I. Table of Contents

Abbreviations used throughout the Decision Memorandum for Renal Denervation (RDN) for Uncontrolled Hypertension

ABP – Ambulatory Blood Pressure
ABPM – Ambulatory Blood Pressure Monitoring
ACC – American College of Cardiology
ADBP – Average Daytime Blood Pressure
AHA – American Heart Association
AHM – Antihypertensive Medications
ASBP– Ambulatory Systolic Blood Pressure
BCI – Bayesian Credible Interval
BMI – Body Mass Index
BP – Blood Pressure
CED – Coverage with Evidence Development
CI – Confidence Interval
CKD – Chronic Kidney Disease
CTA – Computed Tomography Angiography
DBP – Diastolic Blood Pressure
eGFR – Estimated Glomerular Filtration Rate
FDA – Food and Drug Administration
HTN – Hypertension
MRA – Magnetic Resonance Angiography
NR – Not Reported
OBP – Office Blood Pressure
OFF MED – Off Medications (in trial contexts)
ON MED – On Medications (in trial contexts)
PMA – Premarket Approval
RCT – Randomized Controlled Trial
RDN – Renal Denervation
rfRDN – Radiofrequency renal denervation
SBP – Systolic Blood Pressure
SD – Standard Deviation
uRDN – Ultrasound renal denervation
US – United States

I. Decision

A. Decision

The Centers for Medicare & Medicaid Services (CMS) will cover radiofrequency renal denervation (rfRDN) and ultrasound renal denervation (uRDN) (collectively, RDN) for uncontrolled hypertension under Coverage with Evidence Development (CED) according to the provisions in sections (B) and (C) below.

B. Coverage Criteria

RDN is covered for uncontrolled hypertension when furnished according to a Food and Drug Administration (FDA) market-authorized indication, and all the following conditions are met:

1. Patient Criteria

The patient meets all the following criteria:

(a) Diagnosis of uncontrolled hypertension ($\geq$ 140 mm Hg systolic blood pressure and > 90 mm Hg diastolic blood pressure) despite active management by a clinician with primary responsibility for blood pressure management.

(b) Uncontrolled hypertension diagnosed using either ambulatory blood pressure monitoring or serial home blood pressure readings.

(c) On lifestyle modifications and stable doses of maximally tolerated guideline-directed medical therapy (GDMT), with assessment of adherence to the prescribed regimen, for at least six weeks before referral for RDN.

(d) As clinically appropriate, secondary hypertension must be evaluated and treated before determining that blood pressure remains uncontrolled. At a minimum, patients must be screened for primary aldosteronism, obstructive sleep apnea, and drug or alcohol induced hypertension before referral to RDN.

(e) The patient has no contraindications to RDN, consistent with the FDA labeling of the device used.

(f) The primary clinicians must coordinate management of the patient for a minimum of six months before referral for RDN, during which the patient had at least three encounters, with no more than two of the three encounters being virtual.

(g) No prior RDN procedure.

2. Physician Criteria

RDN is furnished by clinicians who meet the following criteria, as applicable:

(a) Clinicians referring Medicare beneficiaries must have longitudinal responsibility for hypertension management.

(b) Physicians performing RDN must have interventional and endovascular skills to perform effective RDN treatments. Additionally, they must be able to manage potential complications either themselves or with institutional support from colleagues who are immediately available to assist in emergency management.

(c) Physicians performing RDN without prior endovascular training or renovascular expertise must complete at least ten supervised cases of diagnostic/therapeutic renovascular procedures, half as primary operator. Additionally, they must complete at least five proctored RDN cases with each approved device used in their practice.

(d) Physicians performing RDN with prior endovascular training and active endovascular experience must complete at least five proctored RDN cases with each approved device used in their practice.

3. Facility Criteria

The RDN device and related items and services are furnished at facilities meeting the following criteria:

(a) Facilities performing RDN must have a hypertension program with contributions from a hypertension clinician with longitudinal patient management responsibility, a hypertension navigator, and access to relevant medical specialties (e.g., internal medicine, endocrinology, sleep medicine, cardiology, and nephrology) as appropriate.

(b) Preprocedural imaging capabilities (e.g., ultrasound, Computed Tomography Angiography, Magnetic Resonance Angiography).

(c) An appropriate interventional cardiology or radiology suite.

4. CED Study Criteria

The RDN device and related items and services are furnished in the context of a CMS-approved CED study. CMS-approved CED study protocols must: include only those patients who meet the criteria in section B.1; furnish items and services only through practitioners who meet the criteria in section B.2; furnish items and services at facilities meeting the criteria in section B.3; and include all of the following:

(a) One or more primary outcomes of ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP), home systolic blood pressure (HSBP), home diastolic blood pressure (HDBP), office systolic blood pressure (OSBP), office diastolic blood pressure (ODBP), worsening renal function, cerebrovascular accident, acute myocardial infarction, incidence of new-onset heart failure, cardiovascular mortality, all-cause mortality, or a composite of these, through a minimum of 24 months. Each component of a composite outcome must be individually reported.

(b) An active comparator.

