J ENDOVASC THER
2014;21:000–000

◆CASE REPORT ◆

Is an Abnormal Vascular Response After Renal Sympathetic Denervation Predictive of Permanent Damage?

An Unusual Case of Late Renal Artery Stenosis After Energy Delivery

Francesco Versaci, MD[1,2]; Antonio Trivisonno, MD[2]; Carlo Olivieri, MD[2]; Gianludovico Magri, MD[1]; Fiorella Caranci, MD[1]; and Francesco Prati, MD[3]

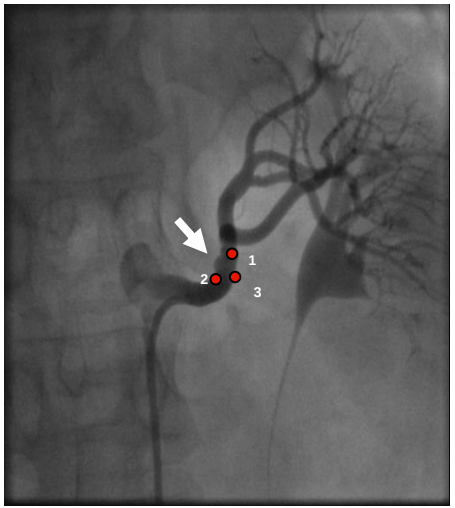
[1]Department of Cardiovascular Disease, Ospedale "Antonio Cardarelli," Campobasso, Italy.
[2]Department of Cardiovascular Disease, Ospedale "Ferdinando Veneziale," Isernia, Italy.
[3]Department of Cardiovascular Disease, Ospedale "San Giovanni-Addolorata," Rome, Italy.

Purpose: To describe the effect of renal sympathetic denervation (RDN) on renal arteries immediately after the procedure and at follow-up.
Case Report: A 52-year-old woman with severe resistant hypertension underwent RDN. A transient spasm occurred in left renal artery immediately after radiofrequency energy delivery, with subsequent complete resolution without any additional therapy. At 6-month follow-up, the blood pressure increased, and imaging revealed a tight stenosis in the left renal artery, which was successfully treated with a stent. In the next days, there was an immediate significant blood pressure reduction.
Conclusion: Renal denervation can be complicated by local tissue injury at the ablation sites that could be a possible trigger of late arterial disease.

J Endovasc Ther. 2014;21:000–000

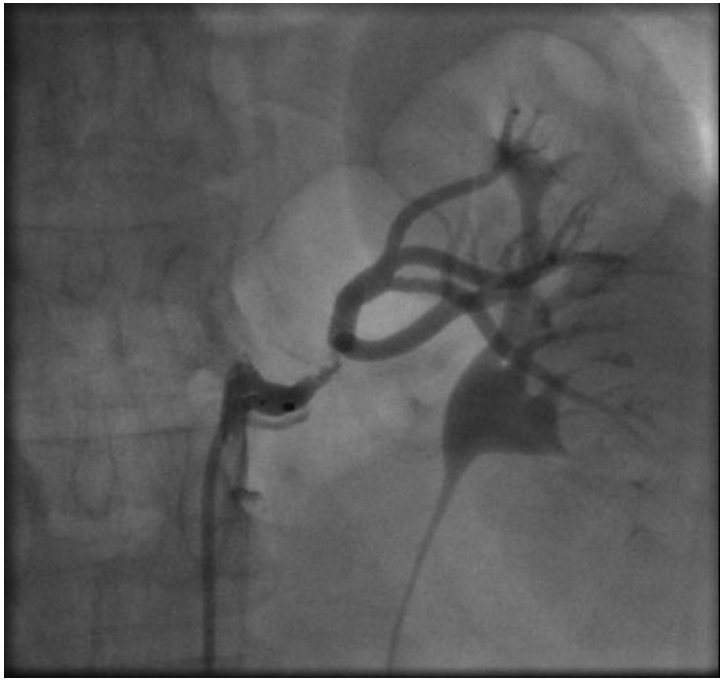
Key words: hypertension, renal denervation, renal artery disease intervention, peripheral/renal angiography, optical coherence tomography, peripheral intervention

Pre RDN



Versaci F, et al. J Endovasc Ther 2014

Post RDN

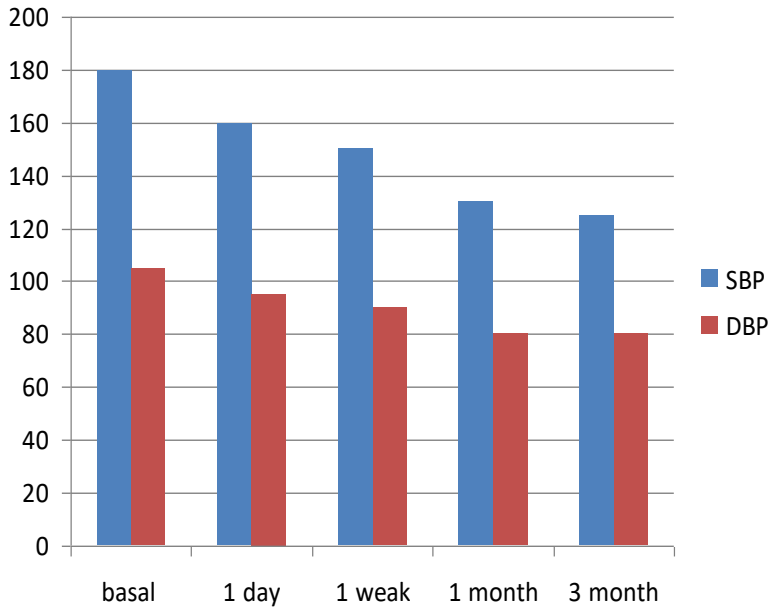


Versaci F, et al. J Endovasc Ther 2014

Five days later

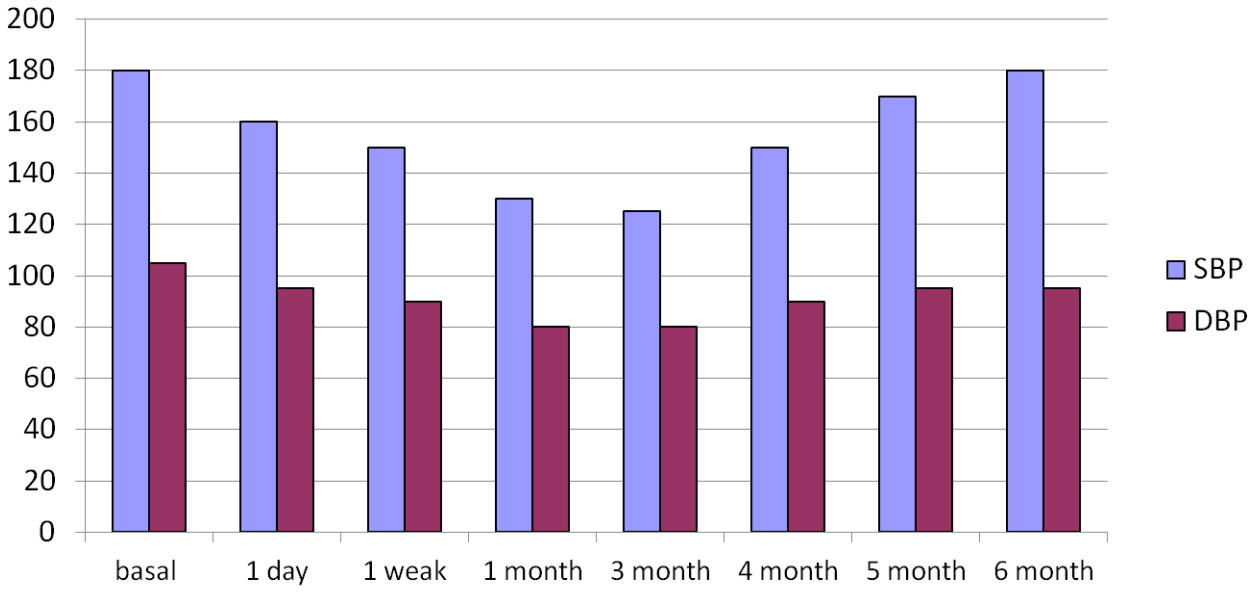
Versaci F, et al. J Endovasc Ther 2014

BP after RDN (3M Follow up)

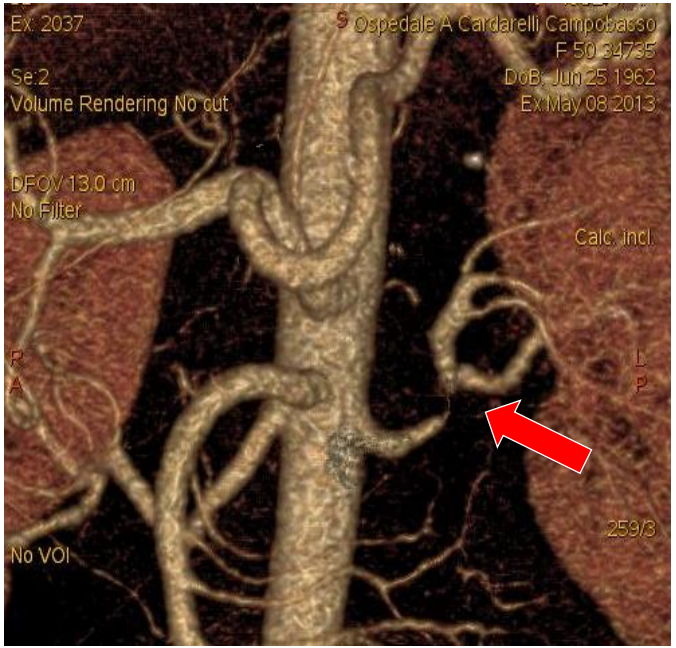


Versaci F, et al. J Endovasc Ther 2014

BP after RDN (6M Follow up)



CT Volume Rendering

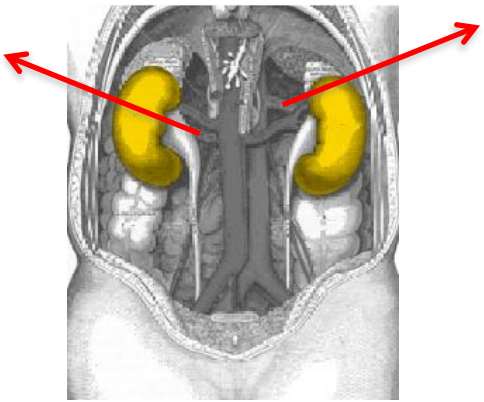


Versaci F, et al. J Endovasc Ther 2014

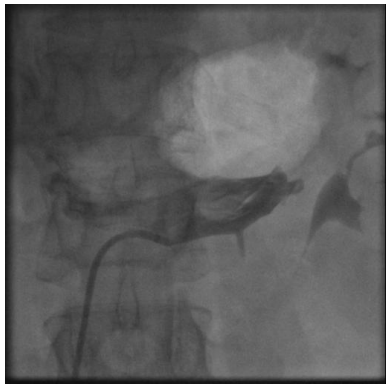
Versaci F, et al. J Endovasc Ther 2014

Renin Venous Activity

Right Kidney 38.0



Left Kidney: 223.0

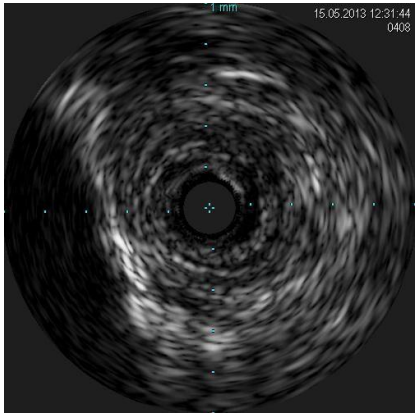


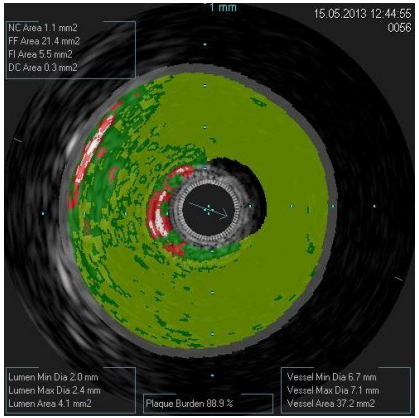
Ratio sx/dx: 5.8

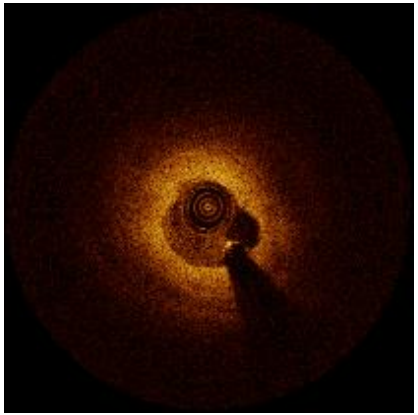
IVUS

OCT

Virtual Hystology

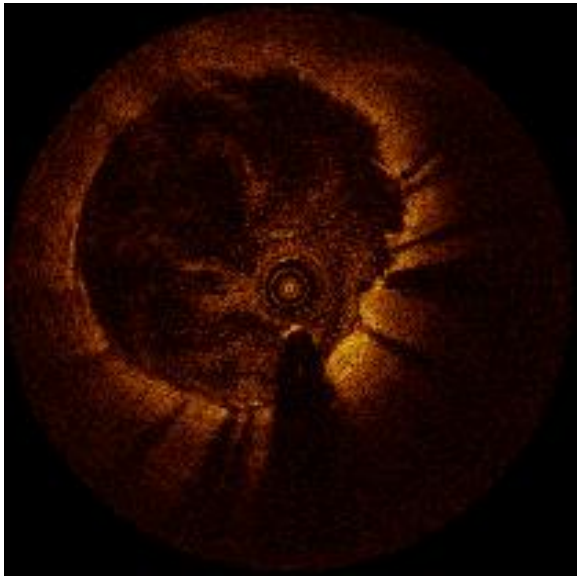






Versaci F, et al. J Endovasc Ther 2014

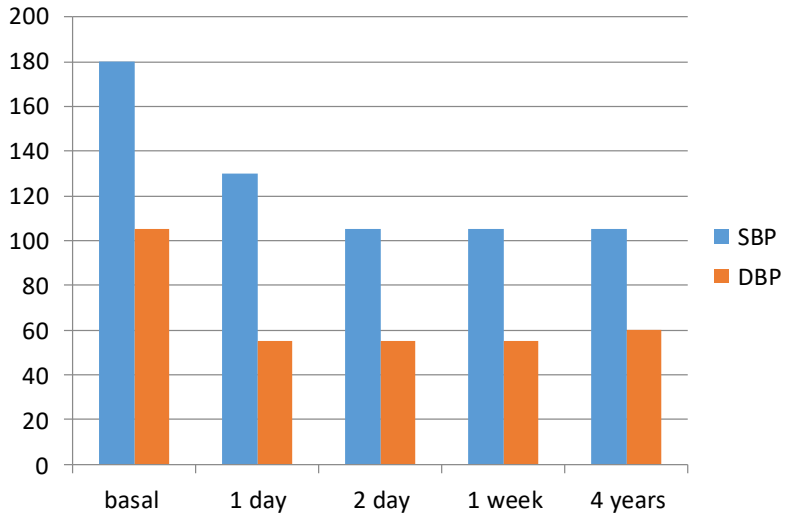
PTA-Stent



Dynamic Renal 5/15 – Biotronik

Versaci F, et al. J Endovasc Ther 2014

BP after PTA



Versaci F, et al. J Endovasc Ther 2014

- High pre
  - Affect
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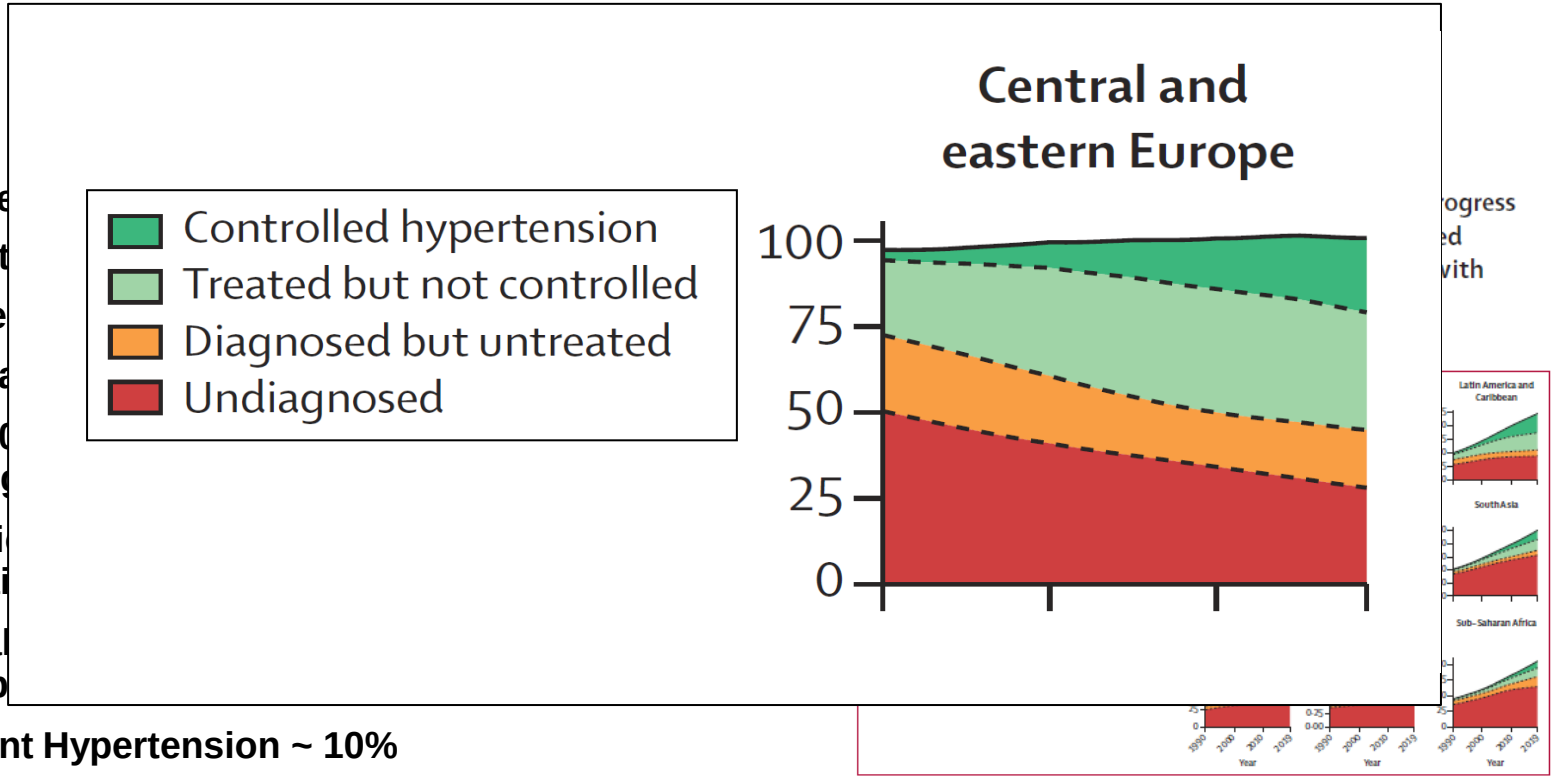
- Resistant Hypertension ~ 10%



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Lancet 2021, Aug 24

TAKE HOME MESSAGE (3)

RDN per la cura della fibrillazione atriale

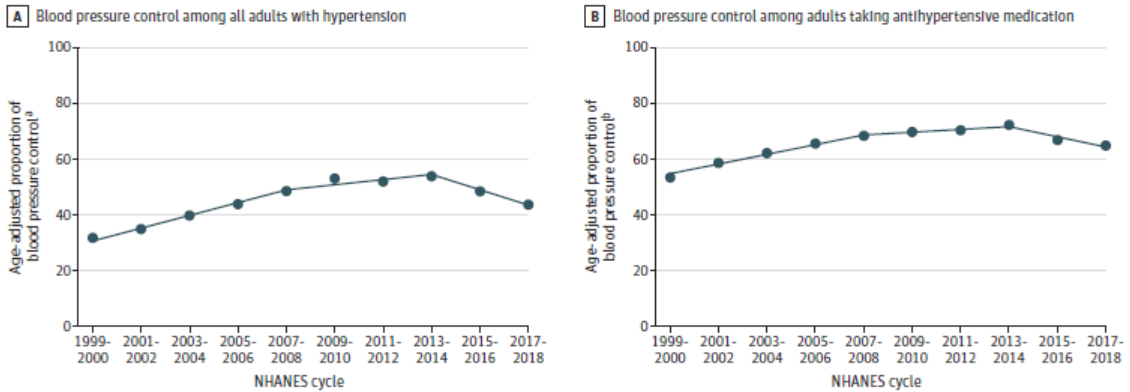
- La modulazione della RDN sul sistema simpatico ha mostrato di poter ridurre non solamente i valori di PA, ma anche avere effetti favorevoli antiaritmici in pazienti sintomatici con FA sottoposti a Isolamento delle vene polmonari, rappresentando pertanto un ulteriore strategia terapeutica.

