The Future of Denervation Technologies

Advances in device platforms for hypertension, access strategies, multiorgan denervation, and emerging applications in hypertension and cardiometabolic disease.

By Shukri W. David, MD, MBA, and Herbert D. Aronow, MD, MPH

Hypertension (HTN) remains the leading modifiable risk factor for cardiovascular and kidney disease worldwide, and yet blood pressure (BP) control rates remain suboptimal despite the availability of effective pharmacotherapy and lifestyle interventions.[1] Global data show a persistent burden of undiagnosed, untreated, and uncontrolled HTN, leading to adverse outcomes such as stroke, myocardial infarction, heart failure (HF), chronic kidney disease (CKD), and premature mortality. Uncontrolled HTN is influenced by biological factors, patient nonadherence, and therapeutic challenges. Even in rigorously monitored clinical trials, estimates suggest that up to 50% of patients exhibit suboptimal adherence.[2]

The kidneys are integral in BP regulation. Increased sympathetic nervous system activity raises BP by augmenting renal tubular sodium and water reabsorption and through stimulation of the renin-angiotensin-aldosterone system (RAAS).[3] Renal denervation (RDN) disrupts these neural pathways, reducing RAAS activation, sodium and water retention, and BP.[3] As a result, device-based therapies targeting the sympathetic nervous system are emerging as potential adjuncts to pharmacologic and lifestyle interventions. Advances in trial design (eg, patient selection, medication protocols, endpoints), device technology, and procedural standardization have produced consistent reductions in BP across diverse patient populations. This article highlights key advances in device platforms, alternative access, multiorgan denervation, and the evidence for expanding applications beyond uncontrolled HTN.

TECHNOLOGY EVOLUTION: BEYOND FIRST-GENERATION RDN

Radiofrequency RDN

Radiofrequency RDN (rRDN) is the most established denervation platform. The first-generation Symplicity Flex system (Medtronic) used single-electrode, point-by-point ablation in the main renal artery. Although early studies were encouraging, SYMPLICITY HTN-3 did not meet its primary 6-month efficacy endpoint, prompting changes to trial design and device technology; interestingly, at 12, 24, and 36 months, rRDN significantly reduced office systolic BP when compared with sham.[4] The newer Symplicity Spyral catheter (Medtronic) introduced a multielectrode helical design to enable more reproducible circumferential ablation, and the treatment strategy expanded beyond the main renal artery to include branch vessels, thereby improving the extent of denervation.[5] The SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies demonstrated favorable safety and sustained BP reduction,[6-8] supporting rRDN as an adjunctive therapy in both patient populations. Three-year data from the SPYRAL HTN ON-MED pilot study demonstrated durable rRDN efficacy and safety.[7]

Ultrasound RDN

Ultrasound-based RDN (uRDN) using the Paradise system (Recor Medical) delivers circumferential ultrasound energy via a balloon-based catheter that is fluid-cooled to protect the arterial wall and create a uniform perivascular lesion.[9] The RADIANCE-HTN SOLO and RADIANCE II trials of patients off antihypertensive medications and the RADIANCE-HTN TRIO trial of patients with resistant HTN on medications all demonstrated short-term BP reductions without any safety concerns.[10-12] Three-year data from RADIANCE-HTN SOLO demonstrated durable uRDN efficacy and safety.[13]

The investigational Therapeutic IntraVascular UltraSound (TIVUS) platform (Boston Scientific Corporation) employs a nonocclusive, nonballoon-based intravascular ultrasound delivery catheter. This design

permits continuous renal arterial blood flow during energy delivery and uses blood-mediated cooling rather than active fluid irrigation.[14] Unlike balloon-based ultrasound systems that occlude the artery, the TIVUS system remains exposed to circulating blood, which cools the arterial wall.[14] A first-in-human case demonstrated successful bilateral uRDN via left radial artery access using a 4-F TIVUS catheter, supporting integration of upper extremity access into contemporary catheterization workflows and potentially reducing femoral access-related limitations.[14] The THRIVE trial (NCT06559891) is currently randomizing patients with uncontrolled HTN who are off antihypertensive medications to TIVUS versus sham and comparing ambulatory systolic BP at 2 months.

