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"Breaking The Cycle : Ultrasound's Novel Approach To Renal Denervation And Hypertension Relief "

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Abstract: Several device-based treatments exist for high blood pressure (1). Catheter-based renal denervation (RDN) has the most supporting evidence (2). RDN lowers blood pressure by affecting the sympathetic nervous system. It disrupts nerve signals in the renal arteries. Early studies on RDN showed great promise. Patients with hard-to-treat hypertension saw big blood pressure drops (12). This excitement faded after the Symplicity HTN-3 trial. This study showed RDN was safe. However, it did not lower blood pressure better than a sham procedure. Early sham-controlled trials gave key insights into trial design. Reviews of these trials and new nerve findings helped improve RDN. Better catheter systems were also created. These advances led to second-generation sham-controlled trials. The European Society of Cardiology (ESC) and European Association of Percutaneous Cardiovascular Interventions (EAPCI) have set quality standards for RDN trials. High-quality trials should be sham-controlled and multicentre. They need proper blinding and use ambulatory blood pressure as the main outcome. Studies must be completed as planned. Second-generation RDN systems and techniques should be used. This review will discuss why RDN is used. It will also summarise results from recent second-generation trials.

Keywords: Blood pressure, cardiovascular disease, hypertension, interventional cardiology, renal denervation, vascular medicine.

I. Introduction

Several devices treat high blood pressure. Catheter-based renal denervation (RDN) has the most proof. RDN lowers blood pressure by affecting nerves. It disrupts nerves around the renal arteries. These nerves control the sympathetic nervous system. RDN was exciting over ten years ago. It greatly lowered blood pressure in early studies(3). These studies involved patients with severe high blood pressure that resisted treatment. But the excitement stopped after a trial called Symplicity HTN-3. This trial showed RDN was safe. However, it did not lower blood pressure better than a sham procedure. The monoelectrode procedure used a radiofrequency catheter (RF) catheter compared with a sham procedure (selective renal angiography only) (4) . First-generation trials gave important insights. They taught about trial design and execution. Reviews of these trials, insights on nerve distribution, and better catheters led to better trials. A European expert group said trials must be high quality. The criteria are: (i) a sham procedure for comparison, done in many centres; (ii) patients and assessors unaware of the treatment; (iii) blood pressure change measured by a monitor as the main result; (iv) study completed as planned with data for nearly all patients; and (v) use of newer RDN systems (2). This review discusses why RDN is used. It also summaries result from newer trials.

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1. Rationale

The autonomic nervous system manages cardiac output and blood pressure to ensure organs are perfused. Increased sympathetic nervous system activity raises blood pressure. This occurs through peripheral vasoconstriction and reduced venous capacitance. It also reduces renal sodium and water excretion (5). The nucleus tractus solitarius and rostral ventrolateral medulla cause sympathetic activation. This activation affects all peripheral organs (6). The kidneys are vital in blood pressure control. Sympathetic nerve fibres stem from abdominal ganglia. They run with the renal arteries, converging on the arteries' outer layer (7,8).

Activation of efferent sympathetic renal nerve fibres triggers renin release. This release happens via beta-1 adrenergic receptors in juxtaglomerular cells. It also increases renal tubular sodium reabsorption via alpha-adrenoceptors. Plus, it decreases renal blood flow (9). Renal afferent sympathetic nerves react to kidney damage through parenchymal nociceptive receptors. They also respond to pelvic pressure changes through pressure-sensitive receptors (9).In the early 20th century, surgical sympathectomy treated severe hypertension. This was an alternative to antihypertensive drugs, which were scarce and poorly tolerated. Surgical sympathectomy lowered blood pressure. It improved survival in patients with severe hypertension (3). However, it caused severe side effects. These included postural and postprandial hypotension, syncope, and incontinence. Sexual dysfunction, high perioperative morbidity, and mortality were also observed (ranging from 0.7% to 10.9%) (10). Despite its risks, surgical sympathectomy proved the sympathetic nervous system's role in blood pressure regulation.