JAMA | Original Investigation

Trends in Blood Pressure Control Among US Adults With Hypertension, 1999-2000 to 2017-2018

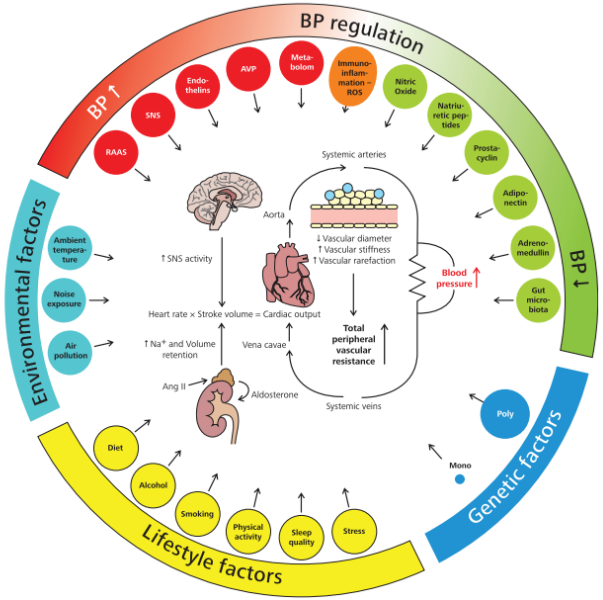
Paul Muntner, PhD; Shakia T. Hardy, PhD; Lawrence J. Fine, MD; Byron C. Jaeger, PhD; Gregory Wozniak, PhD; Emily B. Levitan, ScD; Lisandro D. Colantonio, MD, PhD

Age-Adjusted Estimated Proportion of Adults With Hypertension and Controlled Blood Pressure

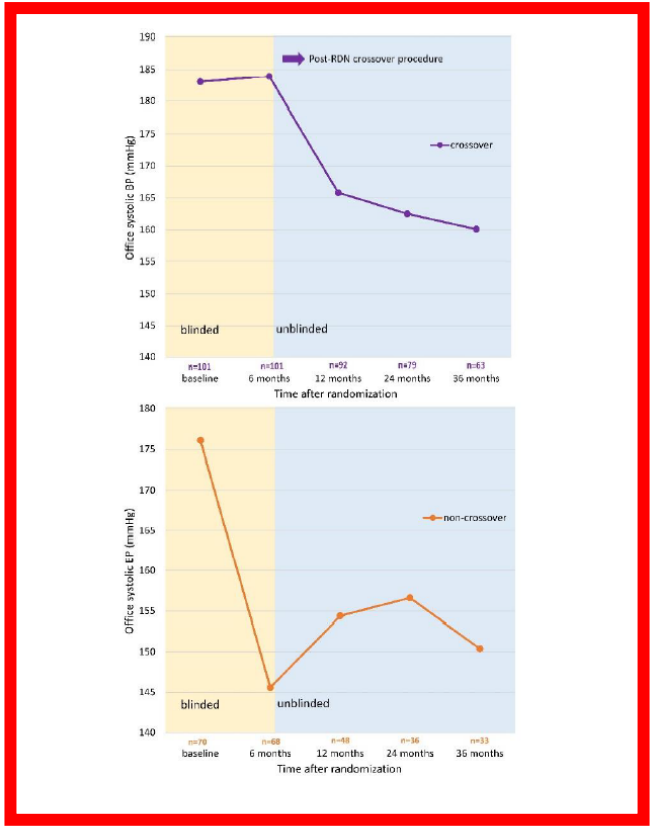


Muntner P, et al. Jama 2020

Mechanisms involved in BP regulation and the pathophysiology of hypertension



Systolic BP in crossover and non-crossover patients from baseline through 36 months



Supplemental Table S6. Safety outcomes in RDN, crossover, and non-crossover patients

% (n)	RDN N=364	Crossover * N=101	Non-Crossover N=70

Bhatt DL, et al. Lancet 2022;400:1405-16.

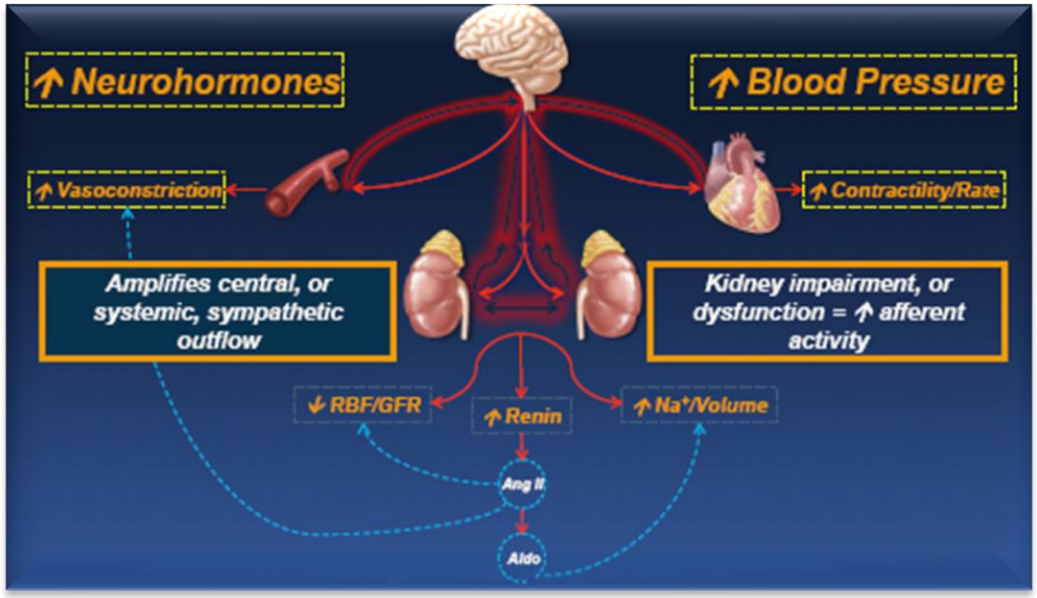
Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

Misurazione della PA ed esami diagnostici da eseguire in tutti i pazienti sottoposti alla procedura di RDN

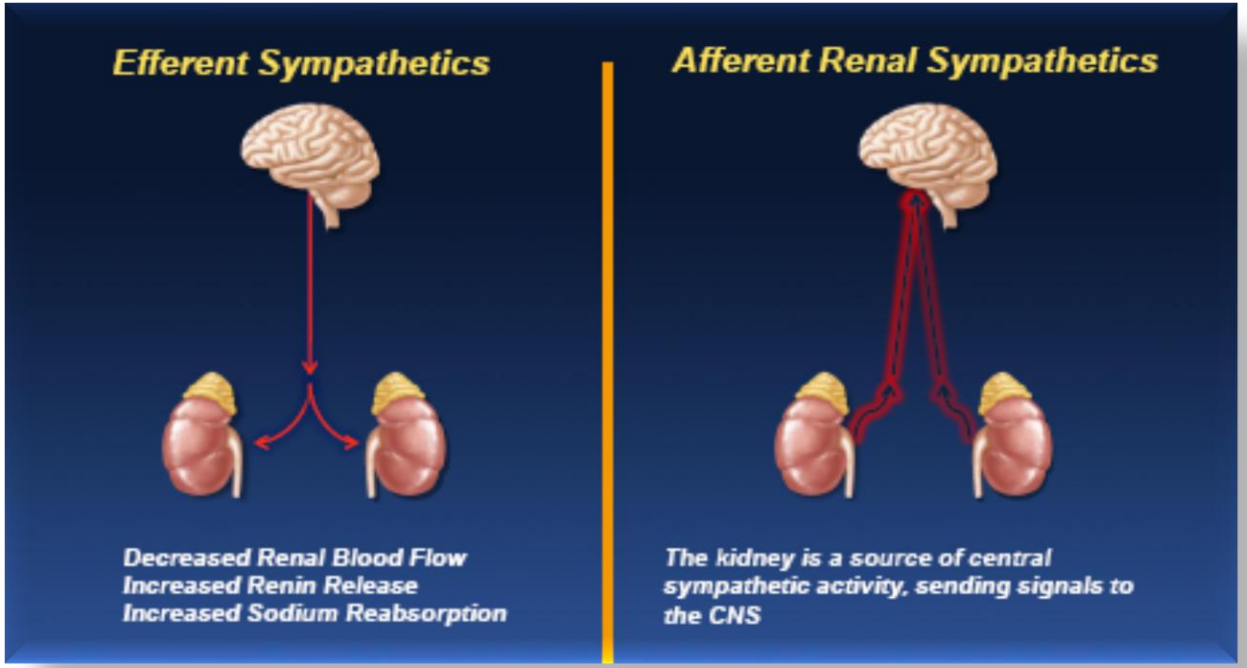
- Misurazione della PA domiciliare, clinica ed ambulatoriale delle 24 ore
- Misurazione della PA clinica ed ambulatoriale delle 24 ore ad 1, 3 e 6 mesi, poi ogni anno
- ECG a 12 derivazioni ad 1 mese e poi ogni anno
- Prelievo ematico per valutazione della funzione renale (creatininemia, filtrazione glomerulare renale stimata, clearance della creatinina stimata, azotemia, sodio, potassio), esame completo delle urine e dosaggio della microalbuminuria e della creatinuria sulle urine del mattino con calcolo del rapporto albuminuria/creatinuria

  ad 1, 3 e 6 mesi, poi ogni anno
- Prelievo per emocromo ad 1 mese e poi ogni anno

Crosstalk Between Renal Nerves and CNS

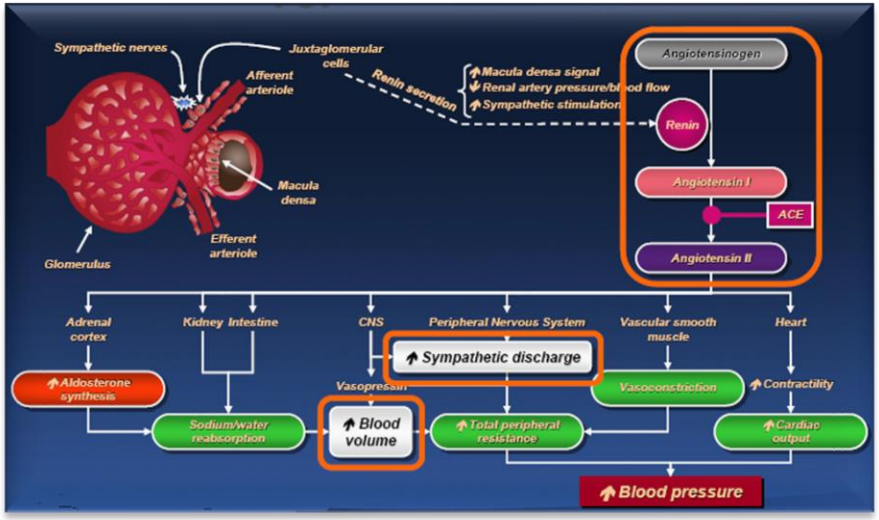


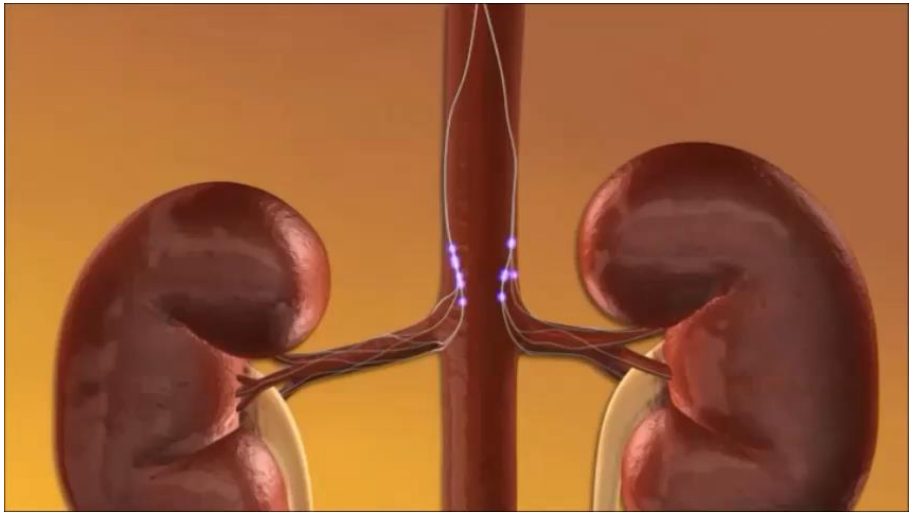
Renal Nerves and the SNS



DiBona GF, et al. Am J Physiol Regul Integr Comp Physiol. 2010;298: R245–R253.
Schlaich MP, et al. Hypertension. 2009;54:1195-1201.

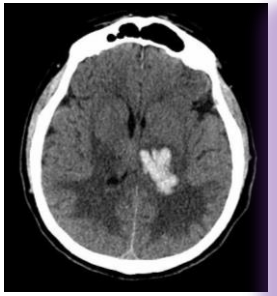
The Interplay Between RAAS, Volume, and SNS

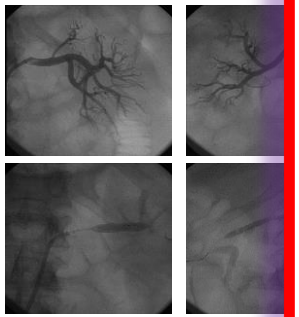


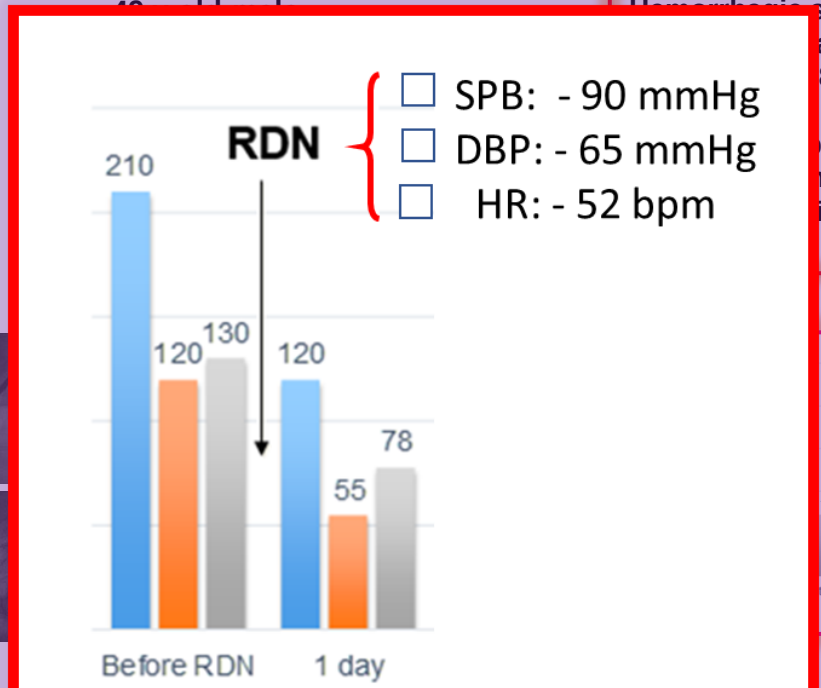


Saseen JJ, Carter BL. Pharmacotherapy A Pathophysiologic Approach. 6th ed. New York, NY: McGraw-Hill Professional; 2005:185-218.

Acute Treatment with RDN in pt with Hemorrhagic Stroke and Resistant Hypertension







stroke
a Scale: 9
8
ertension during
(BP 200/110 mmHg)
ications p.o. and

Versaci F et al. Int J. Neurol Neuro

Versaci F. et al SAGE Open Med Case Rep. 2019


AO
Tempo reale: Pagina 1
Segmento ST: 1
Registro
Tutte
Tempo
FC
SpO2
PNI
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100%
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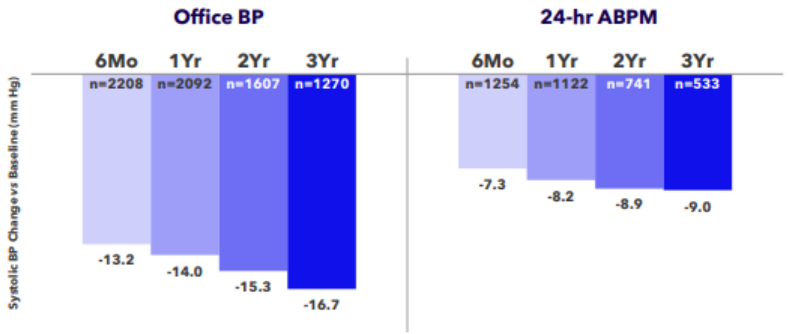
Significant, sustained office and 24hr SBP reductions over 3 years in real-world setting

GSR DEFINE

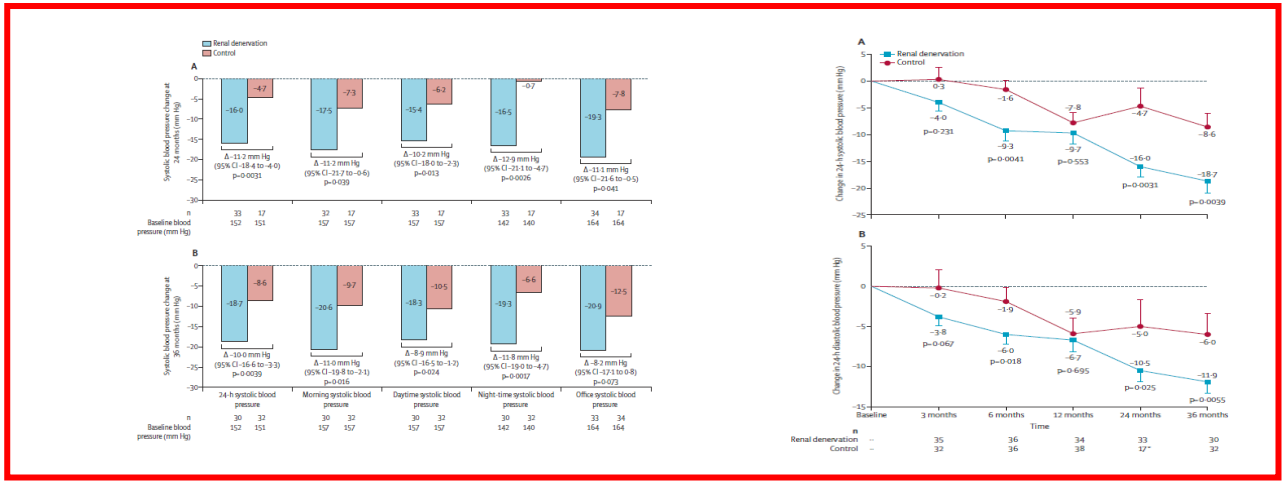


Note: patient numbers reflect who had completed follow-up at the time of analysis.

Mahfoud et al. EuroPCR 2022

Long-term efficacy and safety of RDN in the presence of antihyperthensive drugs (SPYRAL HTN-ON MED):

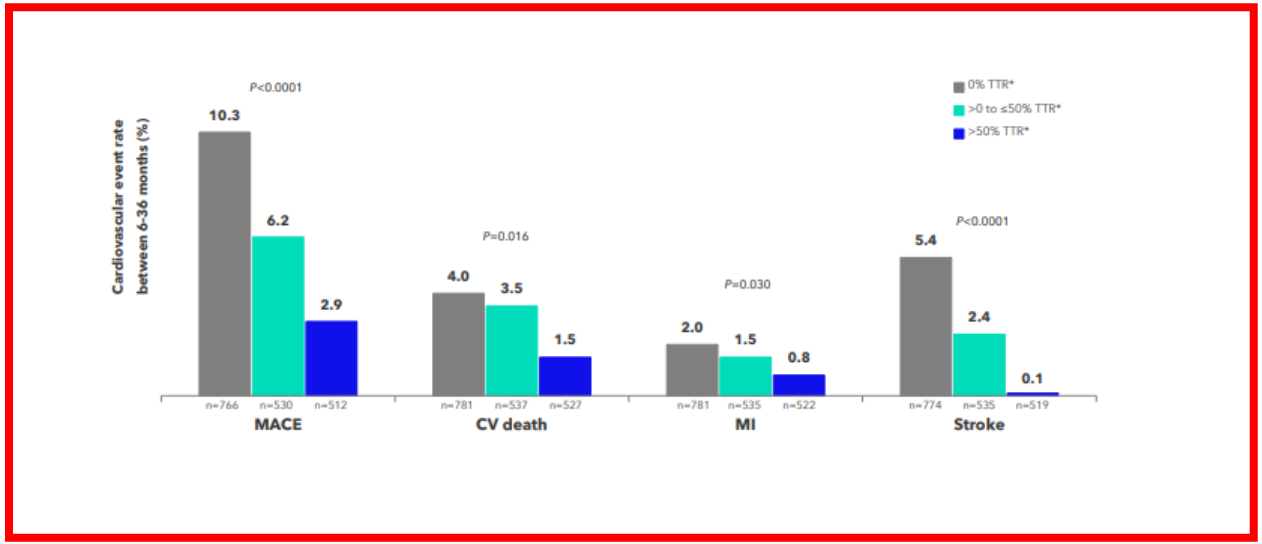
a randomized sham-controlled trial



Mahfoud F, et al. Lancet 2022

Higher TTR associated with significant CV event reductions from 6 to 36 months

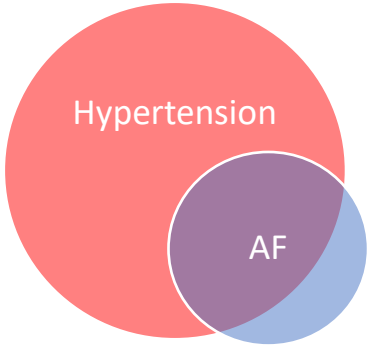
GSR DEFINE



MACE defined as cardiovascular death, MI or stroke. Patients who had events between 0-6 months were excluded from analyses. P-values were calculated using Cochran-Armitage trend tests.
*TTR from baseline to 6 months

Mahfoud et al. EuroPCR 2022.