Chemical Denervation

Chemical denervation (cRDN) involves injecting dehydrated alcohol into the perivascular space of the renal arteries to induce neurolysis. The investigational Peregrine catheter (Ablative Solutions, Inc.) is deployed under fluoroscopic guidance. Once positioned, alcohol is injected through three 0.008-inch microneedles directly into the perivascular, adventitial, and periadventitial spaces of each renal artery where the nerves reside.[15] Early single-arm studies supported feasibility and BP reduction, leading to the sham-controlled TARGET BP program in which 0.6 mL of dehydrated alcohol per main artery was administered, with an additional 0.6 mL to appropriately sized accessory arteries (maximum dose per patient, 2.4 mL).[15,16] Although TARGET BP OFF-MED demonstrated that alcohol-mediated RDN was safe, the primary efficacy endpoint was not met. In the TARGET BP I on-medication trial, a modest but significant reduction in 24-hour ambulatory systolic BP was observed when comparing cRDN with sham treatment, without excess major adverse events.[15]

The RADAR trial (NCT07083765) is a prospective, multicenter, blinded, sham-controlled trial evaluating cRDN using the Peregrine catheter in patients with HTN who are not receiving antihypertensive medications. RADAR is employing a higher ambulatory systolic BP entry threshold (≥ 140 vs ≥ 135 mm Hg) than TARGET BP OFF-MED, which may target patients with a greater potential for BP reduction. The alcohol dosing regimen in RADAR includes infusions of 1.2 mL to each main renal artery or 0.6 mL to the main and 0.6 mL to the accessory renal artery, when one is present.

Other Novel Approaches

Renal pelvic denervation, which targets afferent renal sympathetic nerves in the renal pelvis and urothelium in contrast to the efferent nerves targeted by conventional RDN,[17] and laparoscopic extravascular rRDN using the HyperQure system (DeepQure; currently undergoing first-in-human trials),[18] represent additional novel approaches currently under early phase evaluation, with sham-controlled trial data not yet available.

Precision-Based RDN

One inherent challenge with current-generation RDN systems is that denervation is performed in an empiric, anatomically based fashion without real-time feedback about procedural success. This is particularly important because renal sympathetic nerve distribution varies considerably, both in pattern and density, across individuals.[19] Stimulation-guided mapping plus ablation paradigms aim to reduce response variability by stimulating renal artery sites, identifying active sympathetic regions based on BP increases in response to stimulation, selectively ablating only those responsive sites, and restimulating them to confirm loss of response.

The SMART trial was a prospective, multicenter, randomized, sham-controlled trial of 220 patients enrolled across 15 sites in China comparing the effect of mapping/selective radiofrequency RDN (msRDN) to sham.[20] At 6 months, msRDN allowed patients to achieve noninferior office systolic BP control, with less increase in antihypertensive medication burden compared to sham. Separately, the real-world SMART-RW registry (NCT06780696) will follow safety and effectiveness of msRDN in approximately 1,000 patients over > 3 years. Early data on RDN with selective ultrasound nerve stimulation have also been published.[21]

In addition to these physiologically based efforts at precision RDN, anatomically based procedural adaptations are under investigation. In the SPYRAL DYSTAL pilot study, patients with uncontrolled HTN who were off medications underwent rRDN of the distal main renal artery and its primary branches; results were compared with those of a matched group from the SPYRAL HTN-OFF MED study who underwent complete ablation of the main renal artery and its branches.[6,22] The number of ablations, procedure time, and contrast volume were all significantly less with the distal approach. At 12 months, changes in ambulatory BP favored the distal approach over the standard complete main plus branch approach.[22]

RADIAL ACCESS STRATEGY

Interest in radial access is multifactorial. Given the downsloping takeoff of most renal arteries, coaxial engagement is more easily achieved when approached from above. Additionally, the incidence of vascular access site complications is reduced and patient dis-

comfort minimized when using a transradial approach versus a transfemoral approach. Although transfemoral access remains the contemporary standard for RDN, radial iterations of currently available devices are under development, and upper extremity approaches are currently feasible in selected patients, especially when femoral anatomy is unfavorable.[14]

