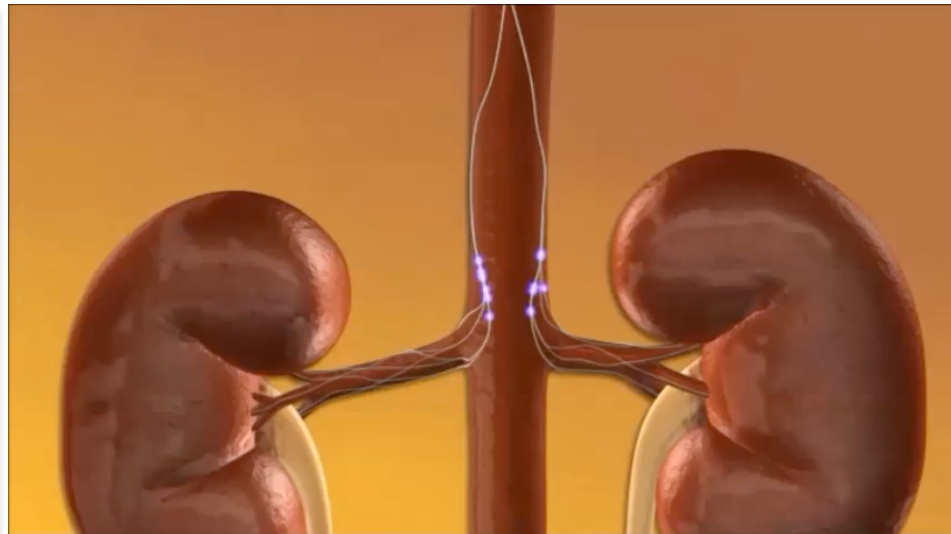
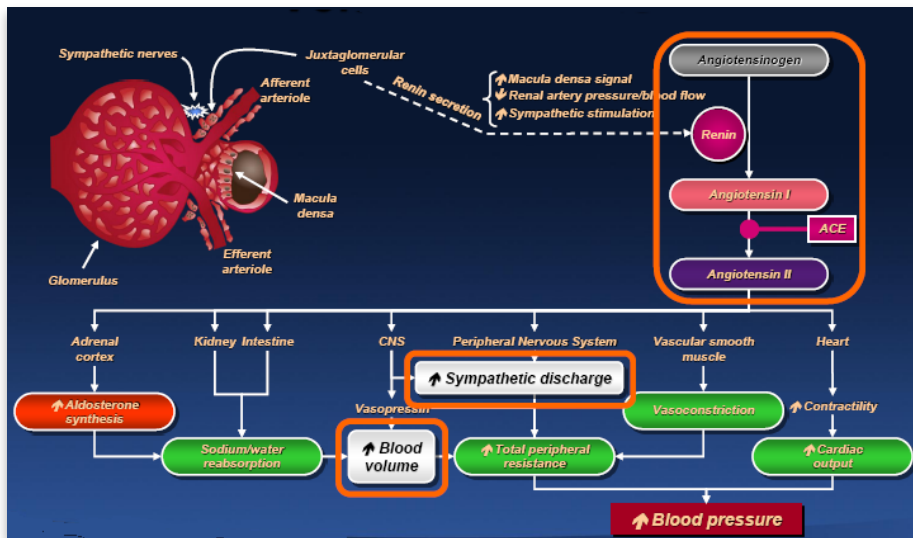


La denervazione renale: una terapia complementare per il trattamento dell'ipertensione difficile da trattare