(c) Design sufficient for subgroup analyses by:

- Age (Stratify <65, 65-74, 75+);
- Other clinically important patient demographic factors;
- Chronic kidney disease (Stratify by CKD Stages);
- Progression of CKD;
- Hypertension phenotype (e.g., resistant hypertension vs. uncontrolled for any reason);
- Medication adherence.

(d) In addition, CMS-approved CED studies must adhere to the scientific standards (criteria 1-17 below) that have been identified by the Agency for Healthcare Research and Quality (AHRQ) as set forth in Section VI. of CMS' Coverage with Evidence Development Guidance Document, published August 7, 2024 (the "CED Guidance Document").

1. Sponsor/Investigator: The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.
2. Milestones: A written plan is in place that describes a detailed schedule for completion of key study milestones, including study initiation, enrollment progress, interim results reporting, and results reporting, to ensure timely completion of the CED process.
3. Study Protocol: The CED study is registered with ClinicalTrials.gov and a complete final protocol, including the statistical analysis plan, is delivered to CMS prior to study initiation. The published protocol includes sufficient detail to allow a judgment of whether the study is fit-for-purpose and whether reasonable efforts will be taken to minimize the risk of bias. Any changes to approved study protocols should be explained and publicly reported.
4. Study Context: The rationale for the study is supported by scientific evidence and study results are expected to fill the specified CMS-identified evidence deficiency and provide evidence sufficient to assess health outcomes.
5. Study Design: The study design is selected to safely and efficiently generate valid evidence of health outcomes. The sponsors/investigators minimize the impact of confounding and biases on inferences through rigorous design and appropriate statistical techniques. If a contemporaneous comparison group is not included, this choice should be justified, and the sponsors/investigators discuss in detail how the design contributes useful information on issues such as durability or adverse event frequency that are not clearly answered in comparative studies.
6. Study Population: The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended population of the intervention, particularly when there is good clinical or scientific reason to expect that the results observed in premarket studies might not be observed in older adults or subpopulations identified by other clinical or demographic factors.
7. Subgroup Analyses: The study protocol explicitly discusses beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion requirements effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. In the protocol, the sponsors/investigators describe plans for analyzing demographic subpopulations as well as clinically-relevant subgroups as

identified in existing evidence. Description of plans for exploratory analyses, as relevant subgroups emerge, are also included.

8. Care Setting: When feasible and appropriate for answering the CED question, data for the study should come from beneficiaries in their expected sites of care.
9. Health Outcomes: The primary health outcome(s) for the study are those important to patients and their caregivers and that are clinically meaningful. A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions. Generally, when study sponsors propose using surrogate endpoints to measure outcomes, they should cite validation studies published in peer-reviewed journals to provide a rationale for assuming these endpoints predict the health outcomes of interest. The cited validation studies should be longitudinal and demonstrate a statistical association between the surrogate endpoint and the health outcomes it is thought to predict.
10. Objective Success Criteria: In consultation with CMS and AHRQ, sponsors/investigators establish an evidentiary threshold for the primary health outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.
11. Data Quality: The data are generated or selected with attention to provenance, bias, completeness, accuracy, sufficiency of duration of observation to demonstrate durability of health outcomes, and sufficiency of sample size as required by the question.
12. Construct Validity: Sponsors/investigators provide information about the validity of drawing warranted conclusions about the study population, primary exposure(s) (intervention, control), health outcome measures, and core covariates when using either primary data collected for the study about individuals or proxies of the variables of interest, or existing (secondary) data about individuals or proxies of the variables of interest.
13. Sensitivity Analyses: Sponsors/investigators will demonstrate robustness of results by conducting pre-specified sensitivity testing using alternative variable or model specifications as appropriate.
14. Reporting: Final results are provided to CMS and submitted for publication or reported in a publicly accessible manner within 12 months of the study's primary completion date. Wherever possible, the study is submitted for peer review with the goal of publication using a reporting guideline appropriate for the study design and structured to enable replication. If peer-reviewed publication is not possible, results may also be published in an online publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with incomplete results).
15. Sharing: The sponsors/investigators commit to making study data publicly available by sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party. The study should comply with all applicable laws regarding subject privacy, including 45 CFR § 164.514 within the regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.
16. Governance: The protocol describes the information governance and data security provisions that have been established to satisfy Federal security regulations issued pursuant to HIPAA and codified at 45 CFR Parts 160 and 164 (Subparts A & C), United States Department of Health and Human Services (HHS) regulations at 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient and HHS regulations at 45 CFR Part

46, regarding informed consent for clinical study involving human subjects. In addition to the requirements under 42 CFR and 45 CFR, studies that are subject to FDA regulation must also comply with regulations at 21 CFR Parts 50 and 56 regarding the protection of human subjects and institutional review boards, respectively.

17. Legal: The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals, although it is acceptable for a study to test a reduction in toxicity of a product relative to standard of care or an appropriate comparator. For studies that involve researching the safety and effectiveness of new drugs and biological products aimed at treating life-threatening or severely-debilitating diseases, refer to additional requirements set forth in 21 CFR § 312.81(a).