Hypertension is the most common underlying disorder in patients with AF

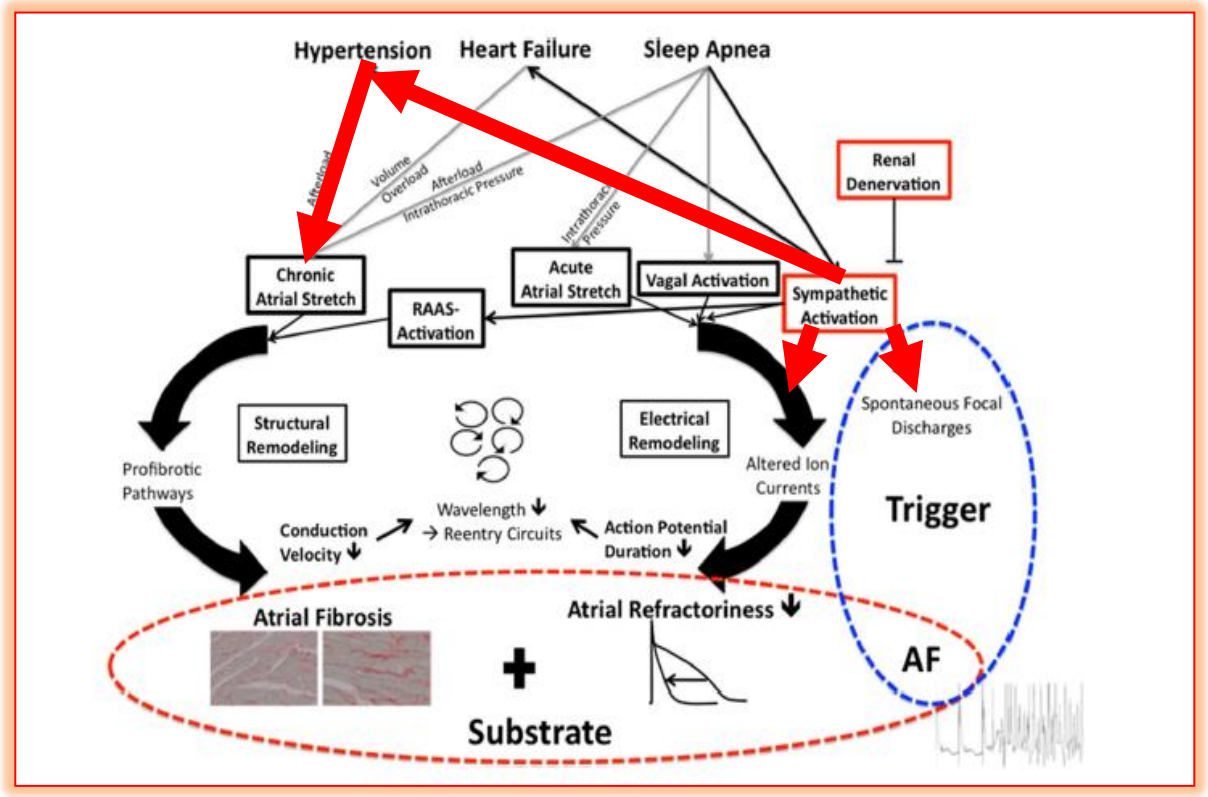


- Hypertension is more prevalent than AF
- Many Patients with Hypertension have AF
- Most Patients with AF have Hypertension
- Prevalence of AF and Hypertension both increase with age

- **Hypertension is main contributor (~20%) of new AF cases[1]**
- **Hypertension is the most important clinical predictor of recurrent AF after catheter ablation[2]**

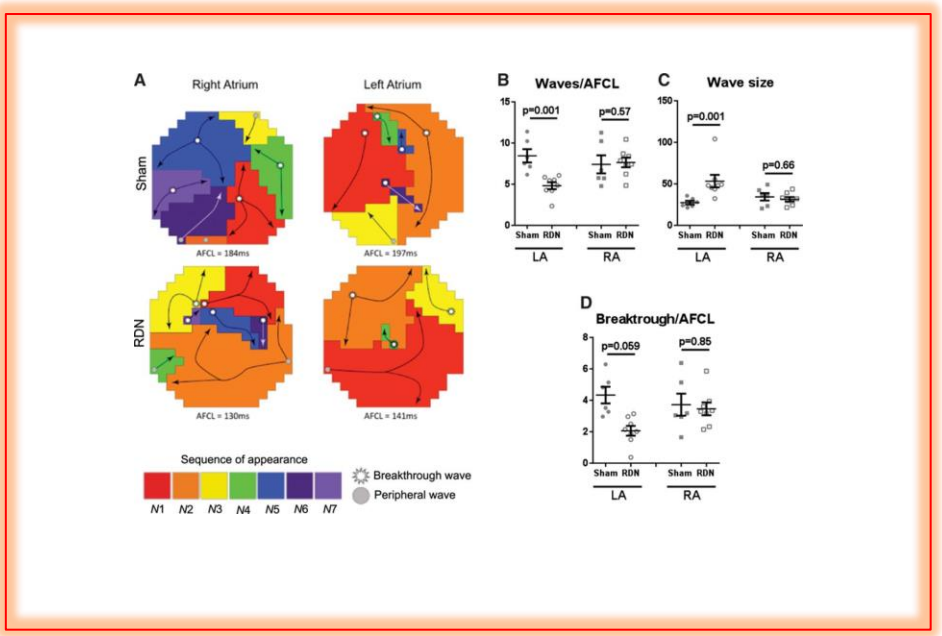
1. Huxley RR, et al. Circulation 2011;123:1501-8
2. Parkash R, et al. Circulation 2017; 135:1788-98

High Sympathetic Tone Can Impact Both Triggers and Substrate Required to maintain AF



Linz et al. Clin Res Cardiol. 2014;103:765-74

RDN and Atrial Electrical Remodeling in Goats



Linz D, et al. Circ Arrhythm **Electrophysiol 2015**

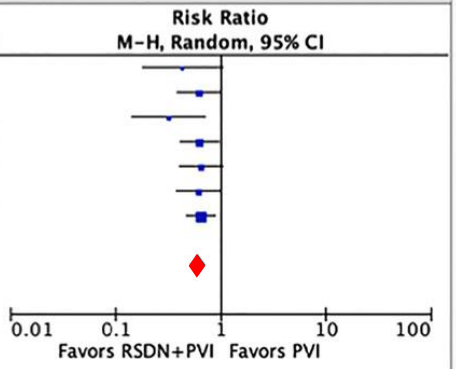
RDN + PVI patients are 40% less likely to have AF recurrence vs PVI only: Meta analysis

Figure 2.1 Overall Recurrence of Atrial Fibrillation in Hypertensive Patients

Study or Subgroup	RSDN+PVI Events	RSDN+PVI Total	PVI Events	PVI Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Pokushalov 2012	4	13	10	14	4.1%	0.43 [0.18, 1.04]	2012
Pokushalov 2014	15	41	23	39	13.8%	0.62 [0.38, 1.00]	2014
Kiuchi 2016	5	21	18	24	5.0%	0.32 [0.14, 0.71]	2016
Kiuchi 2017	15	39	59	96	17.4%	0.63 [0.41, 0.96]	2017
Romanov 2017	15	39	22	37	14.0%	0.65 [0.40, 1.04]	2017
Kiuchi 2018	13	33	23	36	13.3%	0.62 [0.38, 1.01]	2018
Steinberg 2020	43	154	64	148	32.4%	0.65 [0.47, 0.88]	2020
Total (95% CI)		**340**		**394**	**100.0%**	**0.60 [0.50, 0.72]**	
Total events	110		219				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.36$, df = 6 (P = 0.76); $I^2 = 0\%$

Test for overall effect: Z = 5.56 (P < 0.00001)

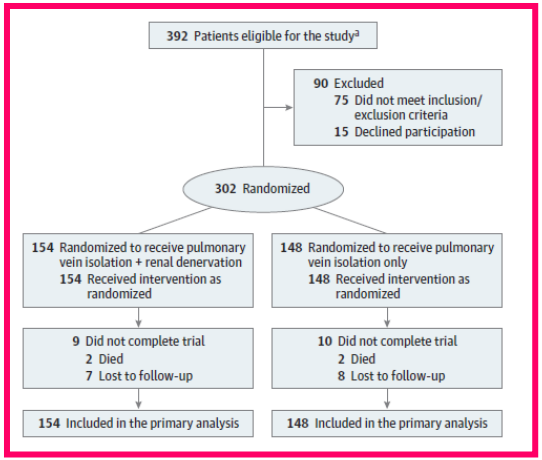


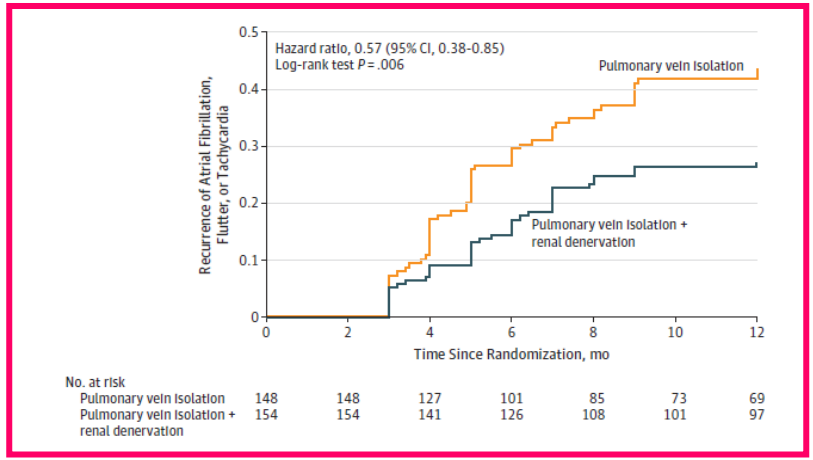
Mujer et al. Pacing Clin Electrophysiol. 2020 Aug;43(8):866-874.

JAMA | Original Investigation

Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients With Paroxysmal Atrial Fibrillation and Hypertension
The ERADICATE-AF Randomized Clinical Trial

Jonathan S. Steinberg, MD; Vitaliy Shabanov, MD; Dmitry Ponomarev, MD; Denis Losik, MD; Eduard Ivanickiy, MD; Evgeny Kropotkin, MD; Konstantin Polyakov, MD; Pawel Ptaszynski, MD; Boris Keweloh, MD; Christopher J. Yao, MPH; Evgeny A. Pokushalov, MD, PhD; Alexander B. Romanov, MD





JAMA. 2020;323(3):248-255

Consensus Document

European Society of Hypertension position paper on renal denervation 2021

Roland E. Schmieder[a], Felix Mahfoud[b], Giuseppe Mancia[c], Michael Azizi[d], Michael Böhm[e], Kyriakos Dimitriadis[f], Kazuomi Kario[g], Abraham A. Kroon[h], Melvin D Lobo[i], Christian Ott[a,j], Atul Pathak[k], Alexandre Persu[l], Filippo Scalise[m], Markus Schlaich[n], Reinhold Kreutz[o], Costas Tsioufis[p], on behalf of members of the ESH Working Group on Device-Based Treatment of Hypertension

J Hypertens, September 2021

EuroPCR 2022

Renal denervation increased time in target range

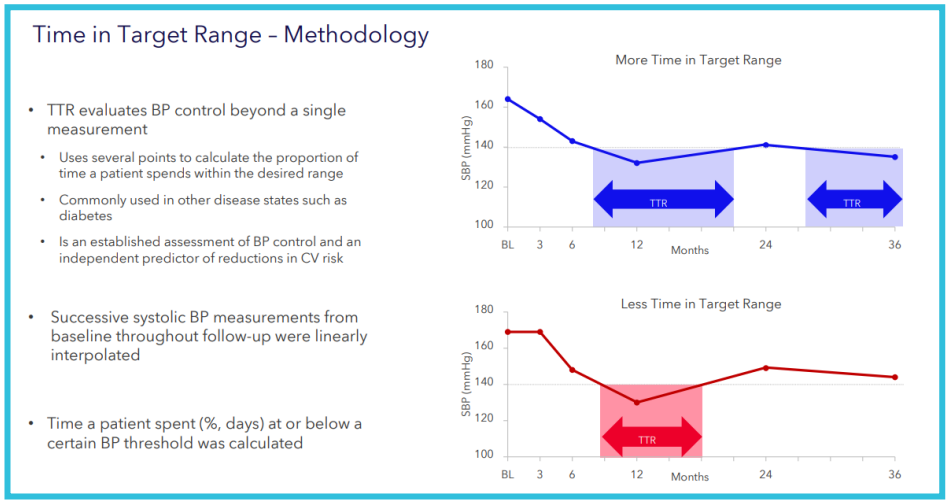
Renal Denervation increases long-term time in target blood pressure range compared with sham control: ON MED pilot data

Blood pressure and MACE reductions after renal denervation: 3-year GSR results

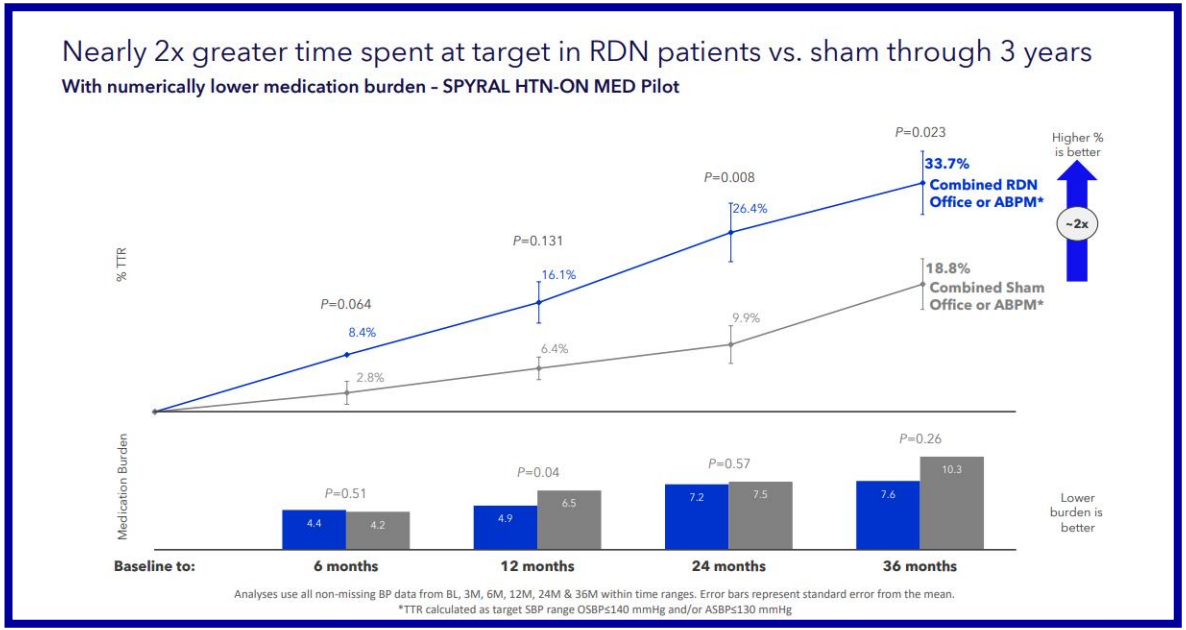
Renal Denervation Increased Time in Target Range

Renal Denervation increases long-term time in target blood pressure range compared with sham control: ON MED pilot data

Blood pressure and MACE reductions after renal denervation: 3-year GSR result



Mahfoud et al. EuroPCR 2022



Kandzari, et al. EuroPCR 2022.

Higher TTR associated with significant CV event reductions from 6 to 36 months

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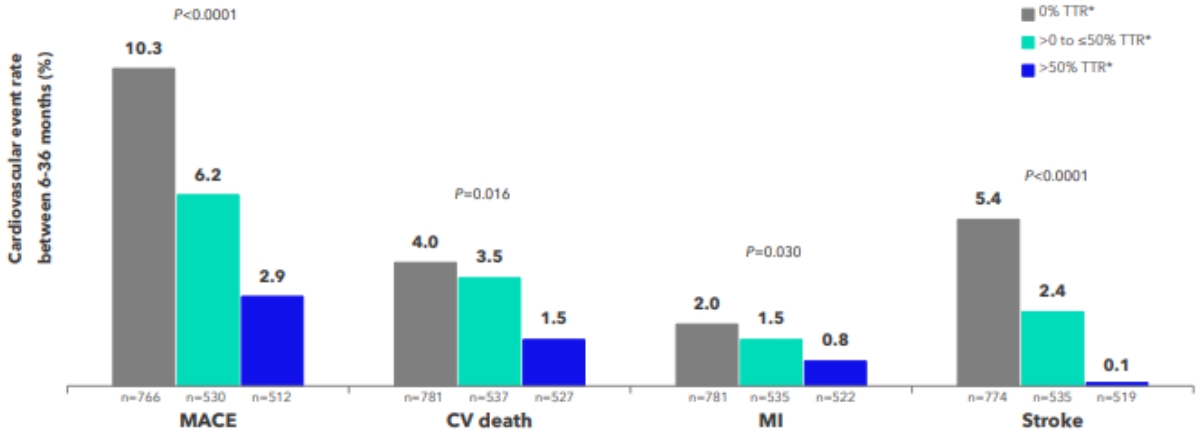
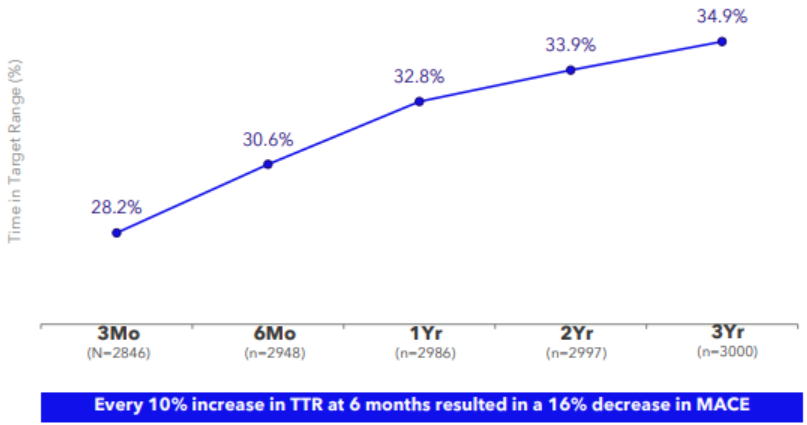


MACE defined as cardiovascular death, MI or stroke. Patients who had events between 0-6 months were excluded from analyses. P-values were calculated using Cochran-Armitage trend tests.
*TTR from baseline to 6 months

Mahfoud et al. EuroPCR 2022.

Time in Target Range increased to nearly 35% over 3 years in a real-world setting

GSR-DEFINE

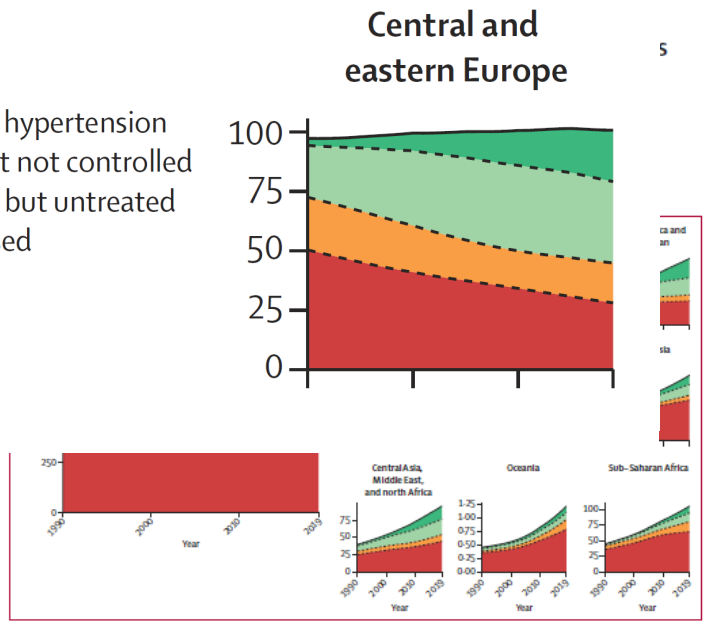


TTR calculated as target SBP range OSBP≤140 mmHg and/or ASBP≤130 mmHg

Mahfoud et al. EuroPCR 2022

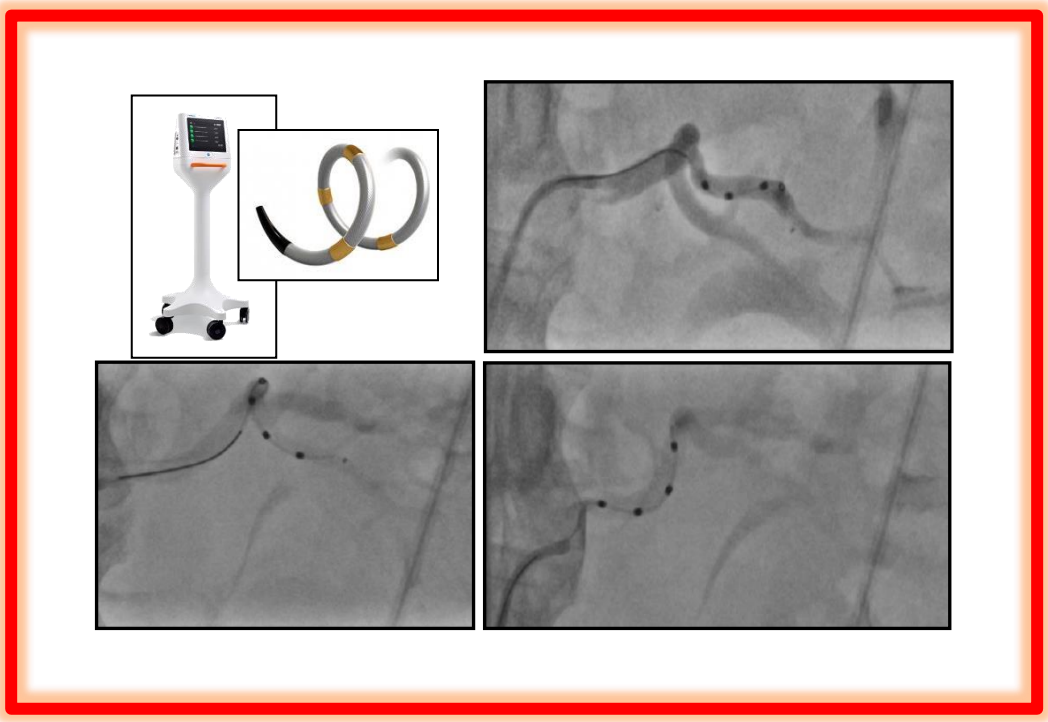
Hypertension Epid

- **High prevalence:**
  - **Affects 1 in 3 adults**
  - **1B people worldwide →**
- **Single largest contributor worldwide**
- **Every 20 mmHg increase i with a doubling of 10-year mortality**
- **Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure**
- **Only half of all treated hypertensives are controlled to established BP targets**
- **Resistant Hypertension ~ 10%**