2. Ultrasound renal denervation

(RDN) uses ultrasound energy to ablate nerves. Two catheter systems are being studied: Paradise (ReCor Medical) (11) and TIVUS (SoniVie) (12). Sham-controlled trial evidence only exists for the Paradise system (13).

Table 1. Characteristics of the most important RDN catheter systems.

Catheter	Design	Access site	Ablation sites	Efficacy confirmed in sham-controlled trial?
Ultrasound				
TIVUS (SoniVie)	Unidirectional steerable or multidirectional, over-the-wire, 30 seconds per emission	F (6 Fr)	Main and accessory arteries (diameter ≥4 mm)	No
Paradise (ReCor Medical)	Piezoelectric ceramic transducer within a fluid-cooled, low-pressure balloon, over-the-wire, 7 seconds per emission	F (7 Fr)	Main and accessory arteries (different catheter sizes for diameters of 3-8 mm)	Yes, multiple studies
F: femoral; Fr: French; R: radial; RDN: renal denervation				

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2.1 Paradise Renal Denervation System

The Paradise catheter has a cylindrical transducer inside a balloon. Sterile water circulates in the balloon. This centres the transducer cools the artery during energy emission (13).The RADIANCE-HTN study tested the Paradise system. It included patients with mild-to-moderate hypertension (SOLO) and resistant hypertension (TRIO) (14,15).The Paradise system lowered blood pressure (BP) in both groups. In the SOLO group, daytime systolic BP fell by 6.3 mmHg. In the TRIO group, it decreased by 4.5 mmHg (15). Long-term follow-up showed the BP reduction lasted up to 36 months. Office BP decreased and control rates improved. The number of medications stayed the same (16).The RADIANCE-II study confirmed these results. Patients were taken off medication and then received RDN or a sham procedure. RDN reduced daytime systolic BP by 6.3 mmHg. A meta-analysis of three trials showed consistent BP reductions. The mean difference between RDN and sham was -5.9 mmHg. Higher baseline BP and heart rate predicted a better response. Orthostatic hypertension was also a predictor. The procedure was safe, with few complications (17).

US-RDN showed a good safety profile. Only one vasovagal event and one vascular issue arose. Both were resolved without lasting problems. The REQUIRE study in Japan and South Korea differed. This study did not meet its main goal. The goal was to see if RDN lowered 24-hour systolic BP better than a sham procedure at three months. At one month, RDN lowered BP more than the sham. However, BP in the sham group also decreased later. This made the difference between the groups disappear (18). The trial had issues, such as doctors knowing who got the real treatment. It also did not check if patients stayed blind to their treatment. Experts have rated this trial as low quality. The BP drop in the sham group likely came from changes in medication. Later analysis showed RDN did lower BP more than the sham in patients who followed their treatment well (19).US-RDN appears safe and works for many hypertension patients. This includes those with resistant hypertension. The RADIANCE-HTN TRIO trial stands out. It is the only sham-controlled trial using a newer method. It only included patients with true resistant hypertension. These patients were on a recommended triple pill. The FDA has approved the Paradise RDN system for treating hypertension.

3. Preprocedural imaging

Imaging before the procedure is a key. It checks for issues like renal artery stenosis or fibromuscular dysplasia. It also identifies unusual anatomy, like extra arteries (2). One study found extra renal arteries in 22% of RDN patients. Renal artery disease was seen in 9% (20). Guidelines advise choosing imaging based on patient needs and local skills. Duplex ultrasonography (DUS) is often a good first choice. It is easily available and avoids radiation or contrast. SPYRAL HTN-OFF MED trial data suggests DUS better shows artery patency (88%) compared to CTA (68%) or MRA (29%) (21).

