European Heart Journal Supplements (2025) **27** (Supplement 3), iii32–iii35
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suaf012

ESC European Society of Cardiology

In these cases, I treat hypertension with renal ablation

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KEYWORDS
Renal denervation;
Resistant hypertension;
Uncontrolled hypertension;
Cardiovascular mortality;
Cardiovascular risk

Systemic arterial hypertension is one of the leading causes of mortality and morbidity worldwide. Despite therapeutic advancements, a significant proportion of hypertensive patients fail to achieve adequate blood pressure control. Renal denervation (RDN) is emerging as an innovative and minimally invasive procedure to treat hypertension by modulating the renal sympathetic nervous system. Recent clinical trials, including SYMPLICITY HTN-3, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO, have shown variable results, influenced by patient selection and study design. The latest 2024 ESC guidelines on systemic arterial hypertension recommend RDN as a therapeutic option in selected cases, especially in patients with resistant hypertension not adequately controlled by pharmacological therapy. However, the response to this approach varies according to individual pathophysiology and the level of sympathetic activation. This article highlights how RDN, performed using ultrasound or radiofrequency technologies, may represent a breakthrough for difficult-to-treat patients, bridging current therapeutic gaps and reducing long-term cardiovascular risk. Finally, it emphasizes the importance of a multi-disciplinary assessment to maximize the benefits of the procedure.

Introduction

Systemic arterial hypertension is a significant cause of mortality and morbidity globally, contributing significantly to the incidence of major cardiovascular events such as stroke and myocardial infarction and promoting the progression of chronic kidney disease. Despite advances in pharmacological treatments, such as adopting anti-hypertensive molecules combined in a single tablet, many patients still do not achieve adequate blood pressure (BP) control. In this context, renal denervation (RDN), a minimally invasive procedure that aims to reduce the activity of the sympathetic nervous system at the level of the renal arteries has gained increasing attention as a complementary therapeutic option. The most recent scientific evidence, supported by major clinical trials, has highlighted the potential benefits of RDN, especially in patients with resistant hypertension. The results of these studies have shown a significant reduction in BP values, both in the office and at home, without significant side effects associated with the procedure. Furthermore, the new ESC 2024 guidelines on systemic arterial hypertension[1] introduce RDN as a therapeutic option for specific groups of patients, recommending its use in selected cases in addition to pharmacological therapy. This article explores the latest scientific evidence, therapeutic implications, and expert recommendations regarding RDN, outlining how this innovative technique can revolutionize the treatment of uncontrolled systemic arterial hypertension.

Epidemiology and global impact of arterial hypertension

Systemic arterial hypertension is one of the leading risk factors for cardiovascular, cerebrovascular, and renal diseases and remains a major cause of morbidity and mortality worldwide. According to the latest estimates from the World Health Organization,[2] more than 1.2 billion people globally suffer from hypertension, with a rising prevalence in low- and middle-income countries where access to care and prevention is often limited. Despite the efficacy of numerous pharmacological

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treatments, a large study conducted by Mills *et al.*[3] highlights that only 50% of hypertensive patients are able to maintain adequate BP control. In particular, resistant arterial hypertension—defined as the failure to reduce BP values below 140/90 mmHg despite the use of a combination of three anti-hypertensive drugs of different classes, including a diuretic—represents a significant clinical challenge. The ESC 2024 guidelines for the management of arterial hypertension emphasize the importance of a thorough assessment to identify and treat potential secondary causes of hypertension, such as primary hyper-aldosteronism or obstructive sleep apnoea syndrome, conditions that may contribute to therapeutic resistance. Furthermore, the guidelines note that resistant hypertension affects ∼5% of the entire population of hypertensive patients. The critical nature of these data is not reflected in the percentage of patients affected by resistant hypertension but rather in the increased mortality observed in this category compared with other hypertensive patients.[4] This scenario underscores the importance of developing personalized therapeutic strategies that take into account not only the patient's genetic and physiological factors but also their socioeconomic characteristics and lifestyles. The 'one-size-fits-all' approach has proven insufficient, and new evidence suggests that integrated and multi-disciplinary management tailored to the individual patient's needs could significantly improve long-term clinical outcomes. It is precisely in this context that RDN, in patients with preserved renal function, represents an additional therapeutic option to conventional pharmacological therapy.