Lancet 2021, Aug 24

Symplicity Spyral™ catheter
reduces procedural variability



Patient Perspectives

10 mmHg SBP Office reduction

Baseline BP

160 mmHg

Fewer drugs
Fewer symtoms
Less effects on lifestyle

Baseline BP

145 mmHg

Free from drugs
No symtoms
No effects on lifestyle

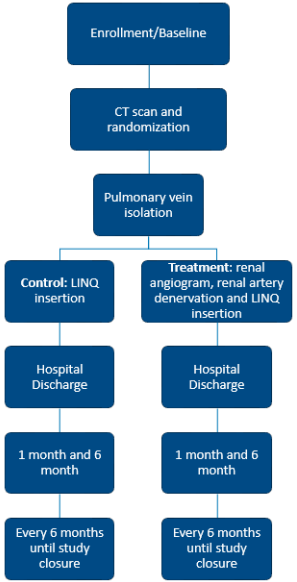
ScillaCuore

Ongoing prospective trials as assessing the effects of RDN in Pts with AF

Trial	Design	Status	Location	Enrollment	Intervention	Outcome
ERDAF study (Effect of Renal Denervation on Atrial Fibrillation) *NCT04055285*	Prospective Randomized Open label	Not recruiting yet	Greece	30 participants with resistant HTN and paroxysmal or persistent AF	RDN and ILR implantation vs. optimal antihypertensive treatment and ILR implantation	Recurrence of AF and AF burden (with the use of ILR)
Ultrasound-Based Renal Sympathetic Denervation as Adjunctive Upstream Therapy During Atrial Fibrillation Ablation (ULTRA-HFIB) *NCT04182620*	Prospective Randomized Single-blinded	Recruiting	USA	130 participants with uncontrolled hypertension and paroxysmal or persistent AF	RDN and catheter ablation vs. catheter ablation only	Recurrence of AF up to 12 months
Treatment of Atrial Fibrillation in Patients by Pulmonary Vein Isolation in Combination With Renal Denervation or Pulmonary Vein Isolation Only (ASAF) *NCT 02115100*	Prospective Randomized Open label	Recruiting	Netherlands	138 participants with resistant hypertension and AF	RDN and PVI vs. PVI only	Recurrence of AF
Renal Nerve Denervation in Patients With Hypertension and Paroxysmal and Persistent Atrial Fibrillation (Symplicity AF) *NCT02064764*	Prospective Randomized, Open label	Active, not recruiting First results in 2020	USA	245-participants with uncontrolled HTN and AF	RDN and PVI (cryoablation) vs. PVI (cryoablation) only	Recurrence of AF

SYMPLICITY AF CLINICAL TRIAL

Reveal LINQ™

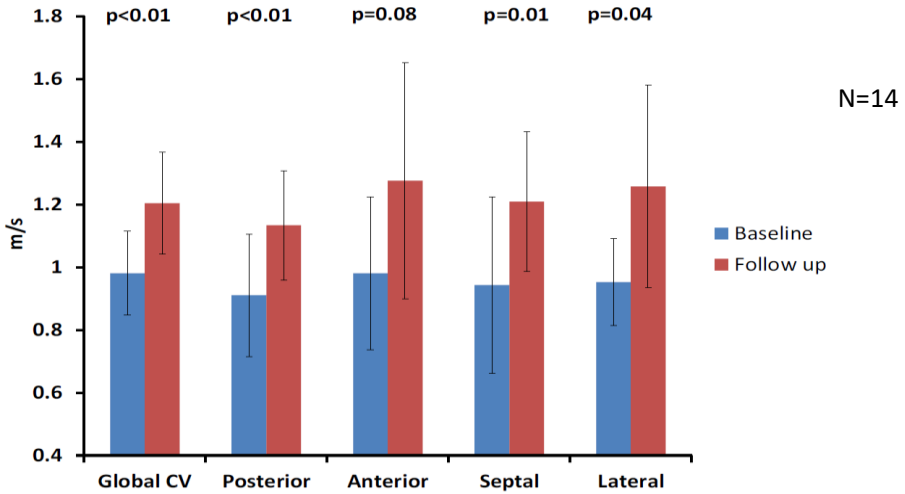


Arctic Front®

Symplicity Spyral™

RDN and Atrial Electrical and Mechanical Remodeling in Hypertensive Patients

Global and regional conduction velocity



N=14

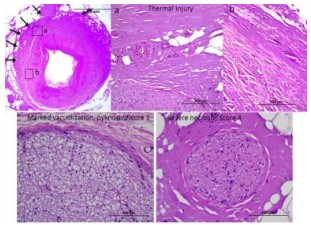
McClellan, Schlaich et al. *Heart Rhythm*, 2015

RDN Technologies Avaible and in Development

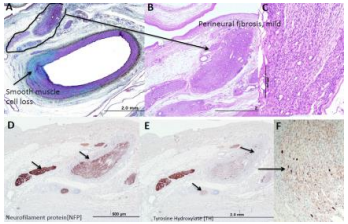
Technology	Device Name (Manifacturer)	Key Characteristics
Radiofrequency	Symplicity Flex (Medtronic, Inc)	Single-electrode catheter
	Spyral (Medtronic, inc)	Spiral-electrode catheter
	EnlighHTN (St.Jude Medical, Inc)	Multielectrode Catheter
	OneShot (Covidien, Manfield, MA)	Irrigated, spiral-electrode catheter
	Vessix V2 (Boston Scientific Corp.)	Multielectrode catheter with bipolar energy deliver
	ThermoCool (Biosense Webster, Inc)	Irrigated, multielectrode catheter
	Iberis (Terumo)	Single-electrode, radial artery access system
	Verve Medical System	Multielectrode, retrouretic access system
Ultrasound	Paradise (ReCor Medical)	Nonfocused endovascular ultrasound energy system
	TIVUS (Cardiosonic)	Nonfocused endovascular ultrasound energy system
	Kona System (Kona Medical)	Externally applied, low-intensity ultrasound
	Sound 360 (Sound Innovations, Inc)	Endovascular ultrasound energy system
Cryoablation	Not yad named (friedrich-Schiller Universuty	Standard cryoablation catheter
Brachitherapy	CyberHeart	Catheter based, beta-radiation Brachiterapy
Pharmacological	Not yad named (Universuty of Athens)	0.1 mg vincristine delivered from six holed proprietary balloon catheter
	Bullfrog (Mercator MedSystems, Inc)	Guanethidine microinjecyion into the adventitia
	Peregrine (Ablative Solutions)	Ethanol Microinjection into the adventitia
	ApexNano System (ApexNano Ther)	Magnetic Nanoparticles Impregnated with Botox

Histology after Renal denervation

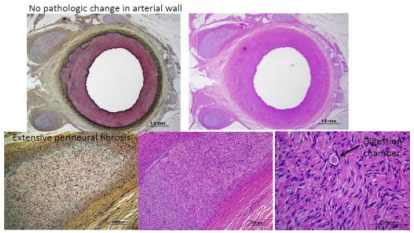
4 Hours after RDN

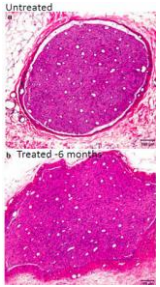


14 days after RDN



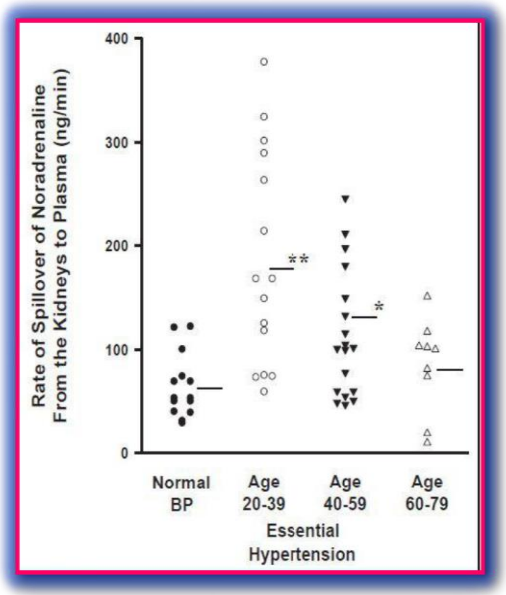
6 Months after RDN





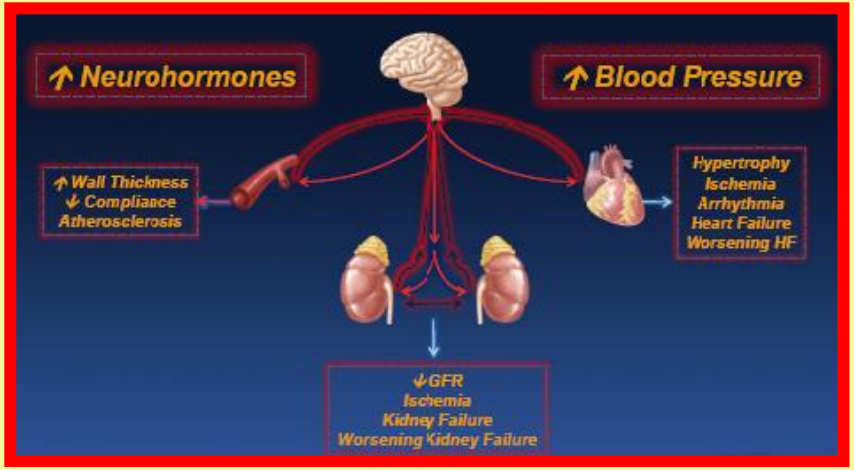
Courtesy of R. Virmani

Renal Sympathetic Activation in Patients with Hypertension



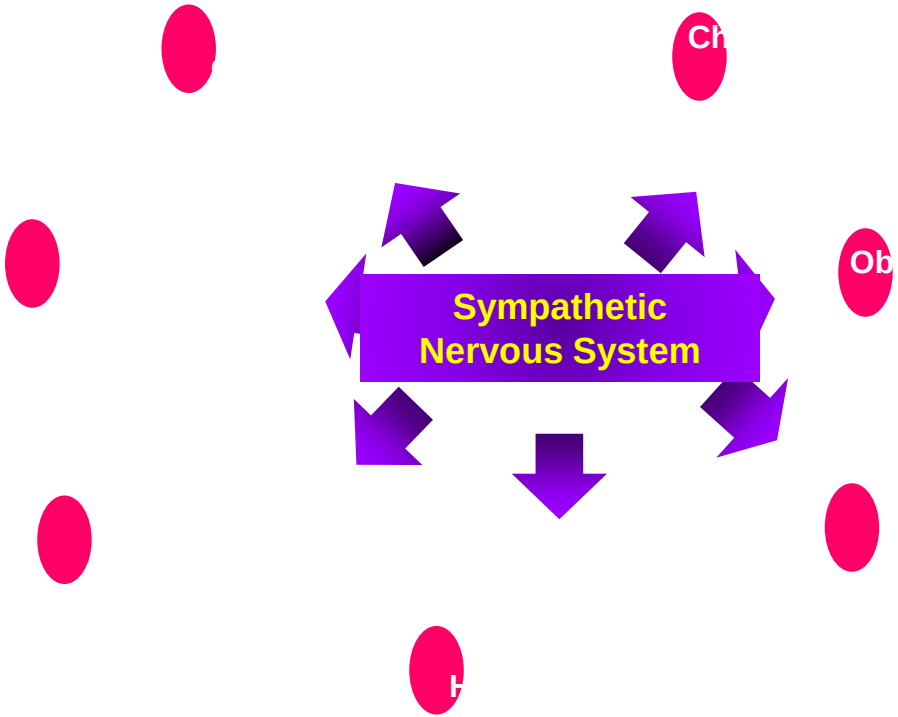
Esler et M al. Clin Exp Hyper 1984

Chronic Effect of Increased Sympathetic Nerve Activity

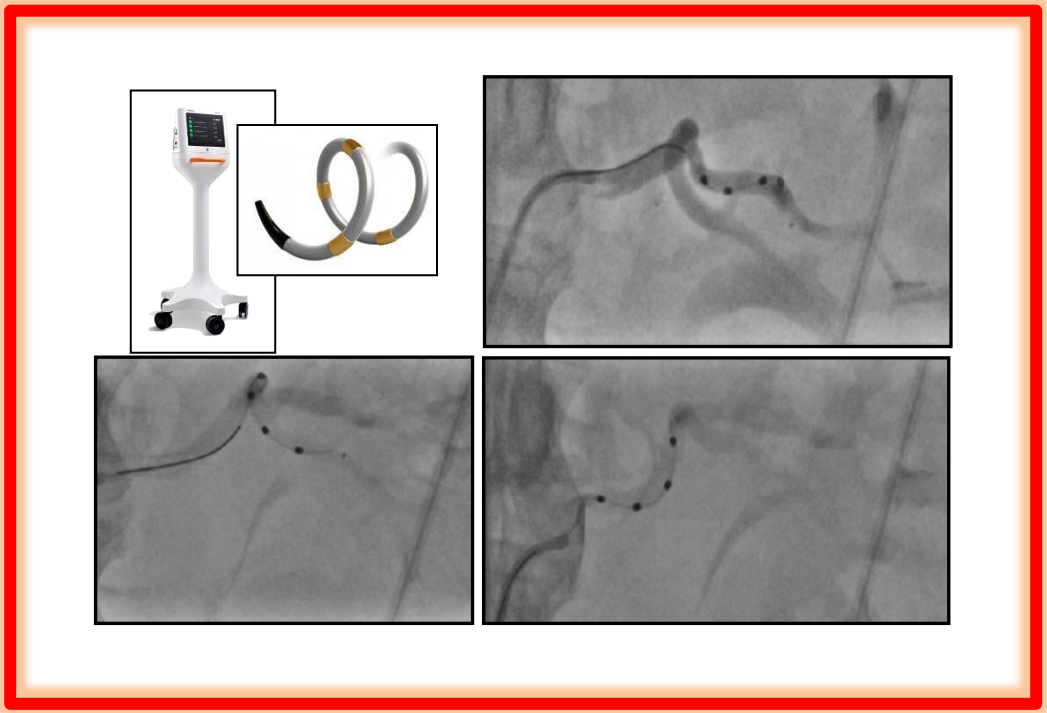


Schlaich MP, et al. Hypertension. 2009;54:1195-1201.

Target-organ Damage and SNS



Symplicity Spyral™ catheter
reduces procedural variability



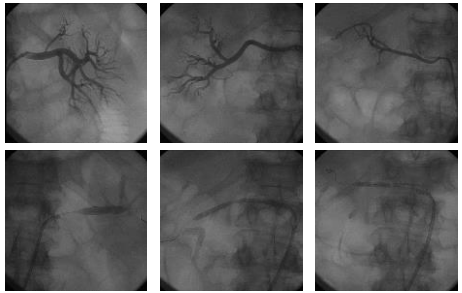
Acute Treatment with RDN in pt with Hemorrhagic Stroke and Resistant Hypertension

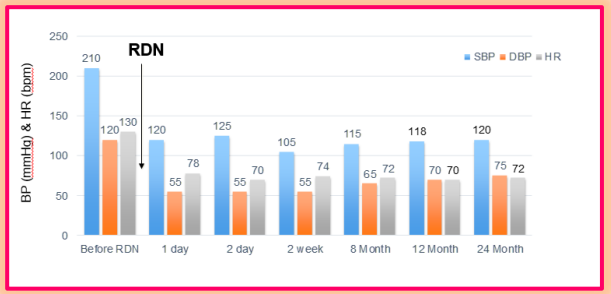
49 y-old-male
Resistant Hypertension despite:

- **Bisoprolol 2.5 mg twice daily**
- **Ramipril 10 mg twice daily**
- **Amlodipine 10 mg twice daily**
- **Furosemide 25 mg twice daily**
- **Metolazone 5 mg**

Hemorrhagic stroke
Glasgow Coma Scale: 9
Norton Scale: 8

Persistent hypertension during hospitalization (BP 200/110 mmHg) despite 6 medications p.o. and urapidil iv



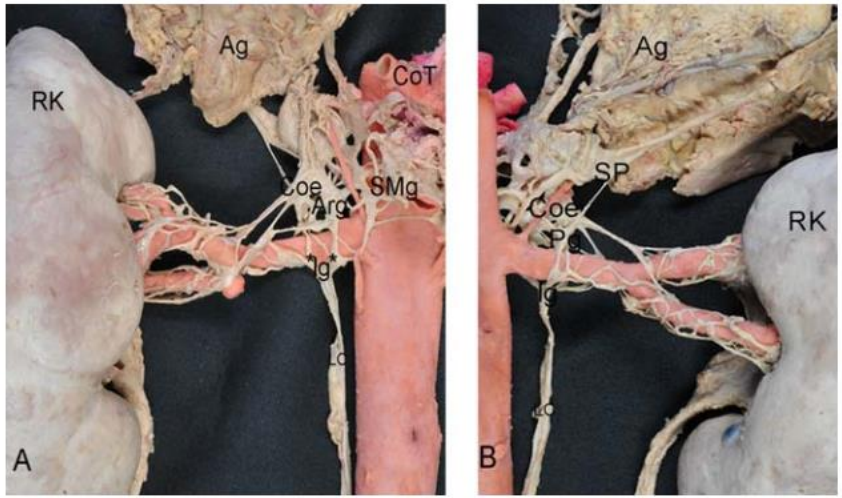


Versaci F et al. Int J. Neurol Neurother 2015

Versaci F. et al SAGE Open Med Case Rep. 2019

The procedure was changed to reflect renal nerve anatomy

Renal nerves have a positional bias on radial distance from arterial lumen; distal nerves are closer



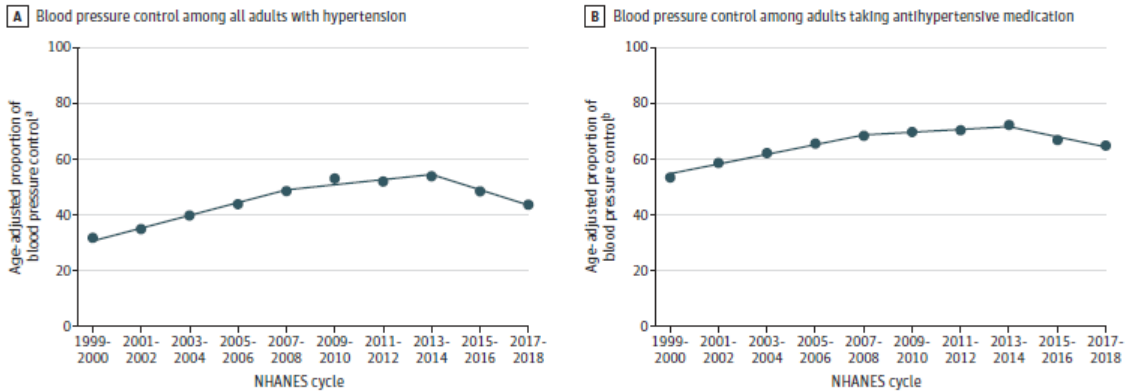
Mompeo B, et al. *Clin Anat*. 2016;29:660–664.

JAMA | Original Investigation

Trends in Blood Pressure Control Among US Adults With Hypertension, 1999-2000 to 2017-2018

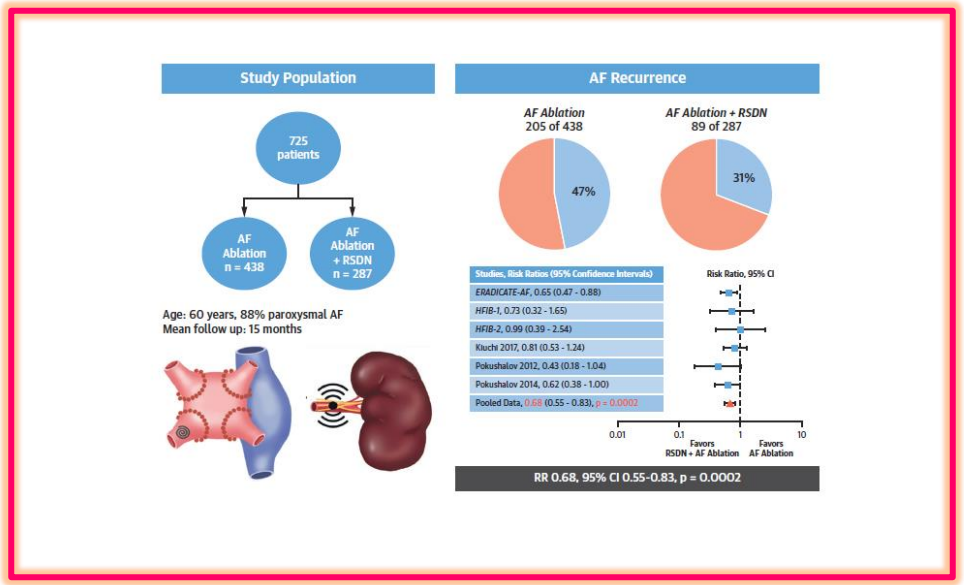
Paul Muntner, PhD; Shakia T. Hardy, PhD; Lawrence J. Fine, MD; Byron C. Jaeger, PhD; Gregory Wozniak, PhD; Emily B. Levitan, ScD; Lisandro D. Colantonio, MD, PhD

Age-Adjusted Estimated Proportion of Adults With Hypertension and Controlled Blood Pressure



Muntner P, et al. Jama 2020

Study Overview Demonstrating Freedom From AF With RSDN



RDN + PVI patients are 40% less likely to have AF recurrence vs PVI only: Meta analysis

Turagam, M.K. et al. J Am Coll Cardiol EP. 2021;7(1):109–23.