BROADER USE

Registry and postapproval data provide insight into the real-world safety and efficacy of novel technologies in expanded populations. SPYRAL AFFIRM (NCT05198674) is a prospective, international, multicenter, single-arm study evaluating the long-term safety, efficacy, and durability of the Symplicity Spyral system in routine practice. In the most recently reported AFFIRM data, significant reductions in office and home systolic BP were observed at 6 months across patients with diabetes, isolated systolic HTN, and CKD, with no corresponding need for increased antihypertensive medication use and no major safety events.[23] These findings support the use of RDN in higher-risk patients.

Analyses from the Global SYMPLICITY Registry DEFINE study, including Symplicity Flex and Spyral procedures, have also extended evidence to real-world populations with greater comorbidity burden and more complex anatomy than was present in sham-controlled trials.[24]

Additionally, small randomized trials have provided a glimpse into potential novel applications for RDN. The randomized, sham-controlled ULTRA-HFIB study of patients with first-ever paroxysmal or persistent atrial fibrillation (AF) and HTN on one or more antihypertensive medication found that compared with sham, uRDN was associated with numerically but not statistically greater freedom from AF or flutter at 12 months.[25] In the ERADICATE-AF trial, patients with uncontrolled HTN and AF were randomized to pulmonary vein isolation with or without concomitant rRDN.[26] Those randomized to RDN had a 43% reduction in the hazard for recurrence of AF, atrial flutter, and atrial tachycardia at 12 months. In another small sham-controlled trial of rRDN in patients with resistant HTN, the hazard for subclinical AF was reduced by 60% at 2 years after RDN.[27] Meta-analytic data also support the AF-reducing efficacy of rRDN using various catheters.[28]

In a meta-analysis of small randomized trials of patients who had HF with reduced ejection fraction, RDN improved the 6-minute walk test and left ventricular systolic function and decreased B-type natriuretic peptide levels, independent of BP changes.[29] Patients who have HF with preserved ejection fraction (HFpEF) represent another cohort in which RDN may be biologically relevant. In the RDT-PEF trial, patients who had HFpEF were randomized to RDN or sham, and while the trial's primary endpoint was negative, improvements in VO2 were observed in RDN-treated patients at 3 months.[30]

Finally, meta-analytic data suggest that pulmonary artery denervation improves pulmonary hemodynamics, prevents clinical deterioration, and reduces rehospitalization in patients with pulmonary HTN.[31]

ROLE OF MULTIORGAN DENERVATION

Beyond BP, sympathetic overactivity influences hepatic and metabolic pathways, resulting in insulin resistance and dysglycemia.[32] High sympathetic nerve density, particularly in the proximal common hepatic artery (CHA), contributes to hepatic autonomic signaling that is involved in glucose regulation and metabolic homeostasis. For these reasons, CHA denervation may complement RDN by targeting a second autonomic axis associated with both BP and metabolic dysfunction.[26] Preclinical studies support the rationale for CHA denervation, demonstrating technical feasibility, procedural safety, and marked reductions in norepinephrine at renal and hepatic targets.[26] The international, multicenter, prospective, single-arm SPYRAL GEMINI pilot study (NCT06907147) is enrolling patients with uncontrolled HTN both on and off antihypertensive medications and evaluating the feasibility, safety, and preliminary BP-lowering efficacy of combined rRDN of the renal and CHAs using the Spyral catheter.