Marco Bernardi, MD, MSc
Ospedale S. Maria Goretti, Latina

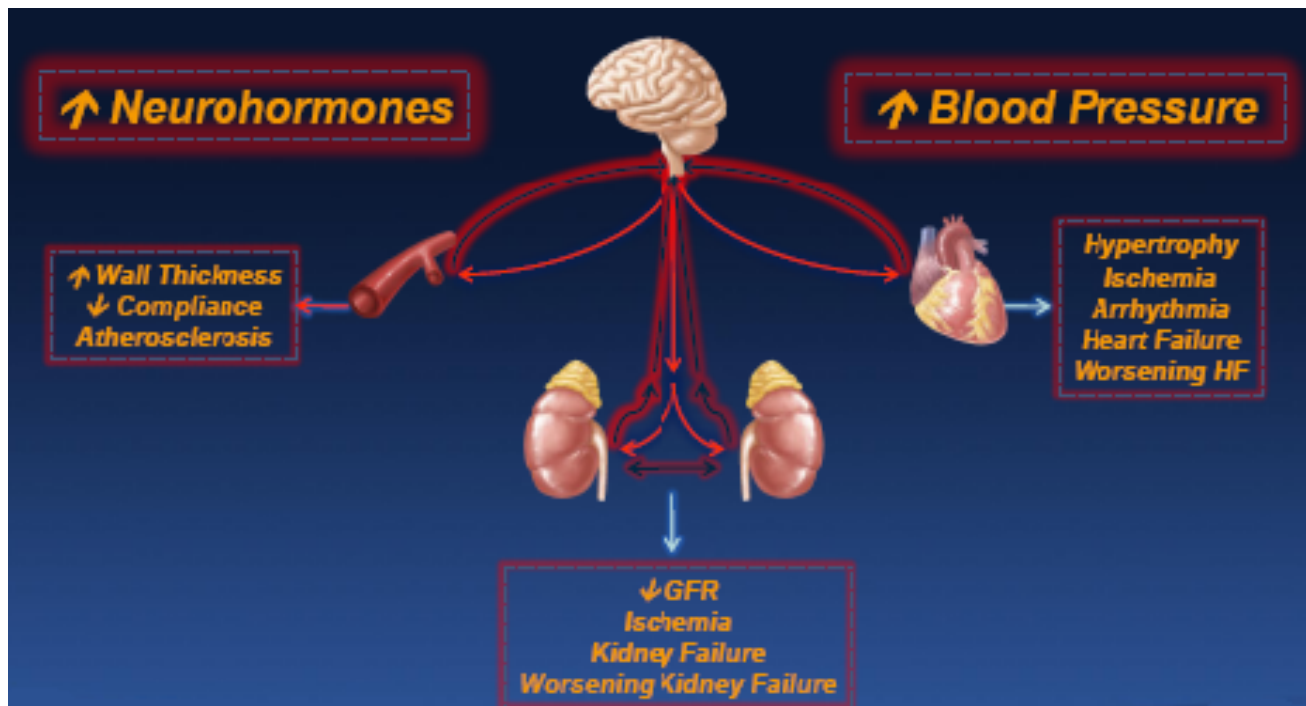




Saseen JJ, Carter BL. *Pharmacotherapy A Pathophysiologic Approach*. 6th ed. New York, NY: McGraw-Hill Professional



Chronic effect of increased sympathetic nerve activity



Schlaich MP, et al.
Hypertension. 2009



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

*Schlaich MP, et al. New
Engl J Med. 2009*

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 com-

plications. 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 μ g 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

N ENGL J MED 361:9 NEJM.ORG AUGUST 27, 2009



Changes in underlying physiology consistent with renal denervation (RDN)

Domain	Parameter	Baseline	Post-RDN
Clinical	Office BP (mmHg)	161/107	127/81 (12 mo)
Sympathetic activity	Renal NE spillover (ng/min)	72 / 79	↓48% / ↓75%
	Whole-body NE spillover	—	↓42%
	MSNA (bursts/min)	56	19 (12 mo)
Neurohormonal / renal	Renin activity (μg/L/h)	0.30	0.15
	Renal plasma flow (ml/min)	719	1126
Cardiac remodeling	LV mass (g)	184	169
Therapy	Antihypertensive drugs	7	5

Schlaich MP, et al.
New Engl J Med. 2009



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 SYMPPLICITY HTN-3 Investigators*