NEUROMODULATION–ATRIAL FIBRILLATION

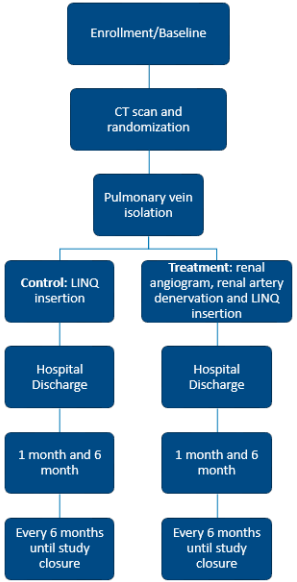
Renal Sympathetic Denervation as Upstream Therapy During Atrial Fibrillation Ablation

Pilot HFIB Studies and Meta-Analysis

Mohit K. Turagam, MD,[a] William Whang, MD,[a] Marc A. Miller, MD,[a] Petr Neuzil, MD, PhD,[b] Arash Aryana, MD,[c] Alexander Romanov, MD,[d] Frank A. Cuoco, MD,[e] Moussa Mansour, MD,[f] Dhanunjaya Lakkireddy, MD,[g] Gregory F. Michaud, MD,[h] Srinivas R. Dukkipati, MD,[a] Sam Cammack, MA, MPH,[a] Vivek Y. Reddy, MD[a]

SYMPLICITY AF CLINICAL TRIAL

Reveal LINQ™



Arctic Front®

Symplicity Spyral™

TABLE 5 Effect of Renal Sympathetic Denervation on Blood Pressure

First Author/Study, Year	N	Follow-Up (Months)	Change in SBP From Baseline (mm Hg)	p Value		Change in DBP From Baseline (mm Hg)	p Value	
				Compared With Baseline	Compared With AF Ablation		Compared With Baseline	Compared With AF Ablation
Pokushalov et al., 2012	13	12	-25 ± 5	<0.001	<0.001	-10 ± 2	<0.001	<0.001
Pokushalov et al., 2014	41	12	-20 ± 14	<0.001	<0.001	-10 ± 6	<0.001	<0.001
Kiuchi et al., 2017*	39	6	-3 ± 2	NS†	NS†	-1 ± 3	NS†	NS†
ERADICATE-AF study	154	12	-16 ± 9	0.001	0.01	-11 ± 6	0.001	<0.001
HFIB-1 study	13	12	5 ± 26	NS†	NS†	0.6 ± 15	NS†	NS†
HFIB-2 study	28	12	-8 ± 25	NS†	NS†	1 ± 12	NS†	NS†

Values are mean ± SD, unless otherwise indicated. Mean change in blood pressure compared with baseline: SBP −12.1 mm Hg (95% confidence interval: −20.9 to −3.3 mm Hg; $p < 0.007$); DBP −5.60 mm Hg (95% CI: −10.05 to −1.1 mm Hg; $p = 0.01$). *24-h mean ambulatory blood pressure monitoring. †$p > 0.05$.

Abbreviations as in Table 1.

Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities

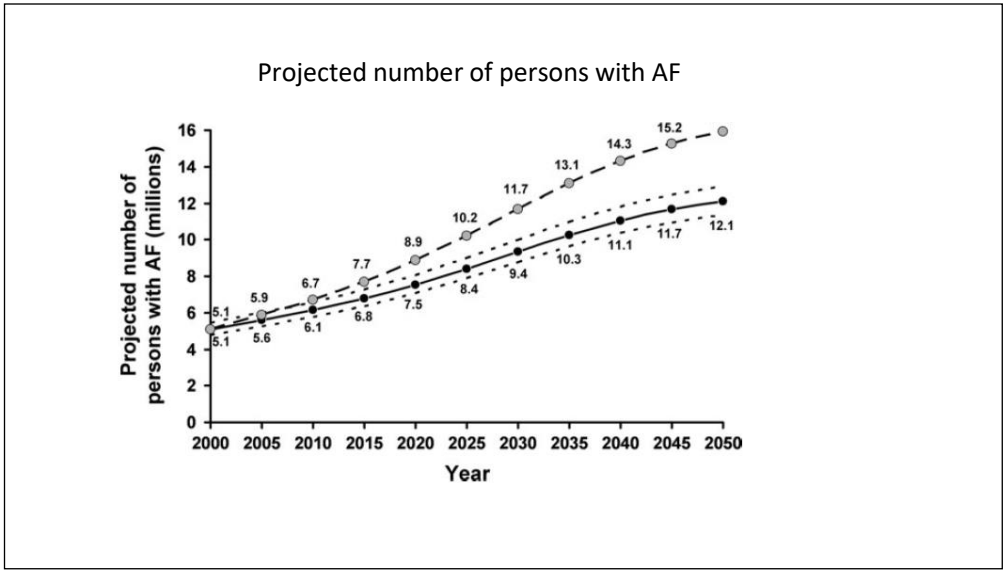
Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

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

ESC/ESH GUIDELINES

The Problem of AF gets larger

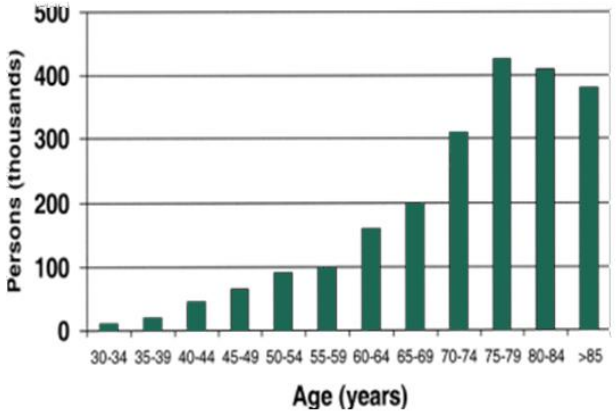
Projected number of persons with AF in the US between 2000 – 2050



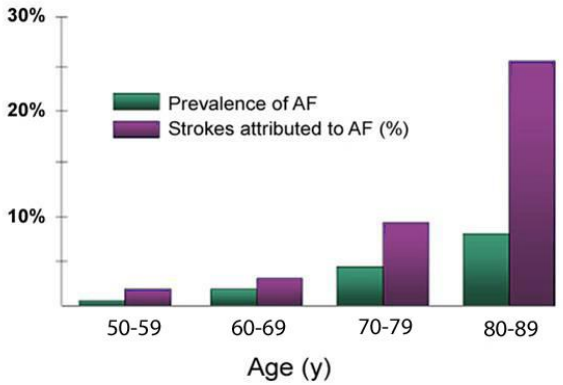
Briffa T, et al. BMJ 2009

Atrial fibrillation and Stroke

Estimated age-specific AF prevalence

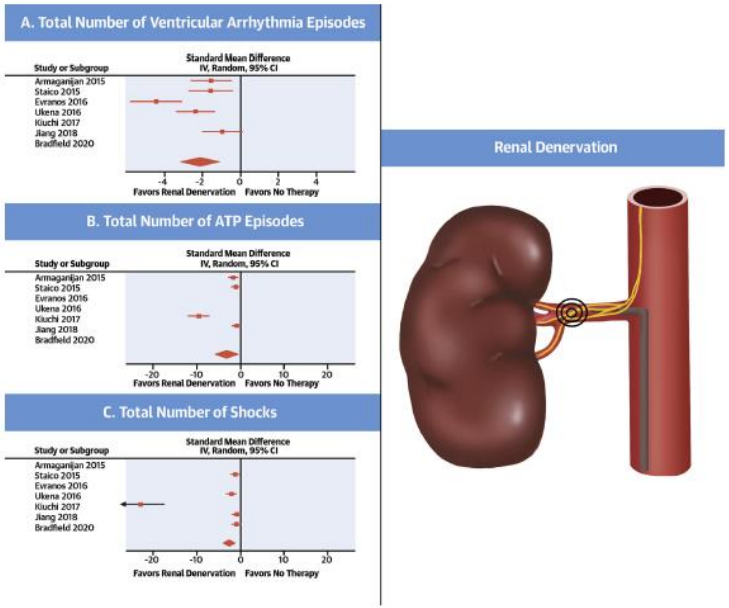


Relationship of AF and stroke



Fuster, et al. Circulation. 2006

Meta-Analysis Demonstrating Impact of Renal Denervation on Ventricular Arrhythmias



Hawson, J. et al. J Am Coll Cardiol EP. 2021;7(1):100–8.

TAKE HOME MESSAGE

European Society of Hypertension: Posistion Statement on RDN in 2021(1)

- On the basis of consistent results of several sham-controlled clinical trials, renal denervation represents an evidence-based option to treat hypertension, in addition to lifestyle changes and blood pressure lowering drugs.

- Renal denervation therefore expands therapeutic options to address the first objective of hypertension treatment, that is to effectively reduce an elevated blood pressure and achieve blood pressure targets.

- Renal denervation is considered a safe endovascular procedure without significant short-term or long-term adverse effects based on data available up to 3 years.

TAKE HOME MESSAGE

European Society of Hypertension: Posistion Statement on RDN in 2021(2)

- Renal denervation is an alternative or additive, not a competitive treatment strategy.
- A structured pathway for clinical use of RDN in daily practice is recommended.
- Patients' perspective and preference as well as patients' stage of hypertensive disease including comorbidities should lead to an individualized treatment strategy in a shared decision-making process, that carefully includes the various options of treatment, including renal denervation.

TAKE HOME MESSAGE

LA DENERVAZIONE DELLE ARTERIE RENALI CON I SISTEMI DI SECONDA GENERAZIONE.
UN RIMEDIO PER L'IPERTENSIONE RESISTENTE?

- Le nuove evidenze dimostrano che la denervazione renale ha tuttora forti potenzialità di sviluppo clinico.

- Sulla base dei risultati dei recenti studi clinici, questa tecnica non è più "confinata" all'ipertensione resistente, ma è possibile proporla ad esempio a pazienti difficili da trattare perché non aderenti od intolleranti alla terapia farmacologica.

- Tuttavia la selezione dei pazienti e l'esecuzione della procedura deve essere limitata a centri con un reale "expertise" di ipertensione arteriosa e di cardiologia interventistica.

Bottom line Summary

- Percutaneous renal denervation interrupts efferent and afferent nerve traffic between the brain kidneys.
- Sympathetic activity effects both the **triggers** and **substrate** required to initiate and maintain atrial arrhythmias.
- Pre-clinical data demonstrates that renal denervation modulates sympathetic nerve activity in the kidneys, and in the heart and central nervous system.
- Clinical trials have demonstrated reverse atrial electrical and mechanical remodeling and reductions in atrial tachyarrhythmia burden following renal denervation.
- The prospective, randomized controlled SYMPLICITY AF trial will evaluate the safety and efficacy of renal denervation and pulmonary vein isolation to further reduce atrial arrhythmia burden.

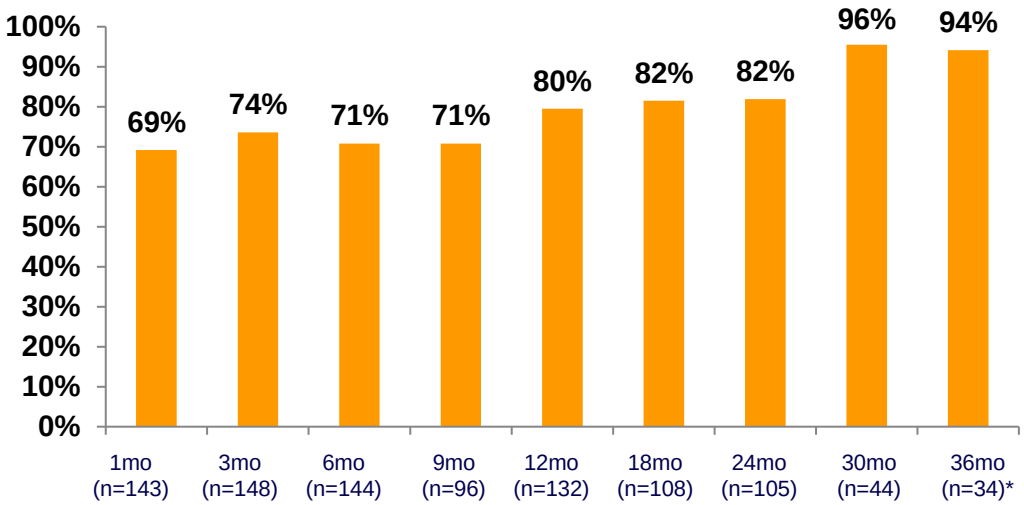
PROOF OF CONCEPT STUDIES IN HYPERTENSION: SPYRAL HTN-OFF MED PIVOTAL TRIAL

KEY INCLUSION & EXCLUSION CRITERIA

Inclusion	1. Patient is either: a. Not on **antihypertensive medications**, OR b. Permitting discontinuation of drug therapy **2. Office SBP** ≥150 and <180 mm Hg **3. Office DBP** ≥90 mm Hg **4. Systolic 24-hour mean ABPM** ≥140 and <170 mm Hg
Exclusion	1. Ineligible **renal artery anatomy** (accessory arteries allowed) **2. eGFR** <45 mL/min/1.73m^2 3. Type 1 **diabetes mellitus** or type 2 diabetes mellitus with HbA1C >8.0% **4. Secondary causes of hypertension**

Böhm et al. Clin Res in Card, 2020

Symplicity HTN-1: Responder Rate Does Not Decrease Over Time – This Clinical Benefit of RDN is Sustained



Responder was defined as an office SBP reduction ≥10 mmHg

* Number of patients represents data available at time of data-lock

Schlaich, M, TCT 2012

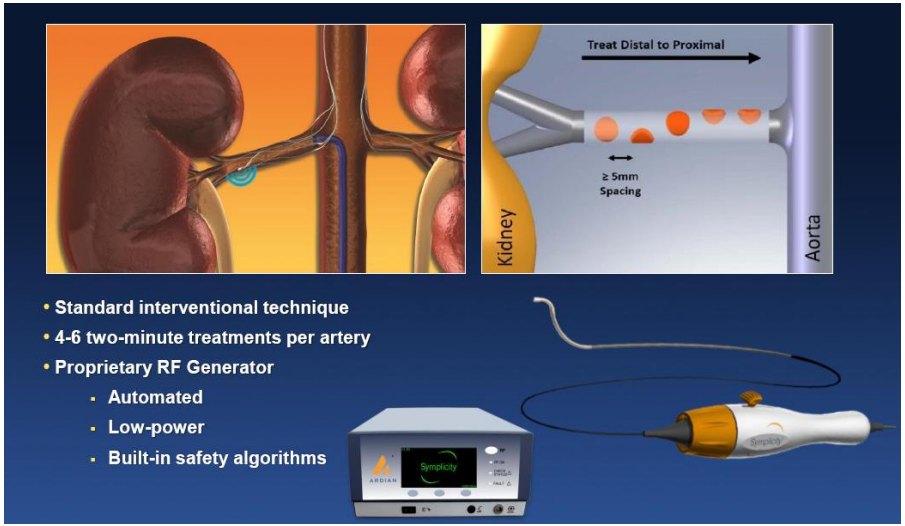
Changes in Underlying Physiology Consistent With RDN

New Engl J Med Case Study

	Baseline	1 Month	Δ
Office BP (mm Hg)	161/107	141/90	
Renal NE spillover (ng/min)			(127/81 at 12 M)
• 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%
Left ventricular mass (g/m^2)	78.8	73.1	-7%

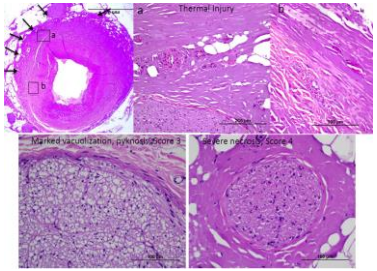
Schlaich MP, et al. New Engl J Med. 2009;361:932-934.

Renal Nerve Anatomy Allows a Catheter-Based Approach

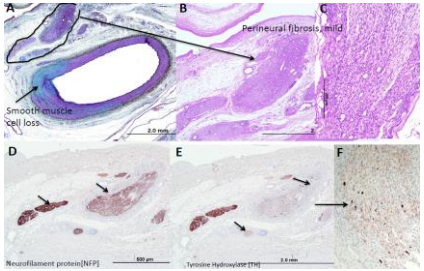


Histology after Renal denervation

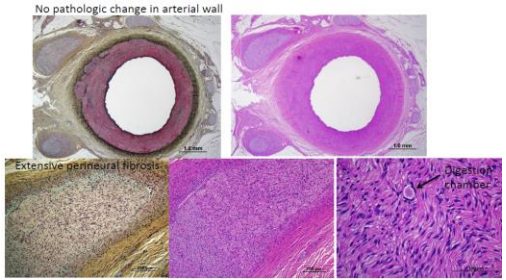
4 Hours after RDN

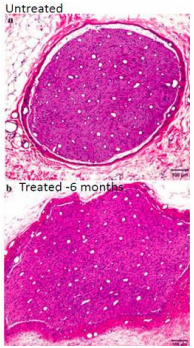


14 days after RDN



6 Months after RDN

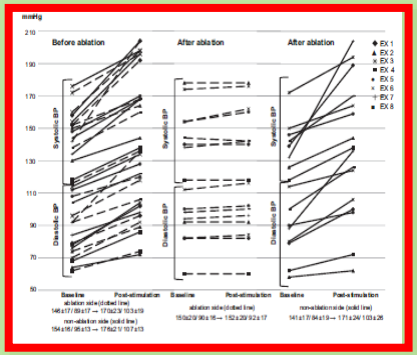




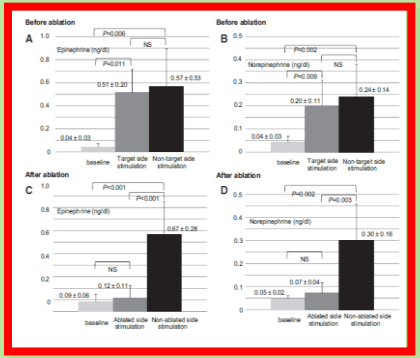
Courtesy of R. Virmani

Blood Pressure and Autonomic Responses to Electrical Stimulation of the Renal Arterial Nerves Before and After Ablation of the Renal Artery

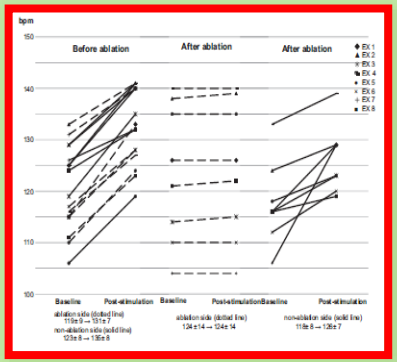
Blood Pressure Responses



Serum Cathecolamine Analysis

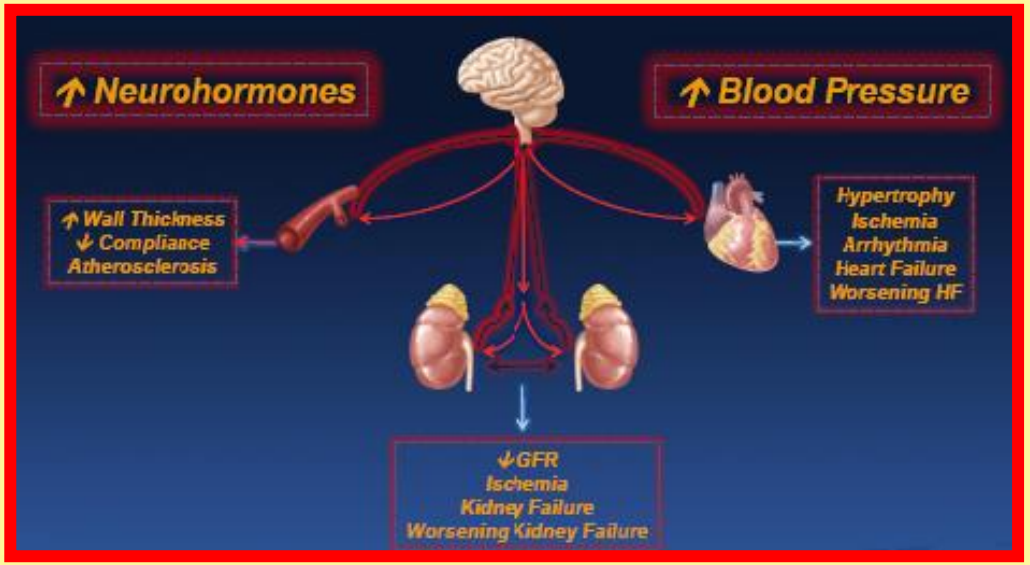


Heart Rate Response



Chinushi M et al. Hypertension. 2013; 61:450-456

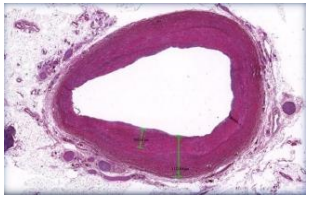
Chronic Effect of Increased Sympathetic Nerve Activity



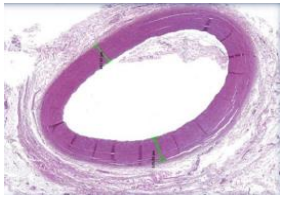
Schlaich MP, et al. Hypertension. 2009;54:1195-1201.