CONCLUSION

RDN for patients with uncontrolled HTN has evolved such that there are now multiple approved device platforms with proven efficacy, safety, and durability, with a growing emphasis on individualized patient selection. Novel vascular access sites, alternative denervation platforms, and multiorgan approaches are under active investigation. Registry and postapproval studies have provided reassuring real-world data, including among higher-risk cardiometabolic populations (eg, CKD and related phenotypes). Novel applications are emerging and include AF and HF. Continued progress will require optimal patient selection, greater procedural standardization, and robust long-term follow-up studies reflective of clinical practice. ■

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957-980. doi: 10.1016/S0140-6736(21)01330-1
2. Writing Committee Members*; Jones DW, Ferdinand KC, Taler SJ, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension. 2025;82:e212-e316. Published corrections appear in Hypertension. 2025;82:e350 and Hypertension. 2026;83:e000262. doi: 10.1161/HYP.0000000000000249
3. Mahfoud F, Mancia G, Schmieder R, et al. Renal denervation in high-risk patients with hypertension. J Am Coll Cardiol. 2020;75:2879-2888. doi: 10.1016/j.jacc.2020.04.036

4. Bhatt DL, Vaduganathan M, Kandzari DE, et alL; SYMPLICITY HTN-3 Steering Committee Investigators. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. Lancet. 2022 ;400:1405-1416. doi: 10.1016/S0140-6736(22)01787-1
5. Lauder L, Kandzari DE, Lüscher TF, Mahfoud F. Renal denervation in the management of hypertension. EuroIntervention. 2024;20:e467-e478. doi: 10.4244/EIJ-D-23-00836
6. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020;395:1444-1451. doi: 10.1016/S0140-6736(20)30554-7
7. Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet. 2022;399:1401-1410. doi: 10.1016/S0140-6736(22)00455-X
8. Kandzari DE, Townsend RR, Kario K, et al. Safety and efficacy of renal denervation in patients taking antihypertensive medications. J Am Coll Cardiol. 2023;82;1809-1823. doi: 10.1016/j.jacc.2023.08.045
9. Cluett JL, Blazek O, Brown AL, et al. Renal denervation for the treatment of hypertension: a scientific statement from the American Heart Association. Hypertension. 2024;81:e135-e148. doi: 10.1161/HYP.0000000000000240
10. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391:2335-2345. doi: 10.1016/S0140-6736(18)31082-1
11. Azizi M, Saxena M, Wang Y, et al. Endovascular ultrasound renal denervation to treat hypertension: the RADIANCE II randomized clinical trial. JAMA. 2023;329:651-661. doi: 10.1001/jama.2023.0713
12. Azizi M, Sanghvi K, Saxena M, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 2021;397:2476-2486. doi: 10.1016/S0140-6736(21)00788-1
13. Rader F, Kirtane AJ, Wang Y, et al. Durability of blood pressure reduction after ultrasound renal denervation: three-year follow-up of the treatment arm of the randomised RADIANCE-HTN SOLO trial. EuroIntervention. 2022;18:e677-e685. doi: 10.4244/EIJ-D-22-00305
14. Tuvali O, Blatt A, Elbaz-Greener G, et al. Radial approach renal denervation: a first-in-man case with the 4-F TIVUS catheter. JACC Case Rep. 2025;30:104440. doi: 10.1016/j.jaccas.2025.104440
15. Kandzari DE, Weber MA, Pathak A, et al. Effect of alcohol-mediated renal denervation on blood pressure in the presence of antihypertensive medications: primary results from the TARGET BP I randomized clinical trial. Circulation. 2024;149:1875-1884. doi: 10.1161/CIRCULATIONAHA.124.069291
16. Pathak A, Rudolph UM, Saxena M, et al. Alcohol-mediated renal denervation in patients with hypertension in the absence of antihypertensive medications. EuroIntervention. 2023;19:602-611. doi: 10.4244/EIJ-D-23-00088