Renal denervation: pathophysiological rationale

The sympathetic nervous system plays a key role in regulating BP. At the renal level, sympathetic activity is mediated by afferent and efferent nerve fibres surrounding the renal arteries: efferent sympathetic nerve fibres contribute to vasoconstriction, renin release, and sodium reabsorption, while afferent fibres are responsible for increased central sympathetic activity.[5] Renal sympathetic hyper-activation has been recognized as a central mechanism in arterial hypertension, especially in resistant forms, where the sympathetic nervous system is chronically stimulated; this contributes to a persistent increase in systemic BP.[6]

Given the pivotal role of the sympathetic nervous system at the renal level, its modulation has been the subject of various trials aimed at determining its efficacy in terms of BP control. The RDN technique is particularly relevant in patients with resistant hypertension, where conventional pharmacological therapy is insufficient to achieve adequate BP control. Specifically, renal nerve fibre ablation can be performed using three main methods[5]:

- Radiofrequency: A catheter equipped with electrodes capable of generating heat is used. The catheter is inserted through the femoral artery and advanced to the renal arteries. Once positioned, the electrodes release radiofrequency energy, which generates heat to destroy afferent and efferent sympathetic nerve fibres while sparing the walls of the renal arteries.
- Ultrasound: The catheter used emits ultrasound waves that can damage renal nerve fibres. At the distal end of the catheter, there is also an inflatable balloon containing a solution that cools the walls of the renal arteries, ensuring that the temperature within the arterial lumen remains lower than that of the perivascular space.
- Neurotoxins: A catheter capable of releasing neurotoxins (e.g. ethanol) into the perivascular space is used, which damages the renal nerve fibres.

Regardless of the method used, denervation leads to a reduction in renal sympathetic tone, resulting in decreased vasoconstriction, renin production, and renal sodium reabsorption.[7] The first trial investigating the efficacy of RDN in patients with hypertension was the DENERHTN (Renal Denervation for Hypertension)[8]; this trial evaluated the effectiveness of RDN added to a standardized and intensified anti-hypertensive therapy (SSAHT) compared with SSAHT alone in patients with resistant hypertension.

The primary outcome, the reduction in daytime ambulatory systolic BP (SBP) at 6 months, was significantly greater in the RDN-treated group compared with the control group [−15.8 vs. −9.9 mmHg; adjusted difference: −5.9 mmHg, 95% confidence interval (CI): −11.3 to −0.5; $P = 0.0329$]. Similar improvements were observed for nighttime BP (−13.9 vs. −7.6 mmHg; adjusted difference: −6.3 mmHg, $P = 0.0296$) and 24 h ambulatory BP (−15.4 vs. −9.5 mmHg; adjusted difference: −5.9 mmHg, $P = 0.0238$). No significant differences were noted in the number of medications used or therapeutic adherence between the groups. Procedure-related adverse events were minimal and non-serious. The study concludes that RDN provides additional benefits in BP control for patients with resistant hypertension, with response heterogeneity likely related to differences in individual sympathetic drive and with an acceptable safety profile.

What evidence is there on renal denervation?

Despite the availability of effective pharmacological therapies, a significant percentage of hypertensive patients fail to achieve adequate BP control, exposing themselves to increased cardiovascular risk. Renal denervation is emerging as a technique capable of addressing important 'unmet needs' in the treatment of systemic arterial hypertension, especially in patients with resistant hypertension. In recent years, several trials have sought to provide solid scientific evidence to enable clinicians to make informed decisions about when to consider this technique (*Table 1*):

SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) was a randomized, sham-controlled trial that enrolled 535 patients with uncontrolled resistant hypertension despite taking three or more anti-hypertensive drugs at the maximum tolerated dose. The aim was to evaluate the efficacy of RDN in reducing SBP. At 6 months, the study showed no significant differences between the RDN group and the sham group (mean SBP reduction of −14.13 mmHg in the RDN group vs. −11.74 mmHg in the sham group; $P = 0.26$). These unexpected results raised questions about the procedure and patient selection. Criticisms were

Table 1 Main trials performed on renal denervation in hypertension

Study	Year	Population	Device	Primary endpoint	Main results
SYMPLICITY HTN-3	2014	Patients with resistant hypertension (BP > 160 mmHg)	SYMPLICITY catheter	Systolic BP reduction (in office)	No significant difference between denervation and placebo (−14.1 vs. −11.7 mmHg, $P = 0.26$)
SPYRAL HTN-OFF MED	2018	Patients not on anti-hypertensive therapy (BP > 150 mmHg)	SPYRAL multi-electrode	BP reduction (outpatient and in office)	Significant reduction in BP both in office (−9.2 mmHg) and ambulatory (−5.0 mmHg) after 3 months
RADIANCE-HTN SOLO	2018	Patients with moderate hypertension (BP 140–159 mmHg)	Paradise catheter	Ambulatory BP reduction (24 h)	Significant reduction in ambulatory BP (−8.5 mmHg denervation vs. −2.2 mmHg control, $P < 0.001$)
SPYRAL HTN-ON MED	2021	Patients undergoing drug therapy (1–3 drugs)	SPYRAL multi-electrode	BP reduction (outpatient and in office)	Significant reduction in BP both in office (−9.4 mmHg) and outpatient (7.4 mmHg) after 6 months
RADIANCE-HTN TRIO	2021	Patients with resistant hypertension (BP > 140 mmHg)	Paradise catheter	Ambulatory BP reduction (24 h)	Significant reduction in ambulatory BP (−8 mmHg denervation vs. −3 mmHg control, $P = 0.022$). Effective denervation in patients with resistant hypertension

Studies demonstrate a variable efficacy of RDN, dependent on patient selection and treatment protocol.

directed at operator experience, variability in drug administration during the study, and the potential for insufficient sympathetic nerve fibre ablation.

To overcome the limitations of SYMPLICITY HTN-3, the **SPYRAL HTN-OFF MED** (Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications) study was designed; this randomized, sham-controlled trial enrolled 80 patients with Grades 1 and 2 hypertension, discontinuing drug therapy to eliminate the influence of medications on the results. At 3 months, the RDN group showed a significant reduction in BP compared with the sham group (mean ambulatory SBP reduction of −5.5 mmHg in the RDN group vs. −0.5 mmHg in the sham group; $P = 0.041$). This study demonstrated that RDN can be effective in patients not on medication, highlighting the importance of controlling for confounding variables and ensuring proper ablation.[9]

The **RADIANCE-HTN SOLO** (A Study of the ReCor Medical Paradise System in Clinical Hypertension) study further investigated the efficacy of RDN using an ultrasound ablation system.[10] This randomized, sham-controlled trial enrolled 146 patients with untreated or discontinued primary hypertension. At 2 months, the RDN group recorded a greater reduction in daytime SBP measured by ambulatory monitoring compared with the sham group (mean reduction of −8.5 vs. −2.2 mmHg; difference of −6.3 mmHg; $P < 0.001$). This study confirmed the efficacy of RDN and suggested that ultrasound technology could improve sympathetic nerve fibre ablation.