2018 ESC/ESH Guidelines for the management of arterial hypertension

Device-based therapies for hypertension

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

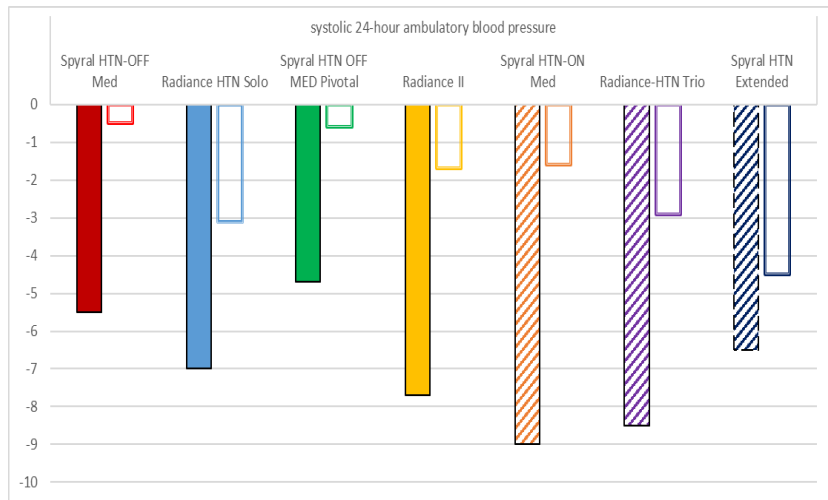
RCT = randomized controlled trial.

^aClass of recommendation.

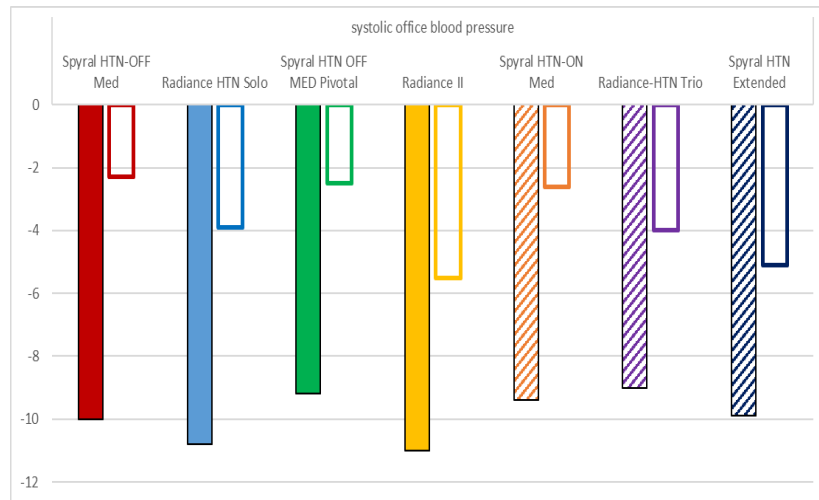
^bLevel of evidence.



Systolic 24h ABPM (-4.1 mmHg)



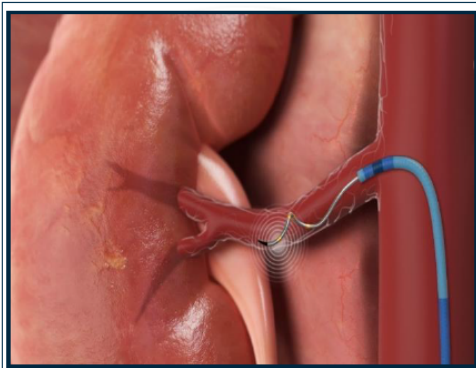
Systolic office BP (-5.7 mmHg)



Meta-analysis of sham-controlled RCTs on RDN

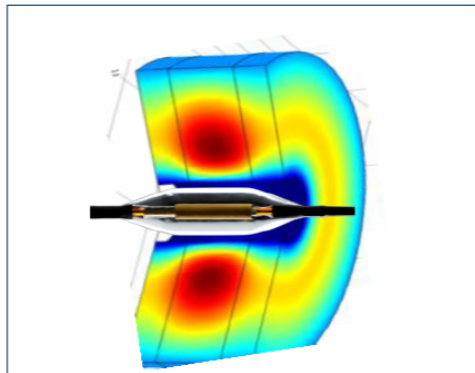
Schmieder RE, et al. Presented ESH 2023





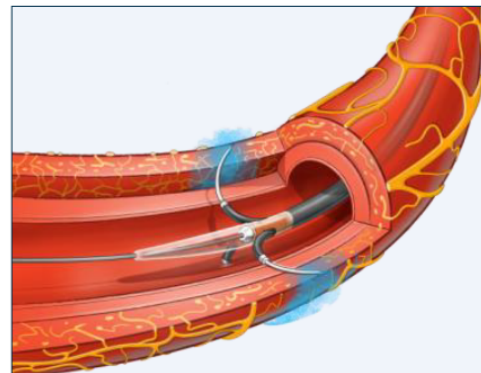
***Radiofrequency
denervation***

- SPYRAL HTN-ON MED
- SPYRAL HTN- OFF MED
- Iberis-HTN



***Ultrasound
denervation***

- RADIANCE-HTN SOLO
- RADIANCE-HTN TRIO
- RADIANCE II



***Alcohol mediated
denervation***



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 <u>resistant hypertension</u> 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 <u>increased CVD risk and uncontrolled hypertension on fewer than three drugs</u> , 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