17. Hering D, Nikoleishvili D, Imedadze A, et al. Transurethral renal pelvic denervation: a feasibility trial in patients with uncontrolled hypertension. Hypertension. 2022;79:2787-2795. doi: 10.1161/HYPERTENSIONAHA.122.20048
18. Park H, Hwang EC, Jo JK, et al. Resistant hypertension treated with extravascular renal denervation. JACC Case Rep. 2025;30:104126. doi: 10.1016/j.jaccas.2025.104126
19. Struthoff H, Lauder L, Hohl M, et al. Histological examination of renal nerve distribution, density, and function in humans. EuroIntervention. 2023;19:612-620. doi: 10.4244/EIJ-D-23-00264
20. Wang J, Yin Y, Lu C, et al. Efficacy and safety of sympathetic mapping and ablation of renal nerves for the treatment of hypertension (SMART): 6-month follow-up of a randomised, controlled trial. EClinicalMedicine. 2024;72:102626. doi: 10.1016/j.eclinm.2024.102626
21. Qian J, Zhou Z, Zheng Y, et al. Catheter-based ultrasound nerve stimulation and selective renal denervation: a preliminary case series study. J Hypertens. 2025;43:1083-1085. doi: 10.1097/HJH.0000000000004005
22. Sharp ASP, Kandzari DE, Townsend RR, et al. A novel, proof-of-concept radiofrequency renal denervation strategy to improve procedural efficiency: 12-month results from the SPYRAL DYSTAL pilot study. Cardiovasc Revasc Med. 2024;68:30-36. doi: 10.1016/j.carrev.2024.04.005
23. Mahfoud F. First report of the SPYRAL AFFIRM Study: reduced home and office blood pressure following radiofrequency renal denervation in a large US cohort of high cardiovascular risk patients. Presented at: TCT 2025; October 25-28, 2025. San Francisco, California.
24. Schlaich MP, Mahfoud F, Böhm M, et al. Renal denervation in patients with moderate to severe chronic kidney disease. Hypertension. 2025;82:2252-2261. doi: 10.1161/HYPERTENSIONAHA.125.25470
25. Whang W, Nair D, Bhardwaj R, et al. Ultrasound-based renal sympathetic denervation as adjunctive upstream therapy during atrial fibrillation ablation: the ULTRA-HFIB pilot. JACC Clin Electrophysiol. 2026;12:71-81. doi: 10.1016/j.jacep.2025.08.028
26. Steinberg JS, Shabanov V, Ponomarev D, et al. 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. JAMA. 2020;323:248-255. doi: 10.1001/jama.2019.21187
27. Heradien M, Mahfoud F, Greyling C, et al. Renal denervation prevents subclinical atrial fibrillation in patients with hypertensive heart disease: randomized, sham-controlled trial. Heart Rhythm. 2022;19:1765-1773. doi: 10.1016/j.hrthm.2022.06.031
28. Nawar K, Choksumritrong P, Mamas MA, et al. Renal denervation for atrial fibrillation: meta-analysis. J Hum Hypertens. 2022;36:1041-1050. doi: 10.1038/s41371-022-00658-0
29. Fukuta H, Goto T, Wakami K, et al. Effects of catheter-based renal denervation on heart failure with reduced ejection fraction: a meta-analysis of randomized controlled trials. Heart Fail Rev. 2022;27:29-36. doi: 10.1007/s10741-020-09974-4
30. Patel HC, Rosen SD, Hayward C, et al. Renal denervation in heart failure with preserved ejection fraction (RDT-PEF): a randomized controlled trial. Eur J Heart Fail. 2016;18:703-712. doi: 10.1002/ejhf.502
31. Cekirdekci EI, Onar LC. Clinical and hemodynamic effects of pulmonary artery denervation in pulmonary hypertension despite optimized pharmacotherapy: an updated systematic review and meta-analysis. J Clin Med. 2026;15:2619. doi: 10.3390/jcm15072619
32. Kiuchi MG, Ganesan K, Keating J, et al. Combined renal and common hepatic artery denervation as a novel approach to reduce cardiometabolic risk: technical approach, feasibility and safety in a pre-clinical model. Clin Res Cardiol. 2021;110:740-753. doi: 10.1007/s00392-021-01814-1

Shukri W. David, MD, MBA
Henry Ford Health
Detroit, Michigan
sdavid4@hfhs.org
Disclosures: Advisory board for Ablative Solutions, Inc. and Medtronic Structural Heart Division.

Herbert D. Aronow, MD, MPH
Henry Ford Health
Detroit, Michigan
haronow1@hfhs.org
Disclosures: Consultant to Medtronic and Recor Medical.