The **SPYRAL HTN-ON MED** (Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension on Standard Medical Therapy) study evaluated the efficacy and safety of RDN in patients with resistant hypertension treated with one to three anti-hypertensive drugs.[11] Among patients outside the USA, RDN resulted in a significant reduction in 24 h ambulatory SBP (-7.4 ± 8.6 mmHg in the RDN group vs. -2.6 ± 9.5 mmHg in the sham group; adjusted difference: −4.8 mmHg, 95% CI: −7.6 to −2.0; $P = 0.0010$) and a significant reduction in ambulatory SBP. However, in the USA, no significant differences were observed in African American patients (-3.6 ± 15.0 mmHg in the RDN group vs. -8.7 ± 10.8 mmHg in the sham group; adjusted difference: 5.4 mmHg, 95% CI: −3.4 to 14.1; $P = 0.22$), likely due to a significant increase in drug burden in the African American sham group ($P = 0.003$). It is hypothesized that this increase in drug burden may have diluted the efficacy of RDN. Thus, the study highlights that RDN offers clinical benefits in selected patients with stable drug burden and underscores the need to control and standardize drug treatment in clinical trials to avoid potential confounding factors.

The **RADIANCE-HTN TRIO** (A Study of the ReCor Medical Paradise System in Clinical Hypertension) study analysed the efficacy of ultrasound RDN compared with a sham procedure in patients with hypertension resistant to a combination of three anti-hypertensive drugs.[12] After 2 months, RDN showed a significant reduction in daytime ambulatory SBP compared with the sham group [median: −8.0 mmHg (inter-quartile range −16.4 to 0.0) vs. −3.0 mmHg (−10.3 to 1.8); between-group

difference: −4.5 mmHg, 95% CI: −8.5 to −0.3; $P = 0.022$]. Similar results were observed for 24 h ambulatory BP (between-group difference: −4.2 mmHg, $P = 0.016$) and nighttime SBP (−3.9 mmHg, $P = 0.044$). The safety of the procedure was high, with only one procedure-related adverse event reported. The study concludes that RDN provides a clinically significant reduction in BP in patients with resistant hypertension, supporting its potential as an alternative to adding additional medications.

In summary, while **SYMPLICITY HTN-3** did not show significant benefits of RDN, subsequent studies demonstrated that under controlled conditions and with improved techniques, RDN can effectively reduce BP. These results highlight the importance of patient selection, protocol adherence, and operator experience in the success of the procedure.

Finally, the Global SYMPLICITY Registry Denervation Findings in Real World evaluated the impact of RDN on BP and cardiovascular outcomes in patients with uncontrolled hypertension. The results showed significant and sustained reductions in SBP, both in office and ambulatory (-16.7 ± 28.4 mmHg and -9.0 ± 20.2 mmHg, respectively) at 36 months. In particular, a 10% increase in the time spent in the therapeutic range (TTR) within the first 6 months after RDN was associated with a 15% risk reduction for major cardiovascular events ($P < 0.001$), 11% for cardiovascular mortality ($P = 0.010$), 15% for myocardial infarction ($P = 0.023$), and 23% for stroke ($P < 0.001$). The study confirms the efficacy of RDN in improving BP control and reducing cardiovascular risk, highlighting the value of TTR as a predictor of long-term outcomes.[13]

In conclusion: when to consider renal denervation?

In light of the available scientific evidence and according to the recommendations provided by the latest ESC 2024 guidelines and the 2020 Società Italiana Ipertensione Arteriosa position paper,[14] RDN is recommended for patients with resistant hypertension, defined as systemic BP inadequately controlled despite rational pharmacological therapy that includes at least three anti-hypertensive drugs of different classes, including a diuretic, at the maximum tolerated dosage. Additional candidates include patients with documented poor therapeutic adherence despite extensive counselling, intolerance to medications (such as spironolactone), or explicit preferences for the procedure. Renal denervation may also be considered for patients with high cardiovascular risk and uncontrolled systolic-diastolic hypertension, provided they are managed in specialized centres with experience in the procedure. A multi-disciplinary evaluation is essential to confirm the patient's suitability and ensure realistic expectations regarding the benefits of the procedure.

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

Disclaimer

This paper was originally published in the Italian language as 'In questi casi curo l'ipertensione con l'ablazione renale', in the Volume degli Atti del Congresso "Conoscere e Cuare il Cuore 2025", published by Centro per la Lotta contro l'Infarto for distribution at the CCC Conference. This paper was translated by Dr. Mario Albertucci, representative of the CLI Foundation, and republished with permission.

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