2024

McEvoy JW, et al. Eur Heart J. 2024



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 contraindicated!)
- No extensive vascular damage
- High/very high lifetime cardiovascular risk
- Patient preferences



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
- Paroxysmic/persistent atrial fibrillation
- High / very high lifetime cardiovascular risk
- Patient preferences



Stabile E, et al. G Ital Cardiol 2023





European Society
of Hypertension, Guidelines for Arterial
Hypertension 2023

Understanding the patients' perspective, exploring their preference and expectation is crucial prior to RDN. Benefits and risks of RDN need to be addressed in a shared-decision making process. In this regard, instead of pharmacotherapy to have the elevated roughly 1/3 of hypertensive patients were prone to prefer RDN BP controlled.¹

Mancia G. et al. *Journal of Hypertension* 2023



European Society of
Cardiology Guidelines for
Hypertension 2024

Renal denervation may be considered if the patients express a preference to undergo renal denervation after a tailored shared decision-making process. The shared decision-making process requires that the patients are fully informed about the benefits, limitations, and risks associated with renal denervation.²

McEvoy et al. *European Heart Journal*
2024



AMERICAN
COLLEGE of
CARDIOLOGY



American
Heart
Association.

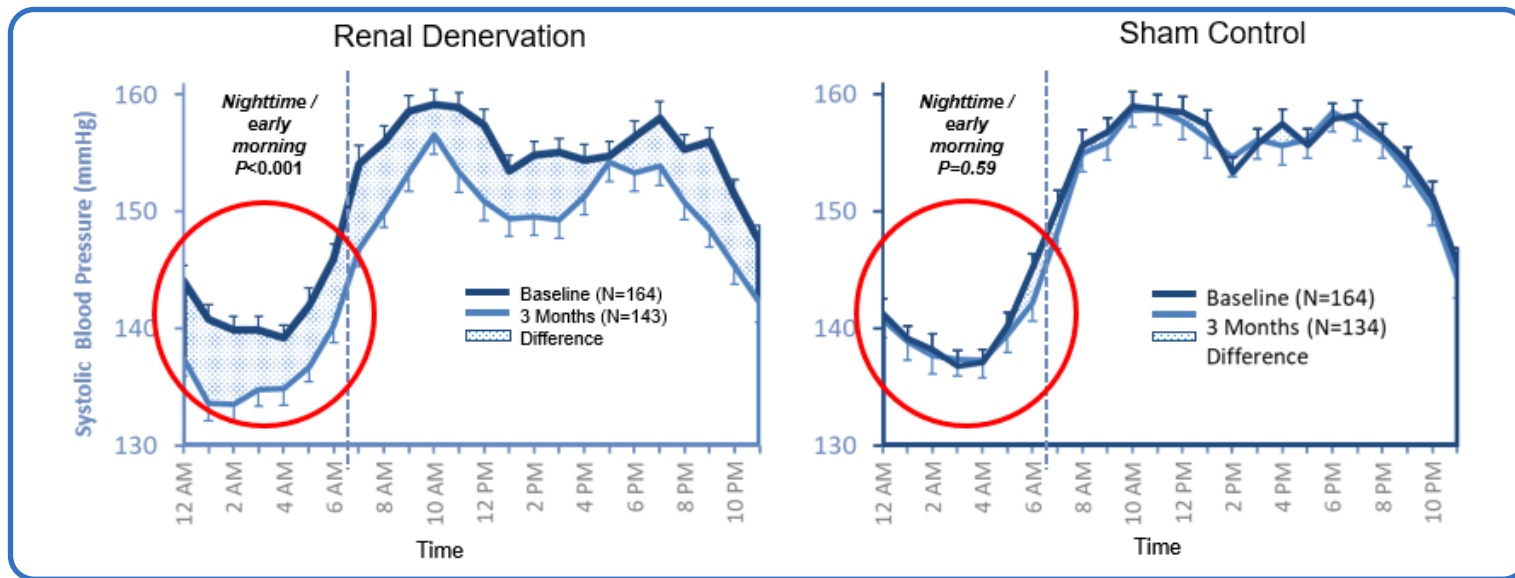
American College of Cardiology |
American Heart Association
Guidelines 2025