Morphometric Evaluation of Renal aa

	Hypertensive RS = 120	Normotensive RS = 120	P
Maximum thickness of intima (μm)	333.0 ± 183.1	197.4 ±135.1	0.01
Thickness of arterial wall (μm)	880.4 ± 209.9	970.4 ± 310.3	n.s.
Cross-sectional luminal stenosis (%)	23.5 ± 4.7	20.7 ± 3.2	0.01
Type of plaque:			n.s.
- DIT	32 (26.7%)	44 (36.7%)	
- stable (FA)	88 (73.3%)	76 (63.3%)	
- unstable	0	0	



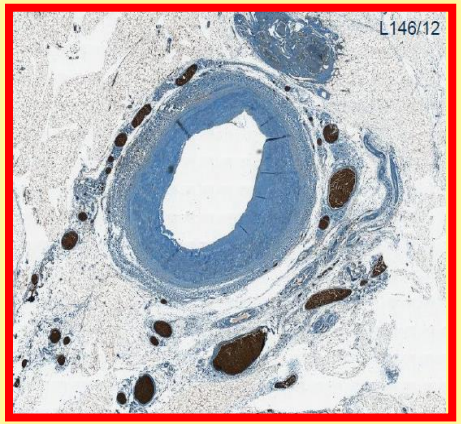
Renal artery in Hypertensive pt



Renal artery in Normotensive pt

Case Example

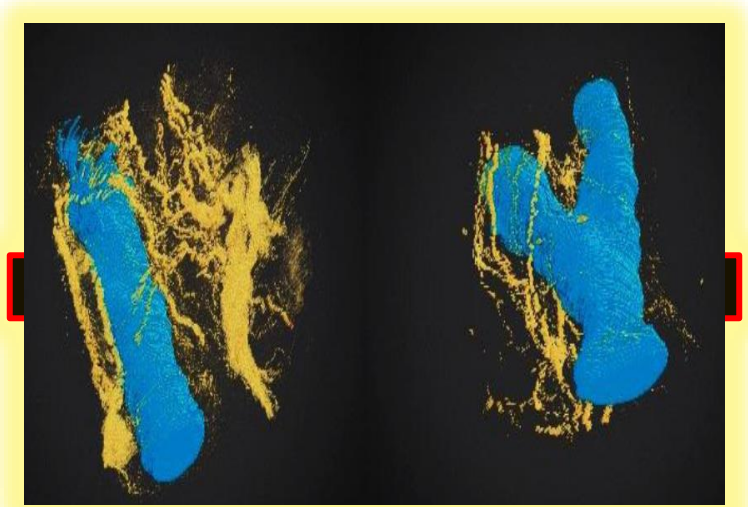
Normotensive



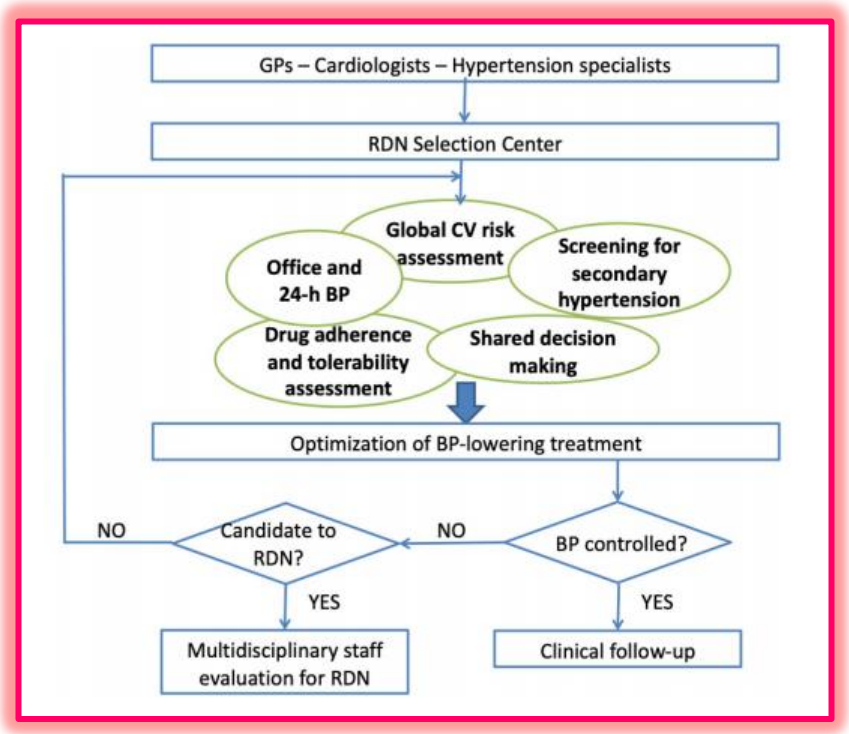
Hypertensive

Courtesy of A. Mauriello

Three Dimensional Nerve Reconstruction in Hypertensive vs. Normotensive Pts



Courtesy of A. Mauriello



SIIA Position Paper, High Blood Pressure &Cardiovascular Prevention 2020

Renal denervation: which patient?

Dynamic definition of the difficult-to treat hypertensive patient:

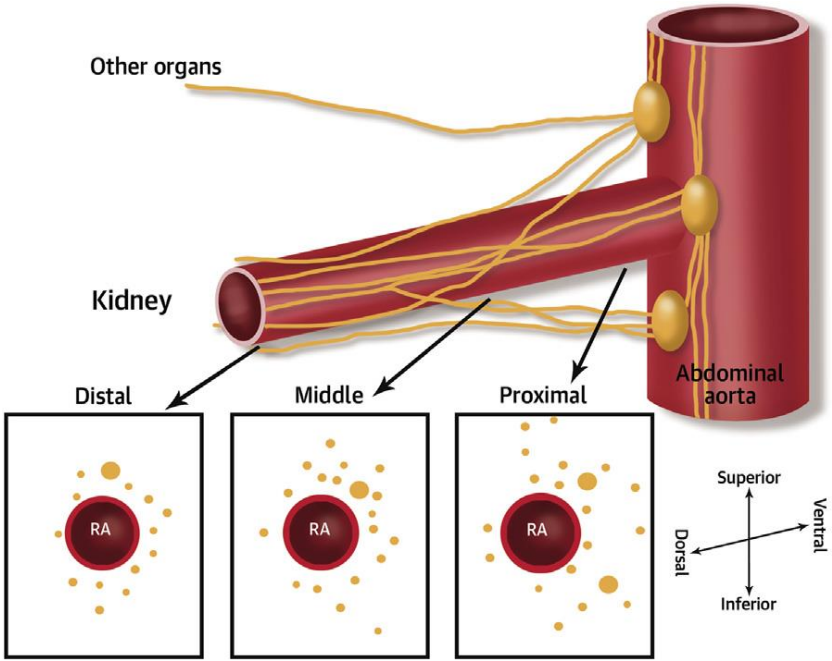
- Screening for secondary hypertension
- Prescription of a rational drug scheme
- Evaluation of drug tolerability and adherence
- Comorbidities / global CV risk
- Patient preferences

PROOF OF CONCEPT STUDIES IN HYPERTENSION: SPYRAL HTN-OFF MED PIVOTAL TRIAL

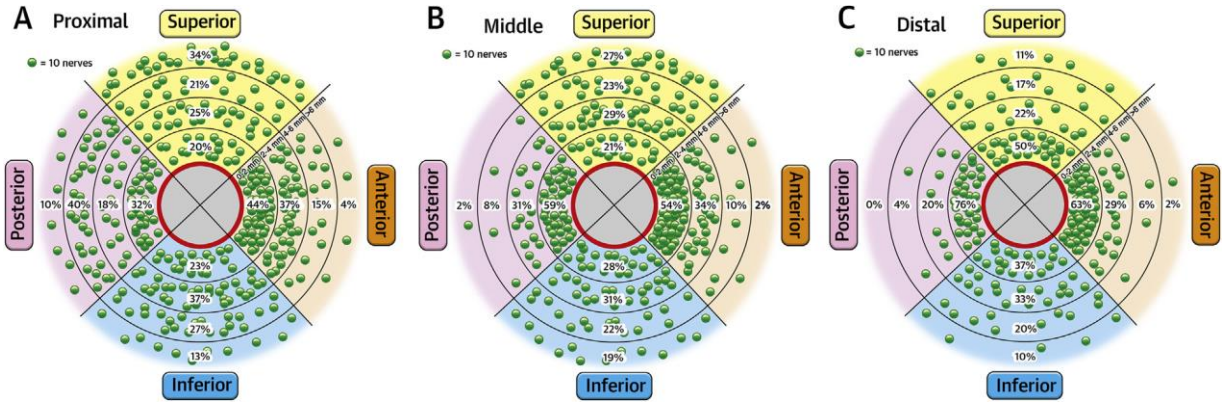
SAFETY RESULTS AT 3 MONTHS

n (%)	RDN (n = 165)	Sham Control (n = 165)
New myocardial infarction	0	0
New stroke	0	1 (0.6%)
Major Adverse Events	1 (0.6%)	0
Death	0	0
New onset end stage renal disease	0	0
Sign. embolic event resulting in end-organ damage	0	0
Renal artery perforation or dissection requiring intervention	0	0
Vascular complications	0	0
Hospitalization for hypertensive crisis/emergency	1 (0.6%)	0
Major bleeding (TIMI)	0	0
Serum creatinine elevation >50%	0	0

Townsend RR, et al. *Lancet*. 2017;390:2160–2170.


Other organs
Kidney
Abdominal aorta
Distal
Middle
Proximal
RA
RA
RA
Superior
Ventral
Dorsal
Inferior

Anatomic Assessment of Sympathetic Peri-Arterial Renal Nerves in Man

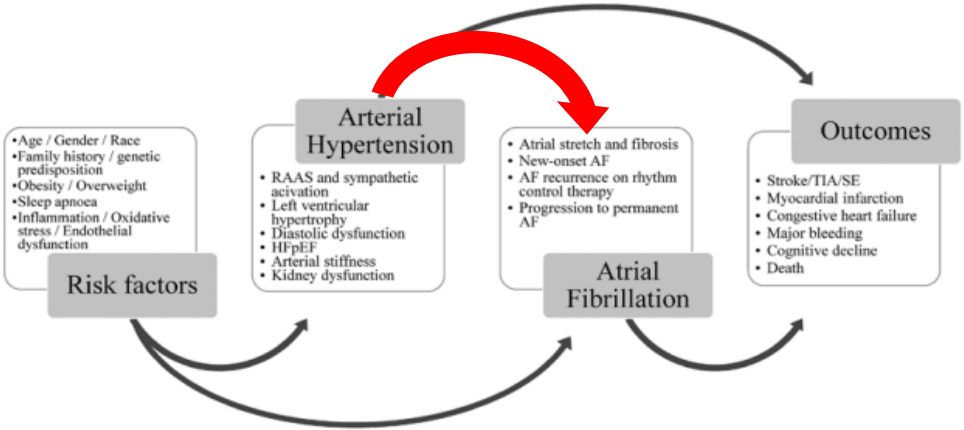


HTN3: Guppo Sham 5.2±1.4 farmaci al giorno a dosaggio pieno

… è eticamente corretto prevedere «a vita» una terapia con 5 o più farmaci a dosaggi così elevati da essere difficilmente gestibile per la presenza di effetti collaterali…

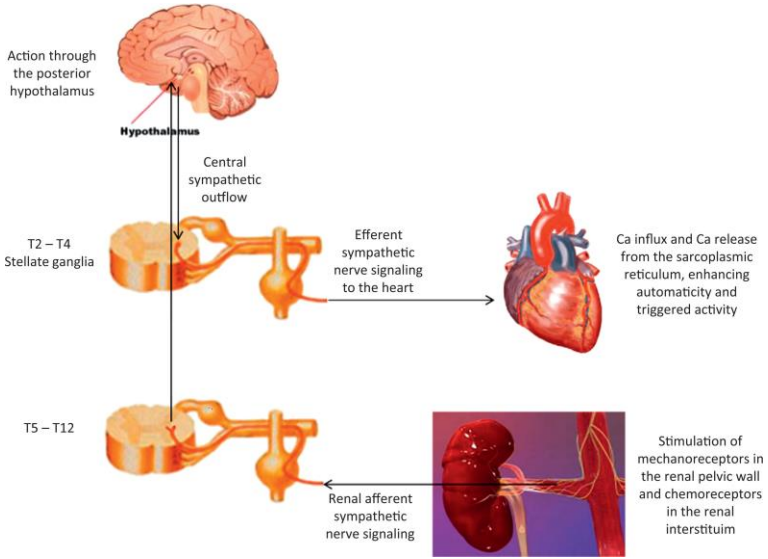
AF as a Symptom of Hypertension?

Hypertension and atrial fibrillation (AF) axis in the cardiovascular disease continuum.



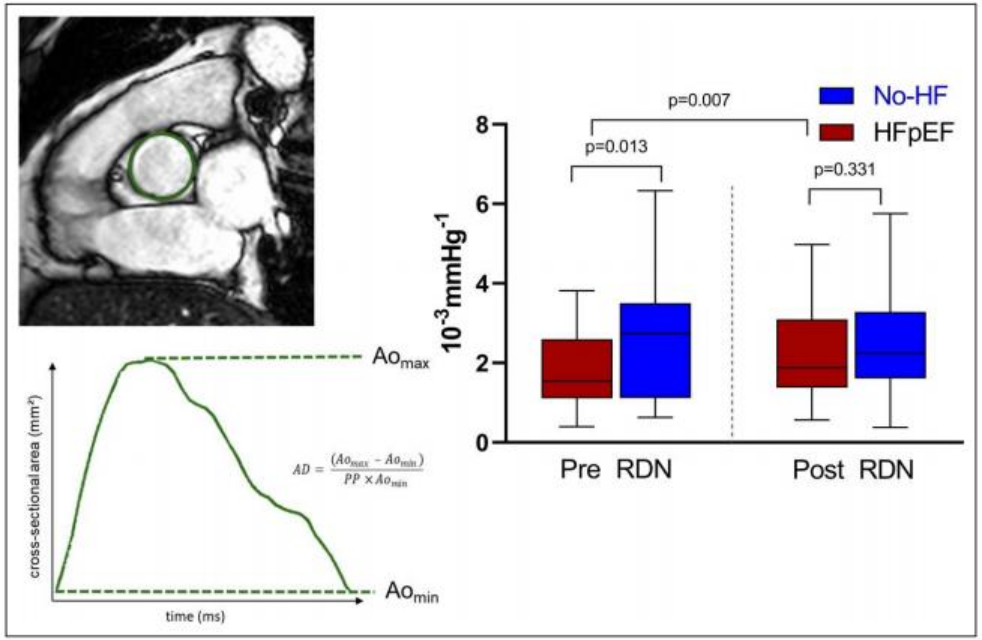
Mikhail S. Dzeshka. Hypertension 2017, Volume: 70, Issue: 5, Pages: 854-861

Arrhythmia triggering through the reno-cardiac axis



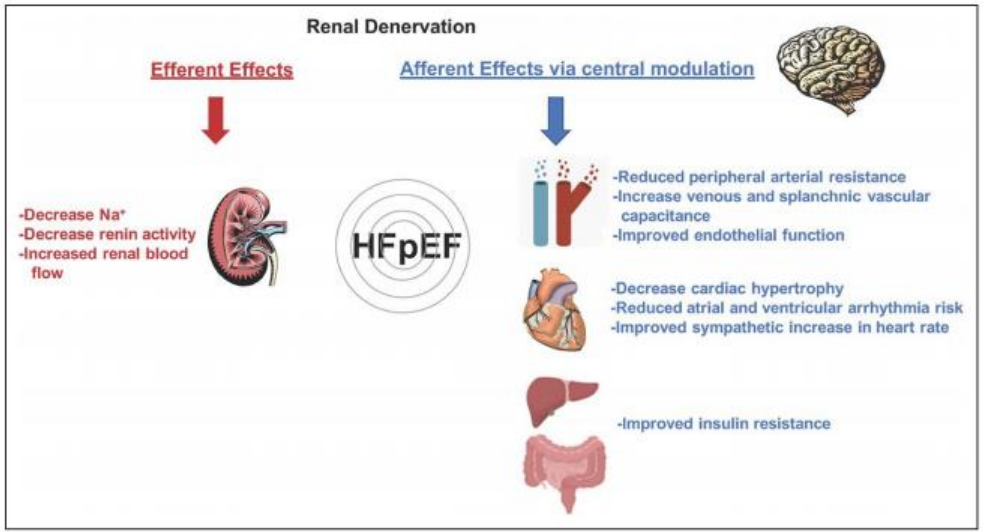
Nammas et al, Heart Rhythm 2016;13:2388–2394.

Changes in aortic distensibility.



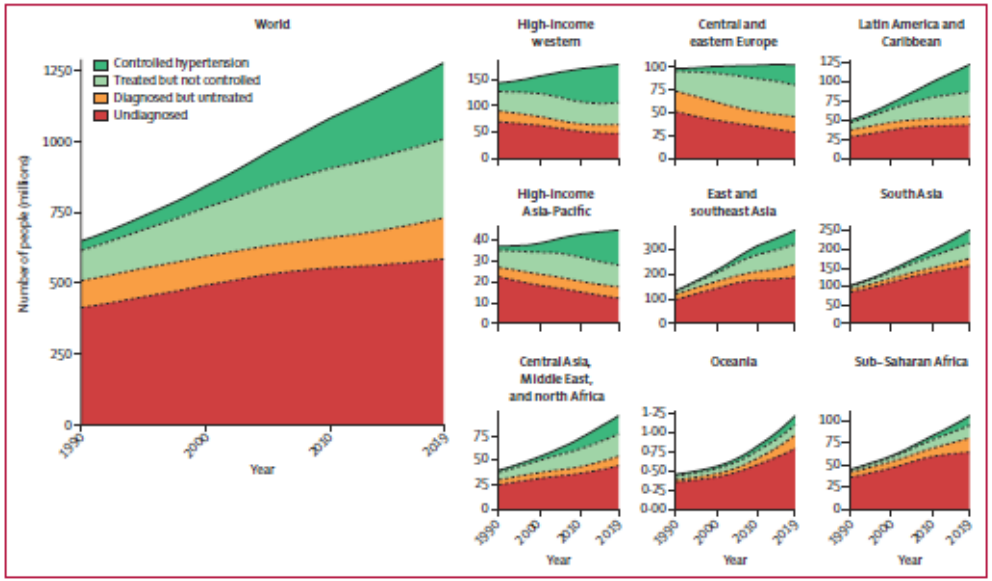
Kresoja KP, et al Circ Herart Fail 2021

Contribution of the sympathetic nervous system to heart failure with preserved ejection fraction (HFpEF)



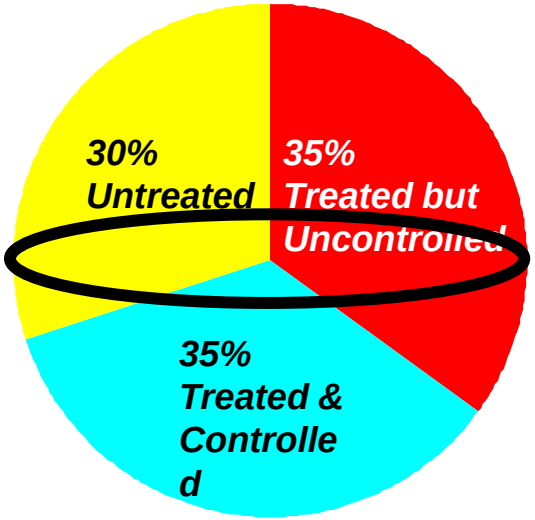
Fudim M, et al. Circ Heart Fail 2021

Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants



Lancet 2021 Aug 24;

Hypertension Epidemiology

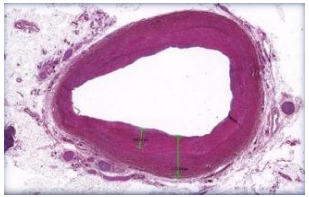


- High prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6 B by 2025
- Single largest contributor to death worldwide
- Every 20 mmHg increase in BP correlates with a doubling of 10-year cardiovascular mortality
- Dramatically increases risk of stroke, heart attack, heart failure, & kidney failure
- Only half of all treated hypertensives are controlled to established BP targets
- Resistant Hypertension ~ 10%

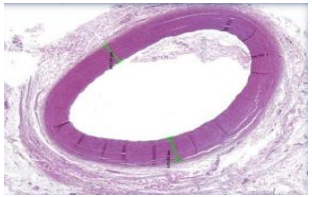
Chobanian et al. Hypertension. 2003;42(6):1206–1252.