4. Procedural considerations

A safe RDN procedure has key steps. It is best to follow standard procedures for each catheter. Experts advise completing at least five supervised RDN cases with each device. Like other procedures using contrast dye, hydration is important. Dilute the dye to reduce its amount, especially for patients with kidney problems. Carbon dioxide is another option for contrast (22). Ablation can cause pain because of nerve fibres in the kidney. Use pain relief and sedation, like low-dose opioids and benzodiazepines. This makes the patient more comfortable. It may also lead to a safer, more effective procedure (2). Monitor vital signs before and after pain relief and sedation. Have a nurse or doctor manage pain and sedation, as local laws require. Give unfractionated heparin during the procedure. Aim for an activated clotting time above 250 seconds. Also, give aspirin, followed by a daily dose for a month (2). RDN is generally safe. There are few safety concerns beyond risks from artery access. Ultrasound-guided puncture is ideal. Use non-hydrophilic guidewires and keep the tip in sight.

When treating the renal artery, consider the nerve distribution. Renal nerves come from various sources and meet on the outer artery wall, mainly in distal segments and branches. The fewest nerves and shortest distance to the artery lumen are in the distal segments after branching (7,8). Radiofrequency (RF) catheters create a lesion depth of 3.8 mm (23). This would affect most nerves in distal segments, but fewer in proximal segments (8).Studies support treating branch arteries along with the main renal arteries when using RF-RDN(24,25). However, avoid targeting artery segments within the renal parenchyma. Treat accessory arteries suitable for RDN (Table 1) if they supply ≥20% of the renal parenchyma. Currently, there is no reliable clinical indicator for successful renal nerve ablation (2).

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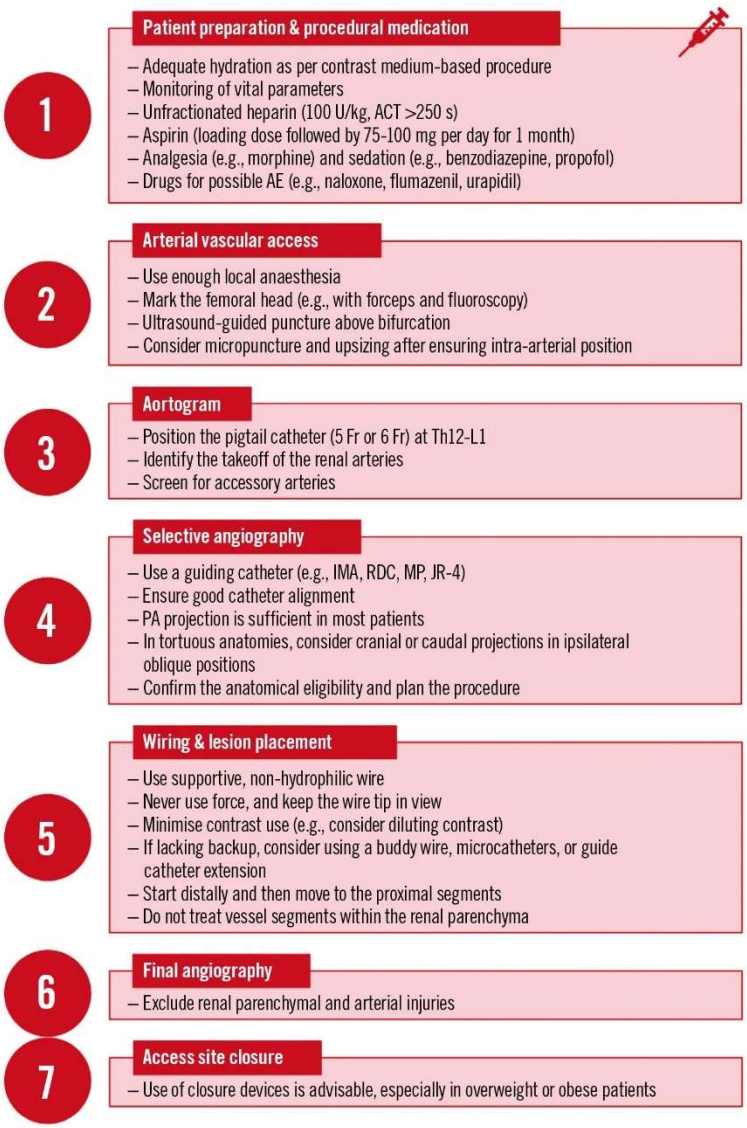