For patients with hypertension for whom RDN is contemplated, the benefits of lowering BP and potential procedural risks compared with continuing medical therapy should be discussed as part of a **shared decision-making process** to ensure **patients choose the therapy that meets their expectations**.³

Jones DW, et al. *J Am Coll Cardiol*, 2025



RDN: an always on effect on 24-hour BP lowering



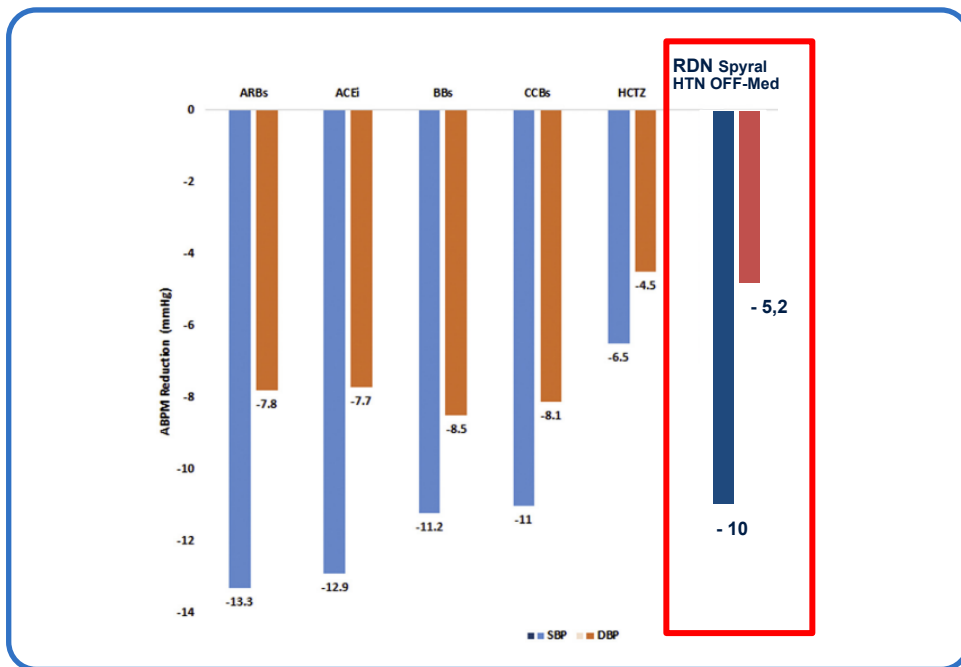
The nighttime / early morning period is a “high-risk zone” associated with increased risk for stroke and cardiovascular events

Böhm et al. The Lancet, 2020.