Morphometric Evaluation of Renal aa

	Hypertensive RS = 120	Normotensive RS = 120	P
Maximum thickness of intima (μm)	333.0 ± 183.1	197.4 ±135.1	0.01
Thickness of arterial wall (μm)	880.4 ± 209.9	970.4 ± 310.3	n.s.
Cross-sectional luminal stenosis (%)	23.5 ± 4.7	20.7 ± 3.2	0.01
Type of plaque:			n.s.
- DIT	32 (26.7%)	44 (36.7%)	
- stable (FA)	88 (73.3%)	76 (63.3%)	
- unstable	0	0	



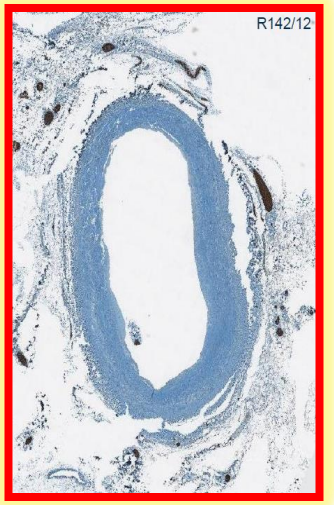
Renal artery in Hypertensive pt



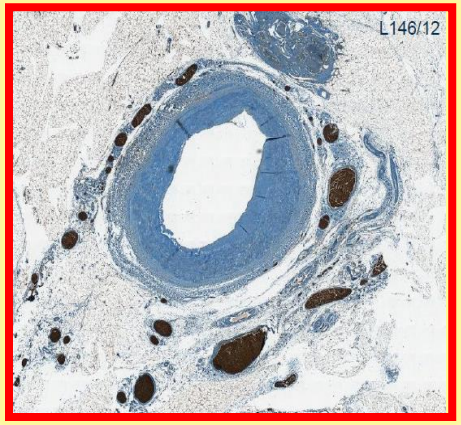
Renal artery in Normotensive pt

Sangiorgi G, et al. TCT 2012

Case Example



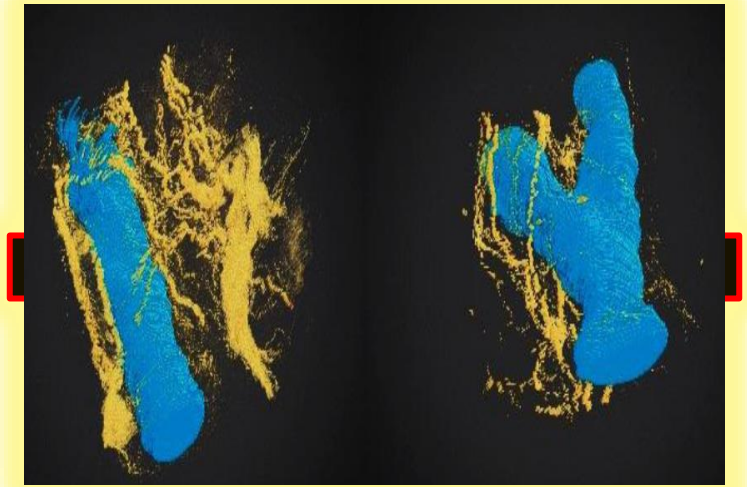
Normotensive



Hypertensive

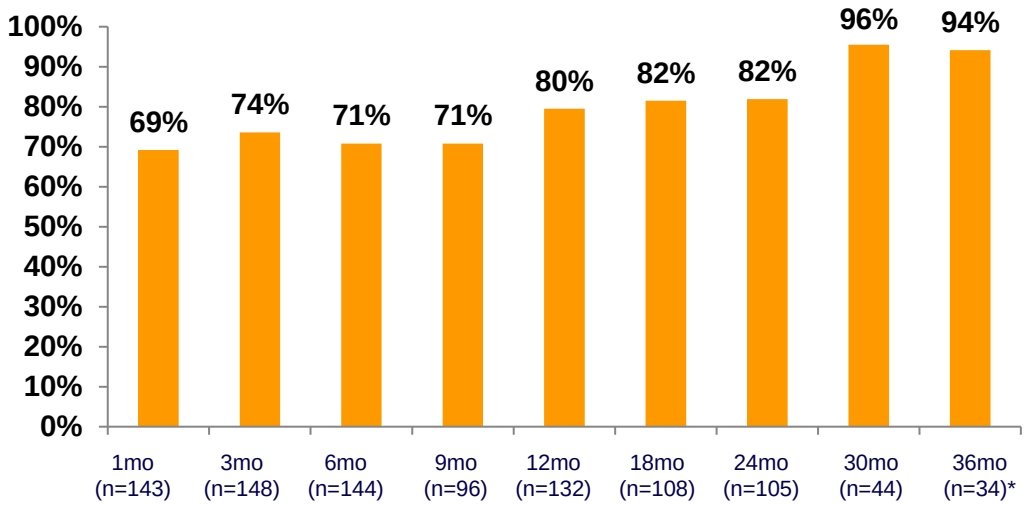
Courtesy of A. Mauriello

Three Dimensional Nerve Reconstruction in Hypertensive vs. Normotensive Pts



Courtesy of A. Mauriello

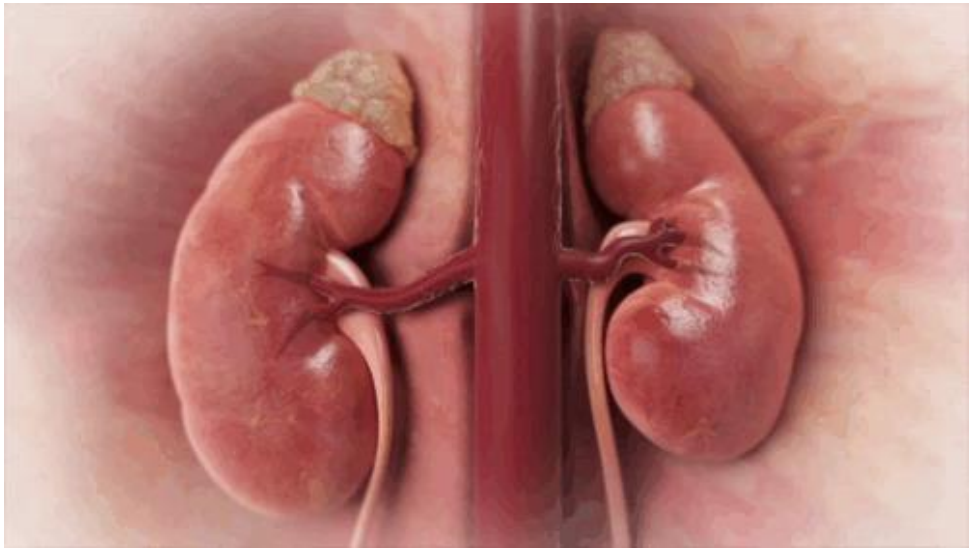
Symplicity HTN-1: Responder Rate Does Not Decrease Over Time – This Clinical Benefit of RDN is Sustained

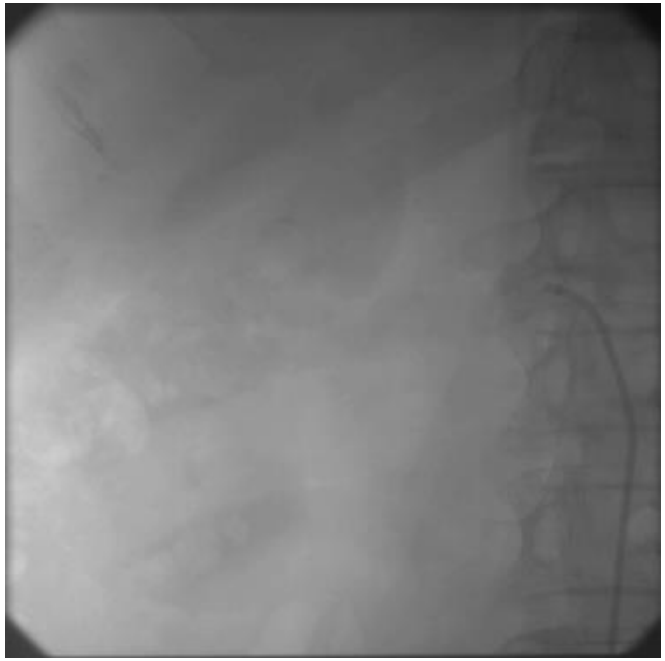


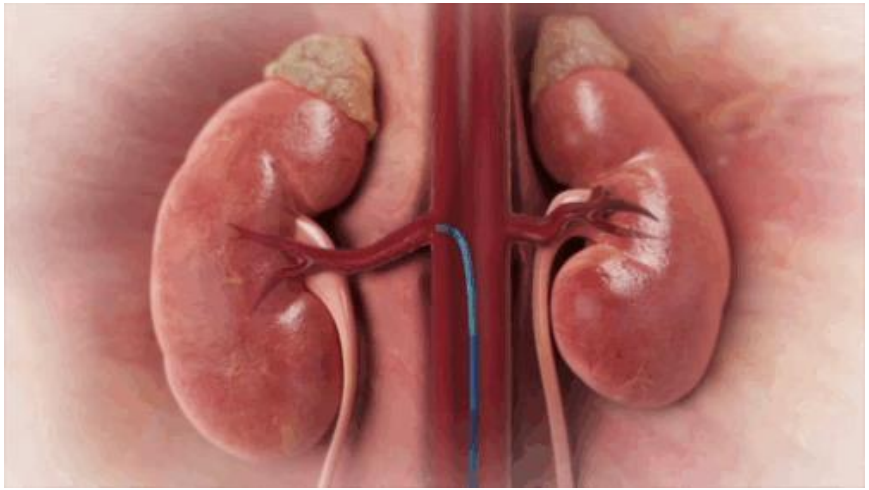
Responder was defined as an office SBP reduction ≥10 mmHg

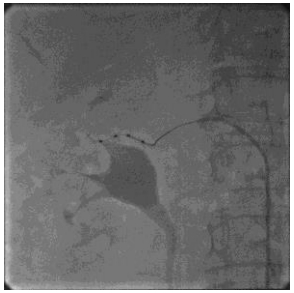
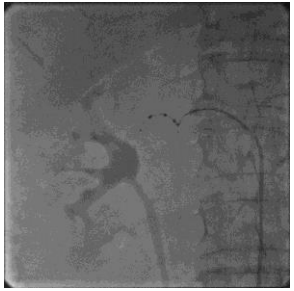
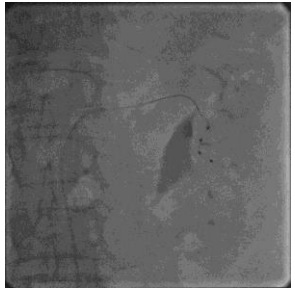
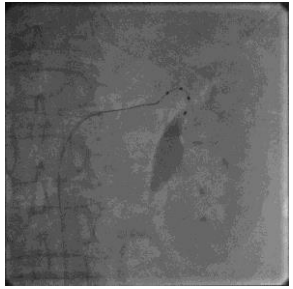
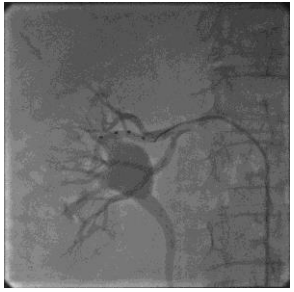
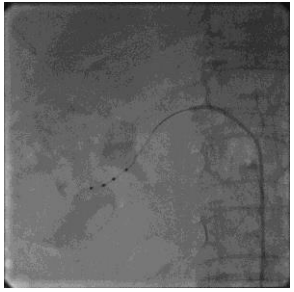
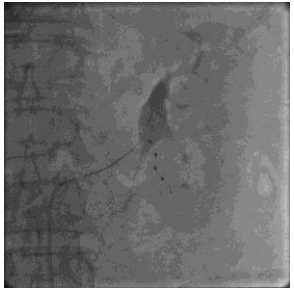
* Number of patients represents data available at time of data-lock

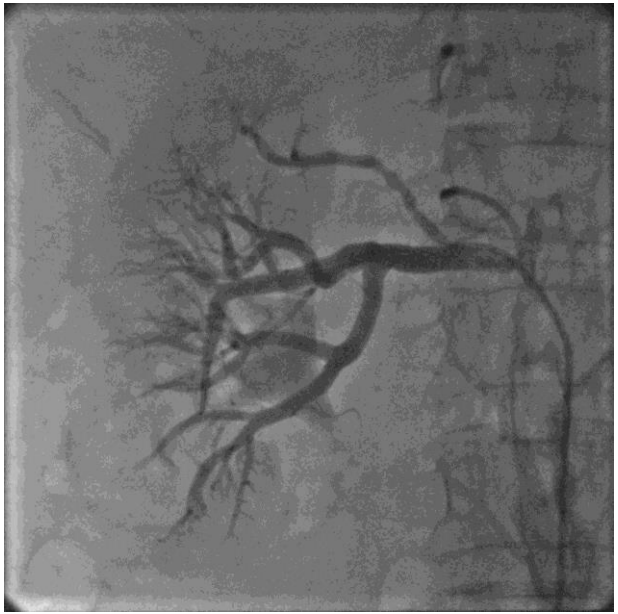
Schlaich, M, TCT 2012

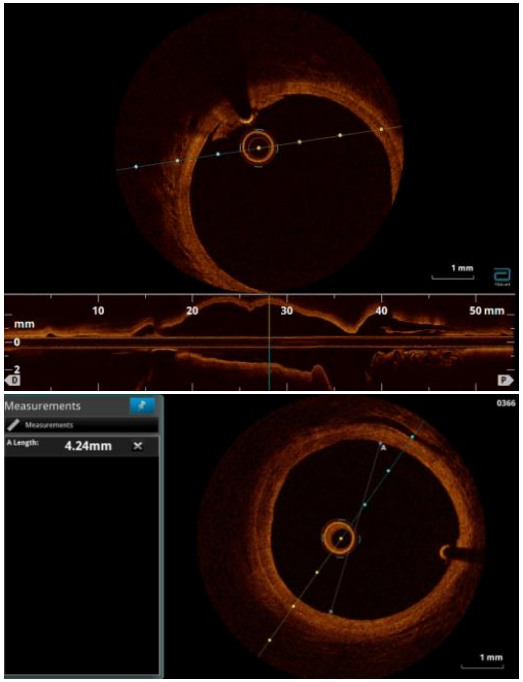






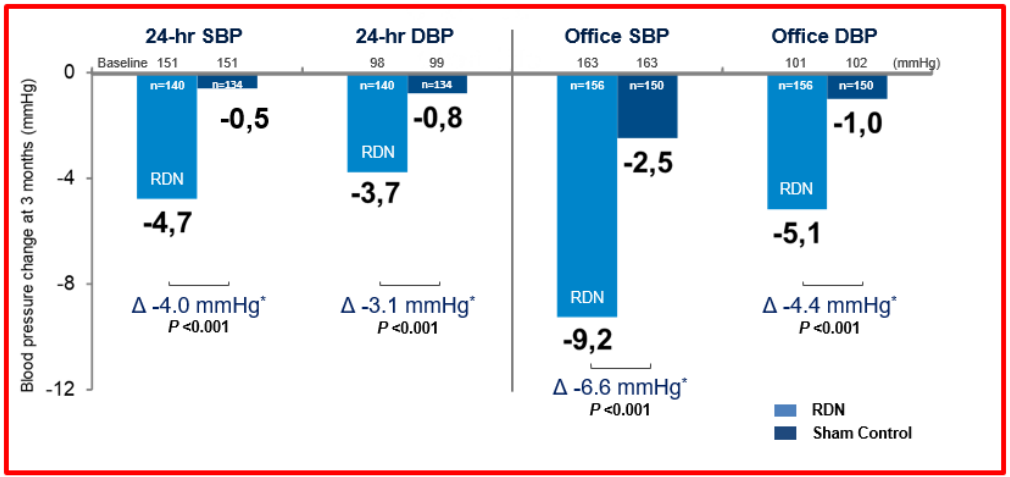











1 mm
10
20
30
40
50 mm
mm
0
2
Measurements
Measurements
A Length:
4.24mm
0366
A
1 mm

PROOF OF CONCEPT STUDIES IN HYPERTENSION: SPYRAL HTN-OFF MED PIVOTAL TRIAL

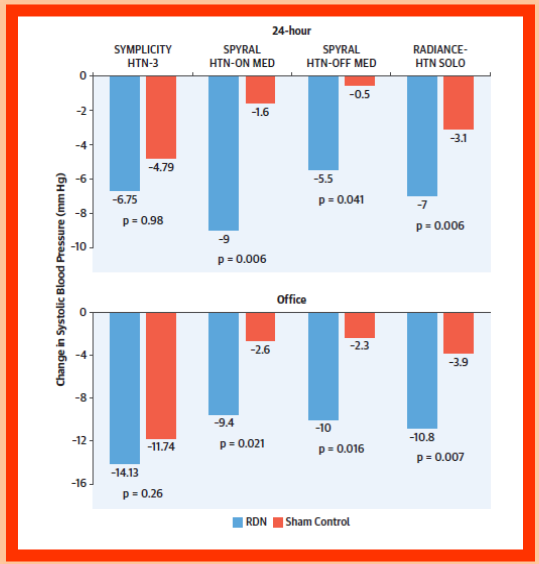
BLOOD PRESSURE CHANGE FROM BASELINE AT 3 MONTHS



Rdn showed significant reductions in all bp measures

Townsend RR, et al. *Lancet*. 2017;390:2160–2170.

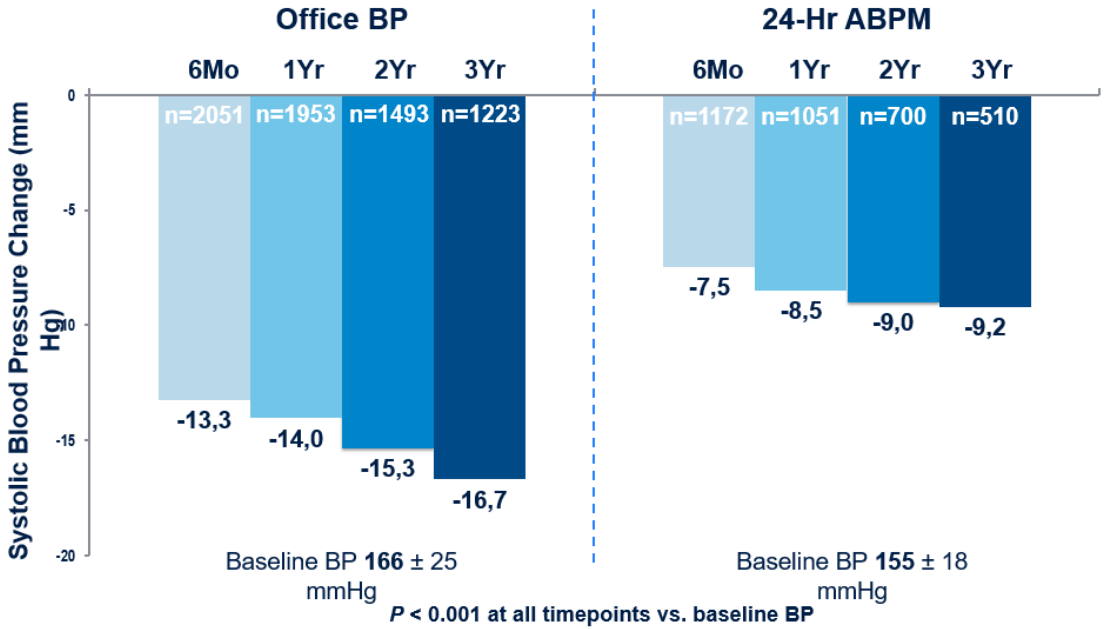
Mean Changes in Systolic BP in 4 Prospective, randomized, sham-controlled trials of renal denervation



Weber, MA, et al. JACC Intv. 2019;12 (12):1095-105

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

BP CHANGE IN HIGH-RISK PATIENTS WAS SIMILAR TO OVERALL COHORT



Mahfoud et al, PCR e-Course 2020

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

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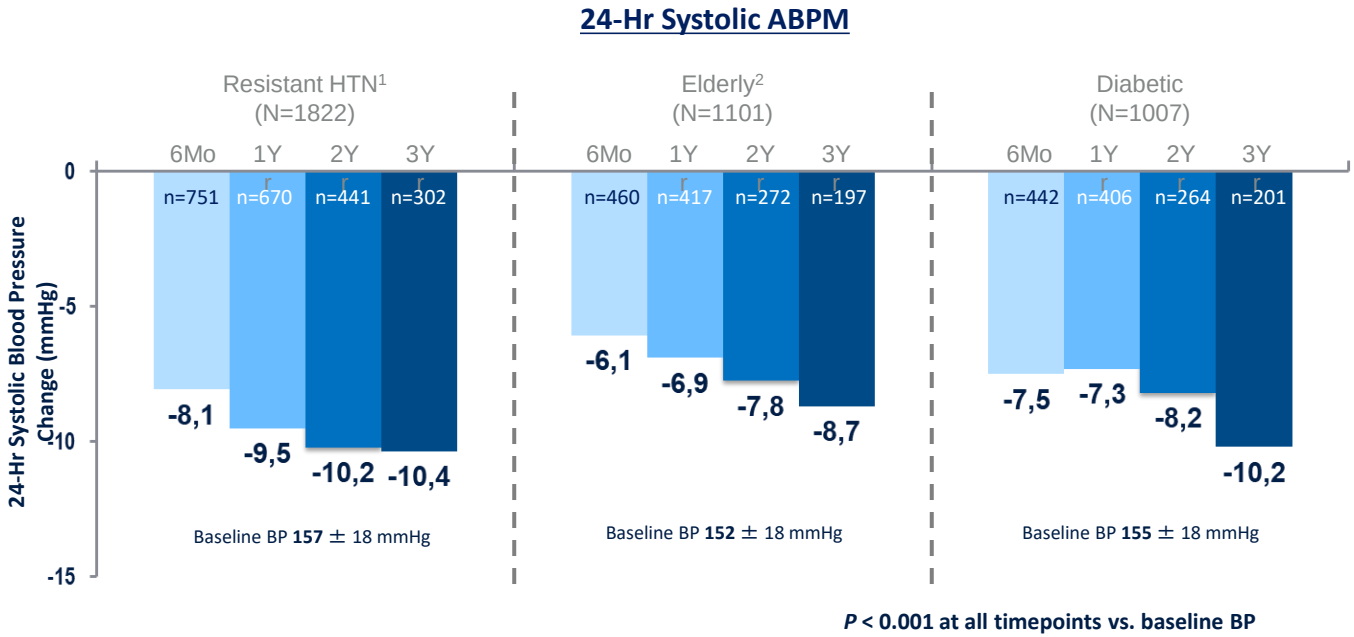
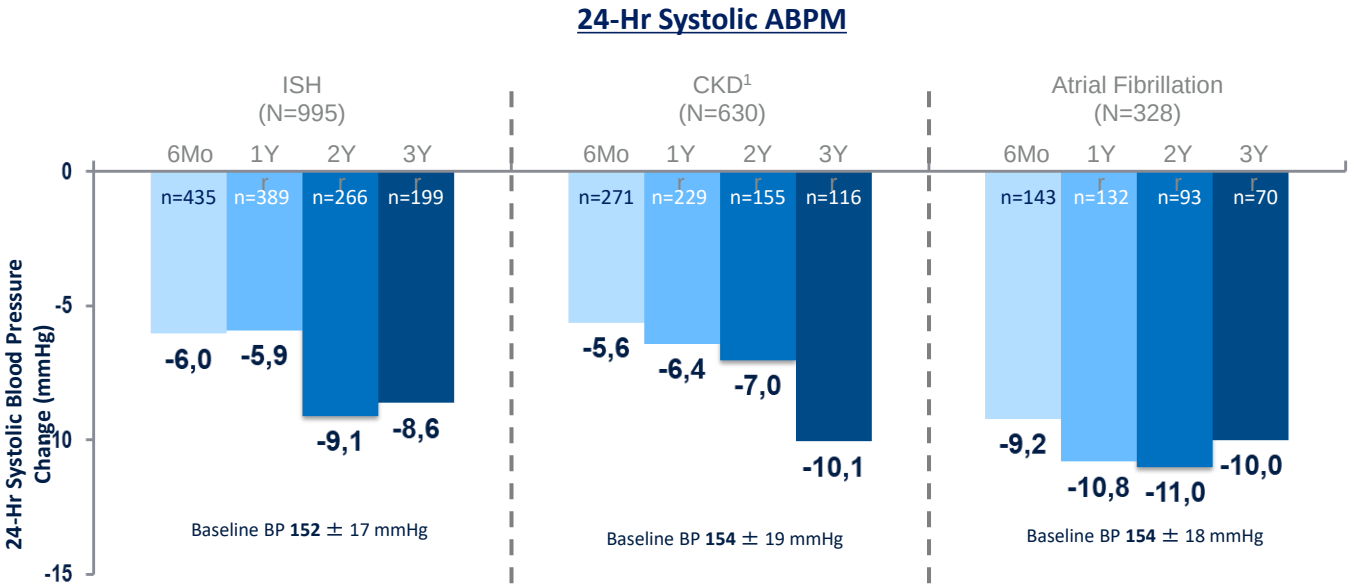


***P* < 0.001 at all timepoints vs. baseline BP**

Mahfoud et al, EuroPCR 2019.