Figure 1. Key components of a safe and effective procedure. ACT: activated clotting time; AE: adverse events; Fr: French; IMA: internal mammary artery; JR: Judkins right coronary; MP: multipurpose; PA: posteroanterior; RDC: renal double curve

5. Recommendations of guidelines and consensus statements

The 2018 ESC/ESH hypertension guidelines advised against routine use of device-based therapies. This was due to limited evidence on safety and efficacy from early trials. Since then, more evidence has emerged (26). Several expert groups have released consensus statements, including the ESC Council on Hypertension and the EAPCI. The ESH has also published new hypertension guidelines (27). Both ESC/EAPCI and ESH now view RDN as an option for some patients. This includes those with resistant hypertension, or uncontrolled hypertension despite drug combinations. RDN is also considered if drugs cause serious side effects and reduce life quality. Both guidelines recommend an eGFR ≥40 ml/min/1.73 m2, a criterion used in trials (2,27). Evidence for patients with worse kidney function comes from smaller studies. Patient selection requires shared decision-making. Patients need to understand RDN's benefits, limits, and risks. They should know that individual responses to RDN vary widely. There is no reliable way to predict blood pressure response. The main goal is blood pressure reduction. Most patients will still need medication. In later trials,

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RDN reduced office systolic blood pressure by 9.0-11.0 mmHg. 24-hour systolic blood pressure decreased by 4.7-8.5 mmHg in RDN groups.

	2022 ESC/EAPCI consensus statement	**2023 ESH hypertension guidelines***
RDN in uncontrolled hypertension…	May be a possible treatment option for patients unable to tolerate antihypertensive drugs in the long term or patients who express a preference to undergo RDN	Can be considered as a treatment option if drug treatment elicits serious side effects and poor quality of life (COR II, LOE B)
RDN in resistant hypertension…	May be used	Can be considered as a treatment option (COR II, LOE B)
Secondary hypertension	Secondary causes of hypertension should be excluded	Secondary causes of hypertension should be excluded
Lower eGFR threshold	≥40 ml/min/1.73 m^2	≥40 ml/min/1.73 m^2
Centre requirements	RDN should be performed at experienced centres with multidisciplinary hypertension teams and a hypertension outpatient clinic, inpatient ward, radiology division, hormone testing, clinical laboratory, catheterisation laboratory, coronary care or intensive care unit, and access to an emergent vascular surgery facility, either onsite or remote. Procedures should only be performed by a highly skilled interventionalist with experience in renal artery interventions	RDN should only be performed in experienced and specialised centres (COR I, LOE C) with an established multidisciplinary hypertension team
Patient preference	The decision-making process should incorporate the preference of a well-informed patient	Patient selection should take place as part of a shared decision-making process after the patient has received objective and complete information (COR I, LOE C)

* The 2023 ESH guidelines applied new criteria for grading the level of evidence. Level of evidence "A" was only considered if cardiovascular outcome data were available. COR: class of recommendation; EAPCI: European Association of Percutaneous Cardiovascular Interventions; eGFR: estimated glomerular filtration

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	2022 ESC/EAPCI consensus statement	2023 ESH hypertension guidelines*
rate; ESC: European Society of Cardiology; ESH: European Society of Hypertension; LOE: level of evidence; RDN: renal denervation		

6. Open Questions

While US- and RF-RDN lower blood pressure safely, key questions remain. Firstly, we lack predictors of RDN response and markers of success. Secondly, RDN lacks cardiovascular outcome trials, unlike standard drugs (2). Low current risk and likely confounding make a trial unlikely soon, although desirable. Blood pressure decrease is a key sign of better cardiovascular outcomes(28). However, RDN-linked changes might not offer similar benefits. The Global SYMPLICITY Registry showed that more time within target blood pressure ranges after RDN linked to fewer major events. Common blood pressure treatments lack cardiovascular outcome trials. These include exercise, surgery, and drugs like clonidine. Cost-effectiveness studies for RDN are also lacking.