Amodeo C, Blood Pressure Monit, 2014

Boggia J, The Lancet, 2007

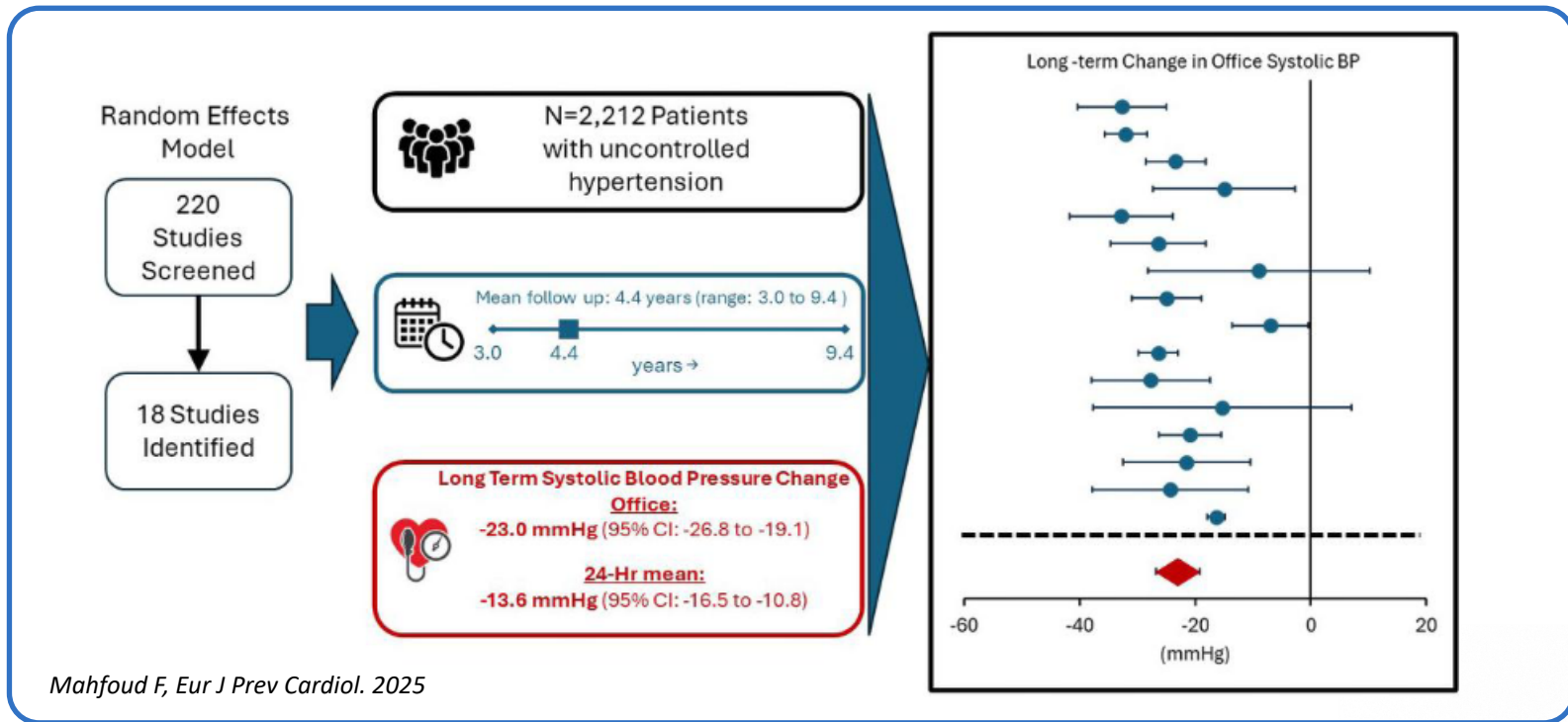




Messerli F, et al. J Am Coll Cardiol Intv. 2020



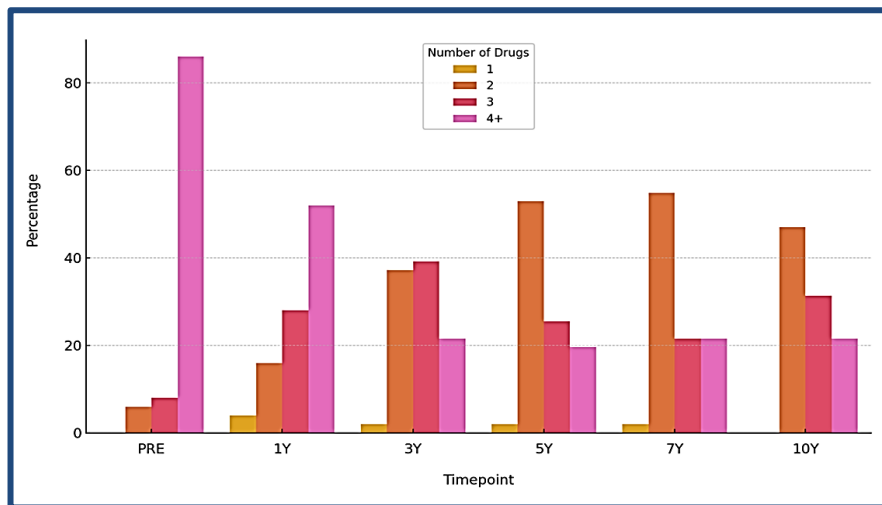
RDN: long term results



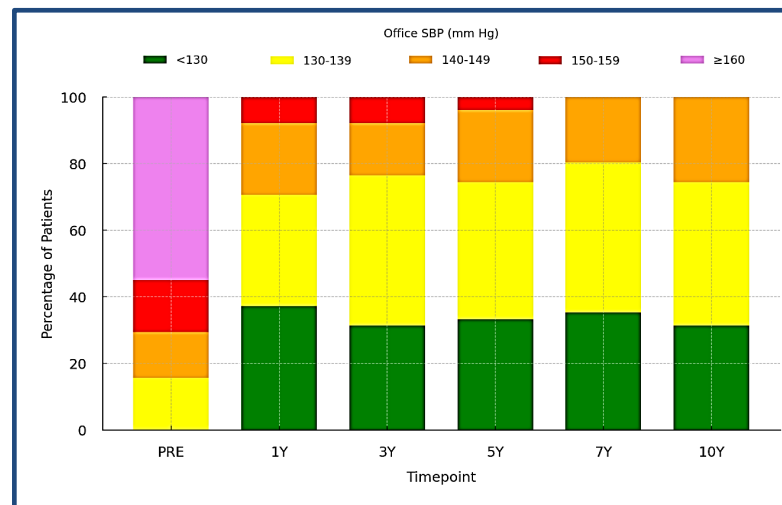
Mahfoud F, Eur J Prev Cardiol. 2025



Changes in intensity of anti-hypertensive therapy from baseline to 10-year follow-up



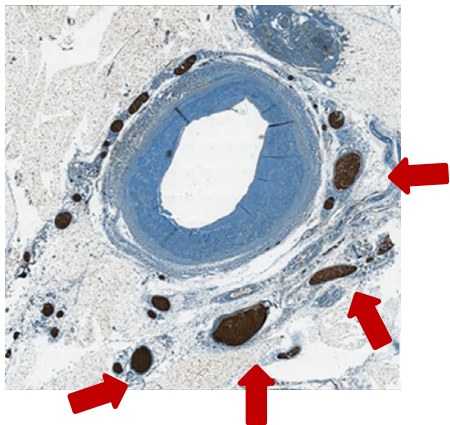
Distribution of office systolic blood pressure (SBP) levels over time



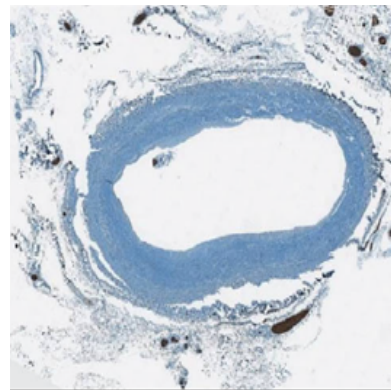
Versaci F. et al. Under revision



Morphological findings of peri-adventitial nerves



DIAL group



CTRL group

*Mauriello A, et al.
Heart Assoc. 2015*



Journal of Nephrology (2025) 38:2053–2065
<https://doi.org/10.1007/s40620-025-02406-2>

POSITION PAPERS AND GUIDELINES

The role of renal denervation for the treatment of hypertension in patients with chronic kidney disease: a position paper of the Italian Society of Nephrology

Sandro Feriozzi¹  · Yuri Battaglia^{2,3} · Calogero Lino Cirami⁴ · Concetta Gangemi⁵ · Gaetano La Manna⁶ · Loreto Gesualdo⁷ · Maria Lorenza Muiesan⁸ · Antonello Pani⁹ · Federico Pieruzzi^{10,11} · Flavio Ribichini¹² · Stefano Taddei¹³ · Stefano Bianchi¹⁴

Table 5 Recommendations for renal denervation in chronic kidney disease

Patient categories	Scale of recommendation	Comments
Patients with eGFR > 40 ml/min/m ²	☆☆☆	Safe and effective procedure
Patients with eGFR < 40 ml/min/m ²	☆☆	Safe and effective after a thorough clinical assessment of the patient
Patients on dialysis	☆☆	Safe and effective after a thorough clinical assessment of the patient and the dialytic schedules
Patients with a kidney transplant	☆	Extremely limited evidence

☆ semiquantitative indication marker



GISE procedural data show regional growth from 2024 to 2025, yet national volumes remain very small.