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

BP CHANGE IN HIGH-RISK PATIENTS WAS SIMILAR TO OVERALL COHORT



***P* < 0.001 at all timepoints vs. baseline BP**

Mahfoud et al, EuroPCR 2019.

Renal denervation: which patient?

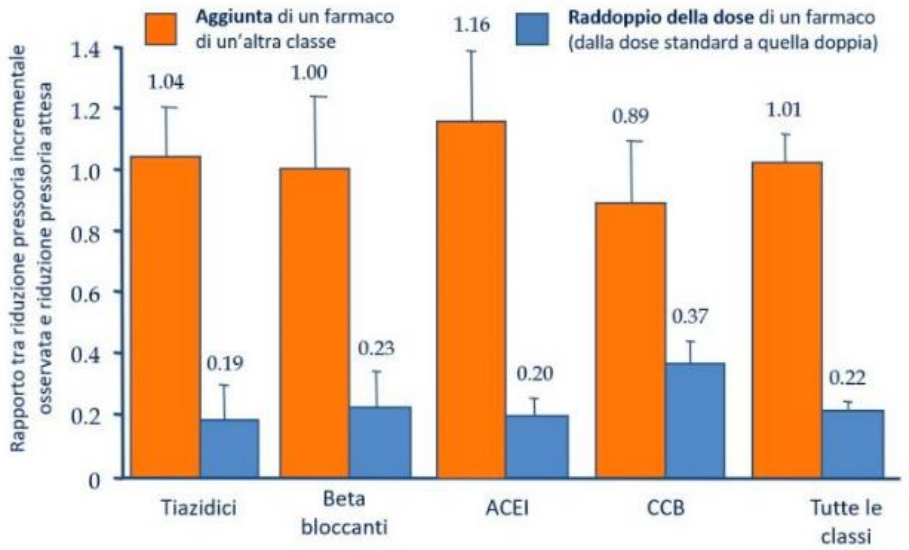
Dynamic definition of the difficult-to treat hypertensive patient:

- Screening for secondary hypertension
- Prescription of a rational drug scheme
- Evaluation of drug tolerability and adherence
- Comorbidities / global CV risk
- Patient preferences

PATIENT PERSPECTIVES

- Choice over therapy
- Patients desire to stay drug free - **absolute**
  - More time before starting meds
  - Taking less meds
  - Taking meds which affect lifestyle less

Razionale per la terapia di combinazione: due farmaci sono più efficaci di uno



Wald et al. Am J Med 2009;122:290-300.

the relationship between BP and risk of AF may be causal (Genetic analysis)

Mendelian Randomization analysis identified a potentially causal association between Hypertension and AF

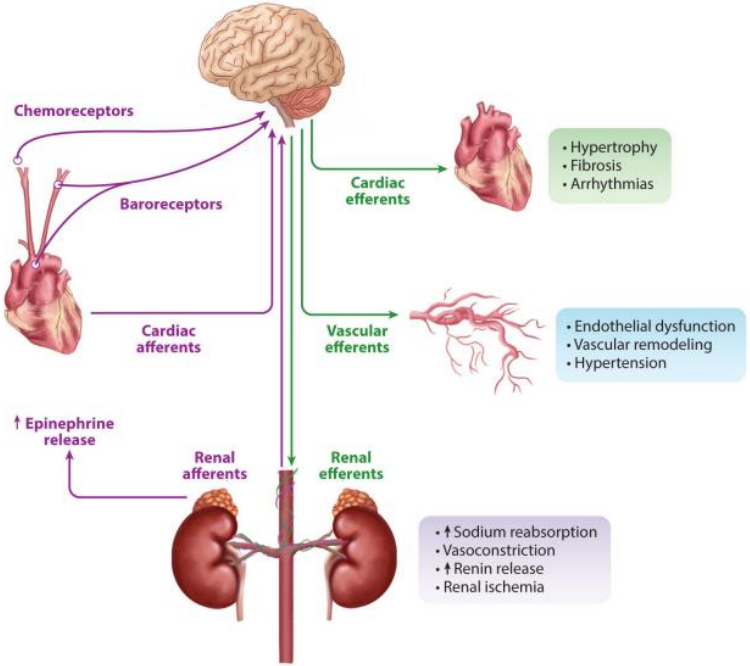
Table I Mendelian randomization estimates between blood pressure traits and atrial fibrillation

		Inverse-variance weighted method				Maximum likelihood				MR-Egger regression						Median-based method			
										Intercept			Slope						
BP trait	N	OR	95% CI		P-value	P-value for heterogeneity	OR	95% CI	P-value	P-value for heterogeneity	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
SBP	266	1.018	1.012–1.024		1E-08	<0.0001	1.019	1.012–1.025	<0.001	<0.0001	1.006	1.002–1.010	0.006	0.998	0.982–0.013	0.763	1.016	1.009–1.023	<0.001
DBP	345	1.026	1.016–1.035		1.5E-<0	<0.0001	1.027	1.016–1.037	<0.001	<0.0001	1.001	0.997–1.005	0.597	1.02	0.997–1.043	0.083	1.021	1.012–1.030	<0.001
PP	283	1.014	1.001–1.028		0.033	<0.0001	1.016	1.000–1.031	0.05	<0.0001	0.998	0.993–1.004	0.533	1.024	0.991–1.058	0.158	1.015	1.005–1.025	0.004

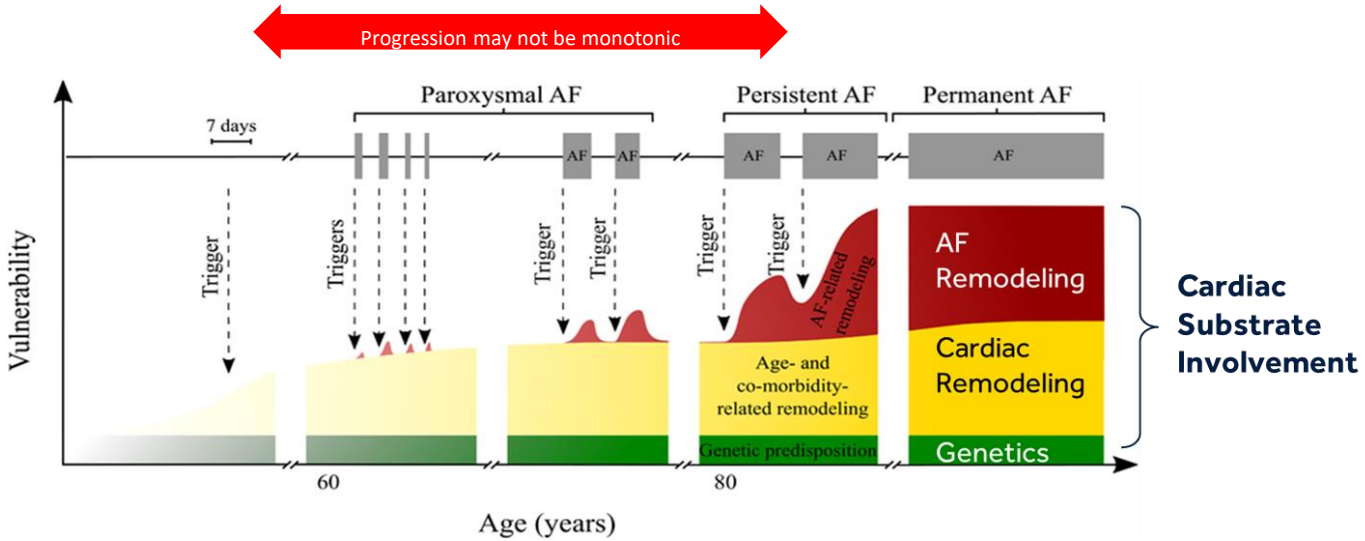
BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; MR, mendelian randomization; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SNPs, single-nucleotide polymorphisms; N, # of SNPs used in MR.

Georgiopoulos, Tsioufis K, et al. European Journal of Preventive Cardiology, 2021doi:10.1093/eurjpc/zwab005

Role of the sympathetic nervous system in heart failure

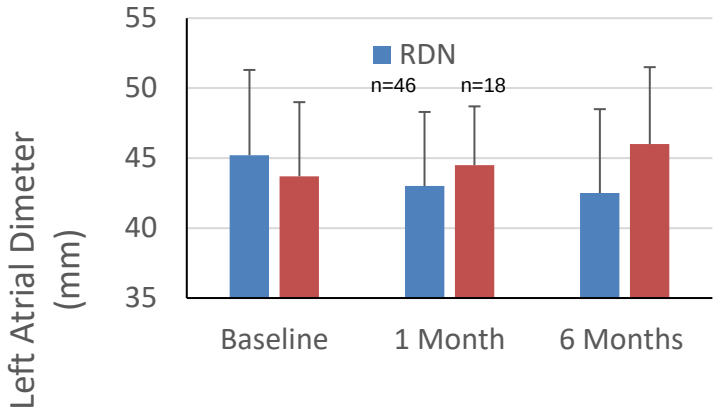


Progression of AF *Theory* (“AF Begets AF”)



Renal denervation associated with left atrial remodeling in refractory hypertensive humans

Renal denervation reduced LV mass, atrial size and improved diastolic function compared to a matched control group.



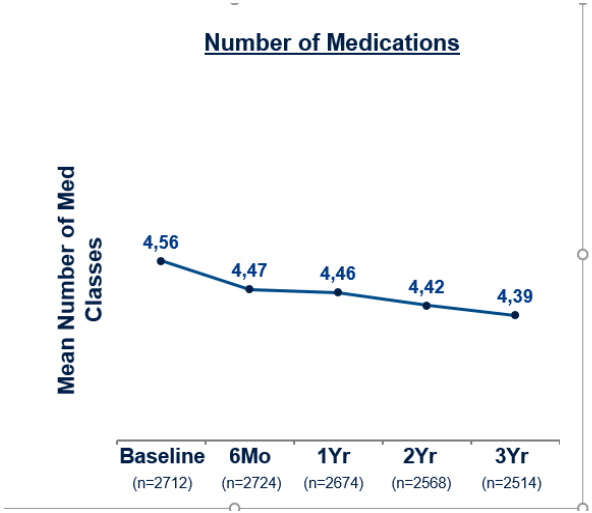
P for trend:
RDN: P<0.001
Control: P=0.49

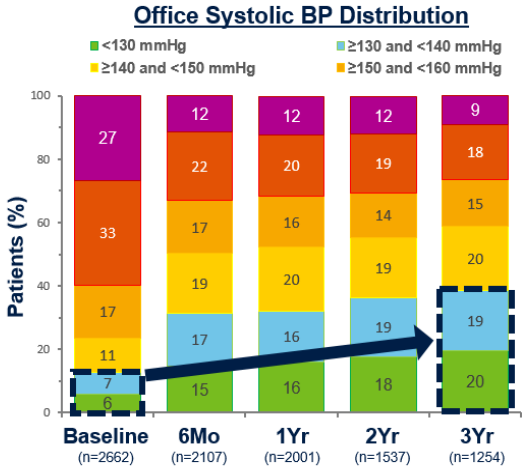
RDN vs. Control; P=0.02

Brandt MC, et al. *J Am Coll Cardiol*. 2012;59:901–9

GLOBAL SYMPLICITY REGISTRY: 3-YEARS FOLLOW-UP

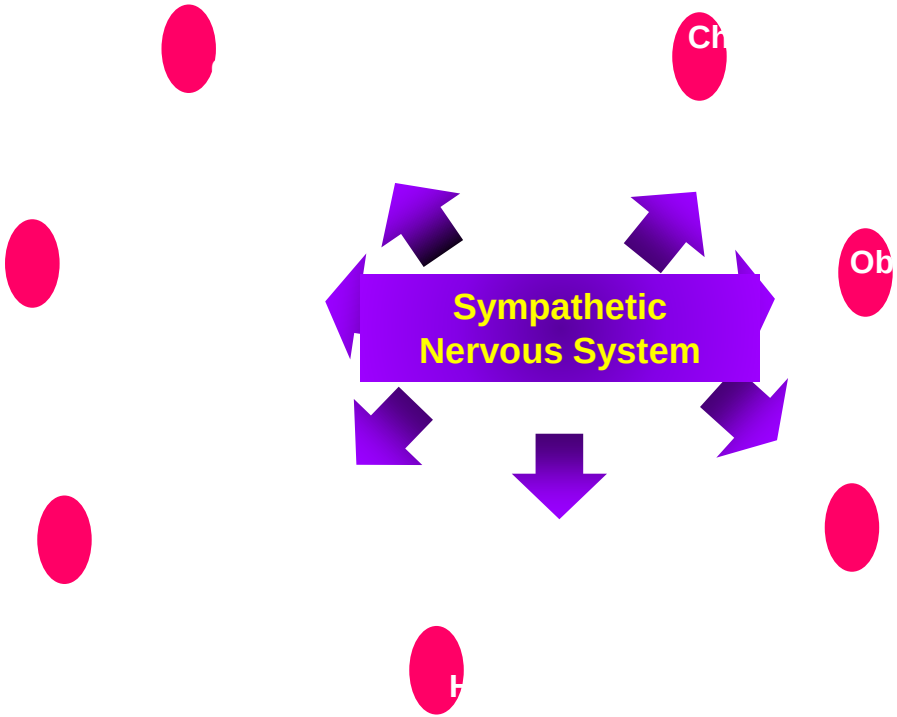
RDN decreased blood pressure without increasing medication burden



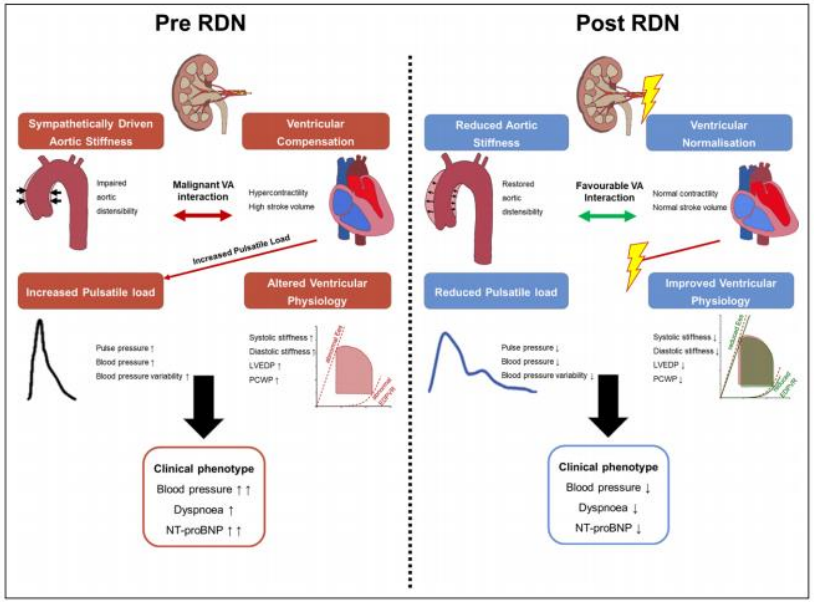


Mahfoud et al, PCR e-Course 2020

Target-organ Damage and SNS

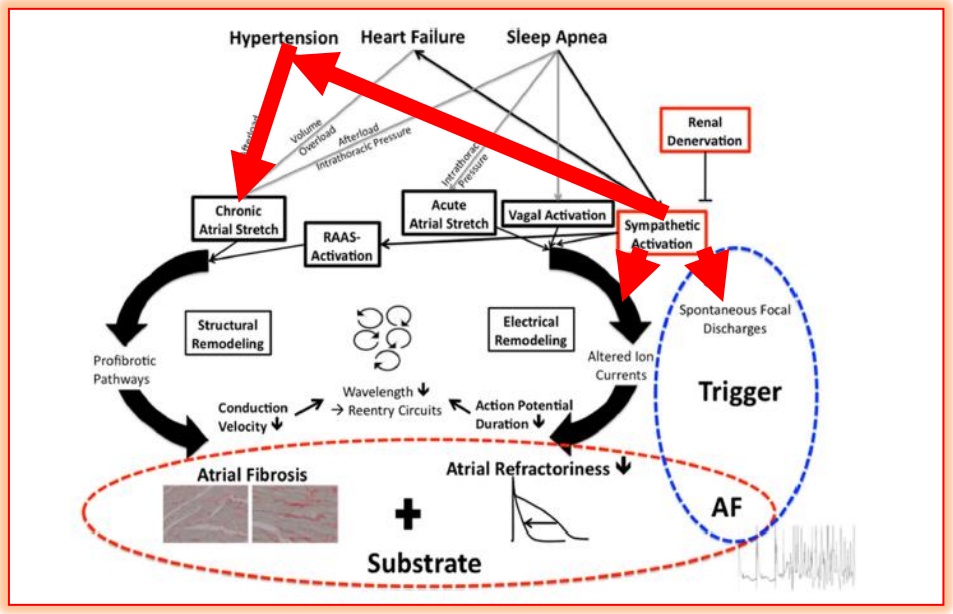


Proposed beneficial mechanism of renal sympathetic denervation in patients with heart failure with preserved ejection fraction (HFpEF)



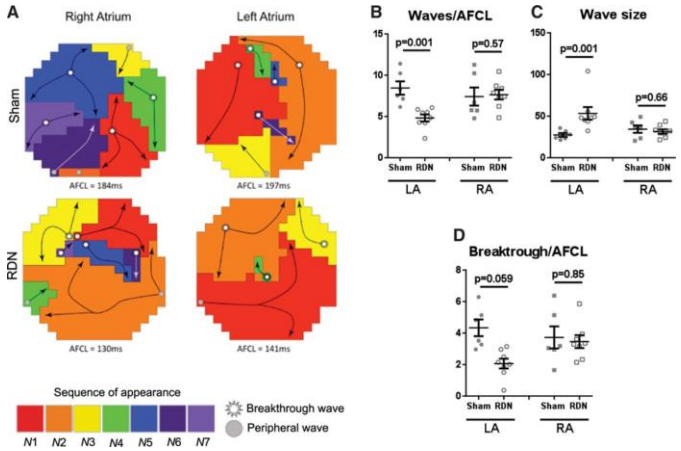
Kresoja KP, et al Circ Heart Fail 2021

High Sympathetic Tone Can Impact Both Triggers and Substrate Required to maintain AF



Linz et al. *Clin Res Cardiol*. 2014;103:765-74

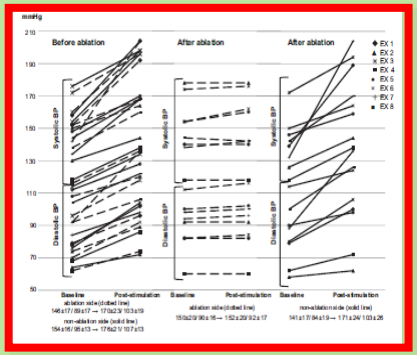
RDN and Atrial Electrical Remodeling in Goats



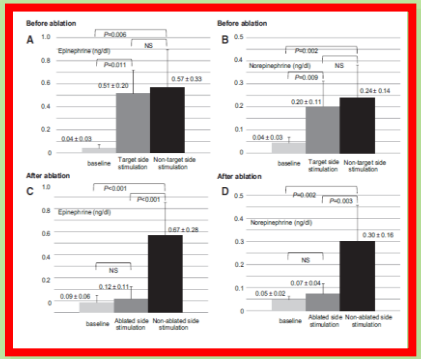
Linz D, et al. Circ Arrhythm Electrophysiol 2015

Blood Pressure and Autonomic Responses to Electrical Stimulation of the Renal Arterial Nerves Before and After Ablation of the Renal Artery

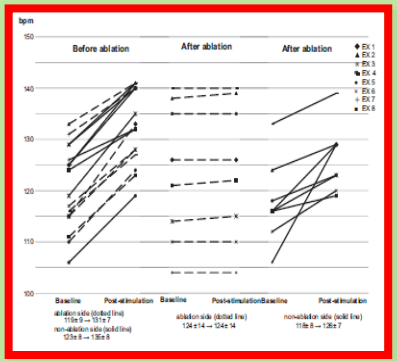
Blood Pressure Responses



Serum Cathecolamine Analysis



Heart Rate Response



Chinushi M et al. Hypertension. 2013; 61:450-456