7. US Food and Drug Administration Approval

Medtronic Inc. and ReCor Medical Inc. sought FDA approval for their RDN devices after positive trial results. The FDA panel met in August 2023 to discuss safety and benefits. They voted on safety, effectiveness, and overall value. The panel unanimously favoured the safety of both devices. For effectiveness, votes supported both systems: (Paradise system [8 votes in favour, 3 votes against and 1 abstaining] and Spyral system [7 votes in favour and 6 against]). The Paradise system was favoured on risk-benefit (10-2). The Spyral system split the panel (6-6-1). The chairperson voted against Spyral to break the tie. The FDA often follows panel a device, but isn't required to. The FDA approved the Paradise urn system in early November 2023. The FDA also approved the Spyral rRDN system, against panel advice. Two devices are now available for use(29).Randomised trials and global registries show that RDN is generally safe and effective. The European Society of Hypertension suggests RDN for uncontrolled hypertension despite drug therapy. It may also suit patients with medication side effects or poor quality of life. A key question is: who benefits most from RDN, and by how much? Identifying these patients is vital. BP-lowering effects may seem small in studies. However, real-world data and longer follow-up show more significant effects. Even small systolic BP drops greatly lower cardiovascular risk. Many patients still have uncontrolled hypertension. So, more treatments are needed to cut cardiovascular risk in the USA. Experts discussed these issues at a 2021 roundtable. They agreed that BP control in the USA is often poor. They also said RDN is safe, effective and lasting. Careful patient selection is essential for RDN (30).

This should consider hypertension severity, other illnesses, and patient wishes. Input from a healthcare team is also important. An European expert group shares these views. They suggest RDN for select patients with uncontrolled hypertension, even with optimal therapy. It may also help patients who cannot tolerate drugs. They stressed shared decision-making and the care team's role. We need standard ways to measure RDN success. Current studies use different measures. These include 24-hour BP, daytime BP, and results at different times. This makes comparisons hard. Studies also lack the power to track major events like death. Ongoing registries should help with this. Patient studies show that people want fewer medications. They also want lower BP. So, a patient-centred approach is important for defining success and for giving advice. It is unclear if CMS will require a team approach for RDN. This was needed for other new technologies. A team approach is vital for treating patients. A comprehensive, team-based approach is key to managing high blood pressure long term. Renal denervation (RDN) is just one tool among many. New centres should set up formal high blood pressure programmes. This will help them identify suitable RDN candidates, now that the FDA has approved it (31).

Financial aspects and reimbursement models are important for both centres and healthcare systems. Current Procedural Terminology (CPT) codes track physician work. They can also guide payment for services from the NHS. Current Procedural

Terminology (CPT) codes fall into three categories: I, II, or III, depending on the service. Category I covers specific medical services. Category II are for performance measurement. Category III are temporary codes for new technologies. Category III codes have no set fees. Payment is decided by insurers or Medicare. Currently, RDN technologies will likely have a category III code. This makes immediate reimbursement difficult. There is often a delay between FDA approval and the NHS's Ambulatory Payment Classification (APC). The APC determines institutional reimbursement. A Medicare add-on payment may temporarily boost RDN reimbursement. This should make initial reimbursement better. However, these add-ons are also usually temporary and delayed. Private insurance companies present further uncertainties. They often follow NHS payment schedules but may have different coverage rules. Because of these factors, building strong, multidisciplinary high blood pressure centres should be the priority. Building a programme focused only on RDN should not be the priority. Even so, now that the FDA has approved RDN, its data and potential benefits offer significant growth opportunities (31).

II. Conclusion

HTN is a major cause of heart disease and death in the USA. Even small blood pressure drops can greatly improve heart health. RDN is a non-drug option for HTN patients. It has proven safe and effective. As RDN becomes available, multidisciplinary teams are vital. So are protocols for screening, treatment, and follow-up. Payment details are still unclear early on. Yet, RDN's potential for growth and other benefits should not be ignored. Research is ongoing into its effects on arrhythmias and heart failure.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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