318

procedures in 2024

386

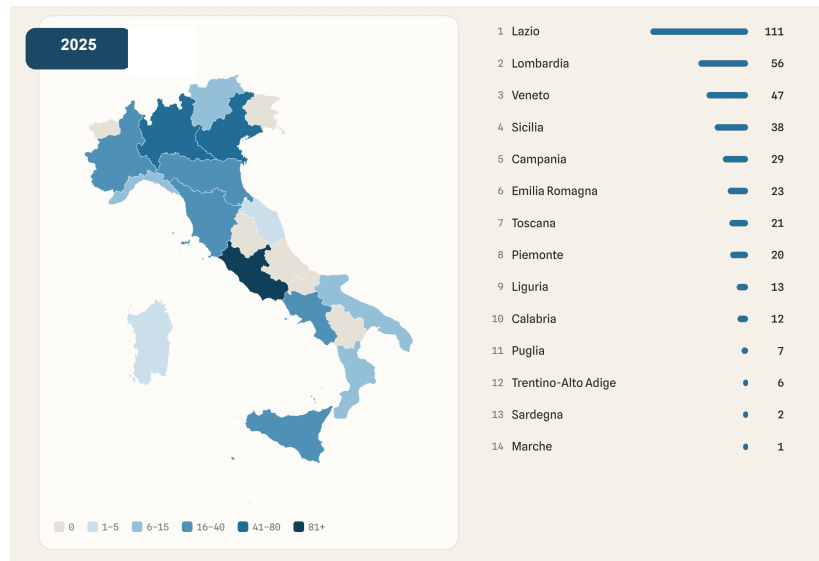
procedures in 2025

+21%

relative increase

78→87

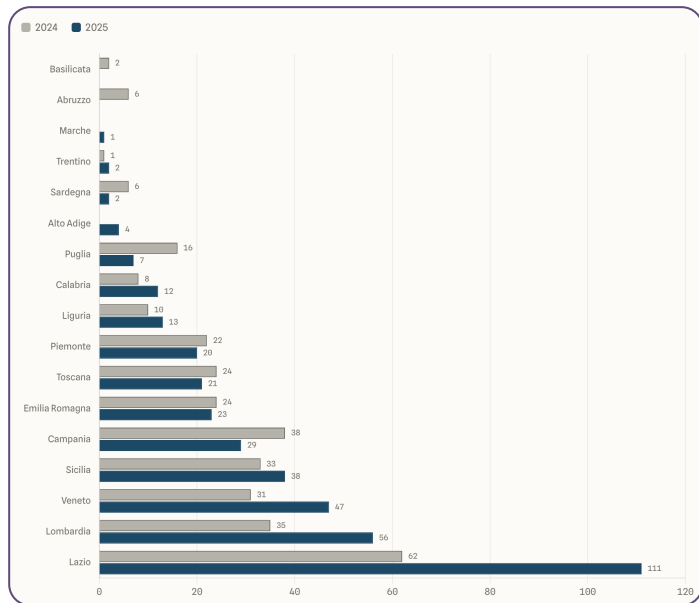
active centers



Source: GISE renal denervation procedural data, 2024–2025. Maps show procedures per Italian region with a common color scale.

The mismatch: millions with hypertension, hundreds of procedures

Regional activity increased in several areas, but RDN remains a low-volume therapy compared with the hypertension burden.



2.4

RDN procedures per 100,000 Italian adults with hypertension in 2025

386 / 16.4 million $\approx$ 0.0024%

386 RDN procedures

16.4M adults with hypertension

Concentration of activity

The top 12 Italian centers performed about 42% of all 2025 procedures. This suggests that expertise is emerging, but activity is not yet broadly distributed.

National total: 318 → 386 procedures (+21%)



- Based on the results of recent RCTs using second-generation devices, RDN represents a **therapeutic option** for the management of hypertension, **alongside lifestyle modifications and pharmacological treatment**;
- **RDN should be considered a complementary strategy**, rather than a competing alternative to medical therapy;
- A **structured clinical pathway** is recommended for the implementation of RDN in routine clinical practice;
- **Personalized, multidisciplinary discussion and shared decision-making with the patient** regarding the indication for RDN are essential for the success of a RDN program.



Thank you for your attention!

Marco Bernardi, MD, MSc
Ospedale S. Maria Goretti, Latina

Contacts