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet all the criteria and standards identified above.

C. Other Uses of RDN

1) RDN is not covered for patients outside of a CMS-approved study.
2) Nothing in this NCD would preclude coverage of RDN through NCD 310.1 (Clinical Trial Policy) or through the Investigational Device Exemption (IDE) Policy.

See **Appendix A** for proposed Medicare National Coverage Determinations Manual language.

II. Clinical Review

A. Background

Hypertension Definition and Classification

The American Heart Association (AHA) defines blood pressure (BP) as a force that pushes blood through a network of arteries, veins, and capillaries. The blood pressure reading is the result of two forces: systolic pressure occurs as blood pumps out of the heart and into the arteries; diastolic pressure is created as the heart rests between heartbeats (AHA, 2024). Elevated blood pressure, or hypertension (HTN), leads to harm by causing tiny tears in the interior lining (intima) of the arteries and coronary vessels, stimulating a local immune response in the endothelial cells within the arterial walls. In these regions, the arterial intima retains apolipoprotein B, which attracts lipid-rich macrophages (foam cells). These preatherotic lesions develop into atherosclerotic plaques, which become increasingly fibrotic and can form fissures, hematomas, thrombi, and calcifications (Swirski and Nahrendorf, 2013). The result is stiff, thickened arteries that narrow the flow of blood to organs and limbs, which both increases pressure on target organs and limits oxygenation of them. There is also the risk of atherosclerotic plaque rupture, resulting in distal vascular obstruction and ischemia and infarction of end organs, such as stroke in the brain (NIH-NHLBI, 2024). **Table 1**, below, outlines the stages of HTN as defined by the AHA.

Table 1: Categories of BP in Adults*

Blood Pressure Category	SBP	and/or	DBP
Normal	< 120 mm Hg	and	< 80 mm Hg
Elevated	120 - 129 mm Hg	and	< 80 mm Hg
Hypertension: Stage 1	130 - 139 mm Hg	or	80 - 89 mm Hg
Hypertension: Stage 2	≥ 140 mm Hg	or	≥ 90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

Source: American Heart Association, 2024
DPB: diastolic blood pressure; mm Hg: millimeters of mercury; SBP: systolic blood pressure

Uncontrolled HTN is defined as persistently elevated BP above SBP 140 mm Hg and DBP 90 mm Hg (Yaxley and Thambar, 2015; Mancia et al., 2023). Resistant hypertension is defined as BP above goal despite treatment with 3 antihypertensive medications with complementary mechanisms of action, including a diuretic at maximally tolerated doses or BP at goal but requiring >4 medications (Jones et al., 2025).

Epidemiology

HTN is a common condition in Westernized countries, affecting approximately 32% of adults and accounting for 8.6% of all primary care visits. Of these cases, about 10% are estimated to be resistant HTN (Yaxley and Thambar, 2015). In the 2013-2016 National Health and Nutrition Examination Survey (NHANES), the prevalence of hypertension (defined at that time as SBP ≥140 or DBP ≥90) in the US was 30.5% (CDC, 2017). The rate of uncontrolled hypertension among known hypertensives was 55.4%. Hypertension was somewhat more prevalent in men than women (31.5% vs. 29.3%, respectively), but men were much more likely to have uncontrolled hypertension (60.9% vs. 46.7%). Blacks had a higher prevalence of hypertension than whites, Latinos, or Asians (42.4%, 29.2%, 29%, and 27%, respectively). By age, 67.4% of women 65-74 years and 78.7% of women 75 years and older had hypertension. Among men, the prevalence was 61.1% and 67.4%, respectively (CDC, 2017).

While it is estimated that about 12% to 15% of patients treated for HTN have apparent resistant HTN (Carey et al., 2018), its true prevalence is unknown due to pseudo-resistant HTN. Pseudo-resistant HTN occurs when other factors, such as poor medication adherence, conflicting medications, measurement error, or white coat hypertension, cause what appears to be resistant HTN. Obesity and older age are the strongest risk factors for this condition, though black race, chronic kidney disease, and diabetes are also associated. Cardiovascular disorders such as heart failure, stroke, ischemic heart disease, and renal failure are of great concern for this population, as HTN is a risk factor for these conditions (Carey et al., 2018).

Treatment and Response to Therapy

Current management of HTN involves both pharmacologic therapy and lifestyle modification, which includes dietary changes, behavioral adjustments such as smoking cessation and decreased alcohol consumption, treatment of sleep apnea, and increased physical activity. There is a dearth of randomized trial data to guide drug treatment for resistant HTN, and since most cases are of unknown etiology, initial management essentially mimics that of essential HTN. Per the 2025 Multispecialty Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, thiazide diuretics, long acting dihydropyridine calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers are considered first-line therapy for Stage 1 HTN (Jones et al., 2025). Stage 2 HTN can warrant two first-line therapies of different classes adjusted to the optimal dosages and types. Spironolactone or eplerenone is a preferred add-on therapy to a standard treatment regimen for patients with resistant HTN who do not have concomitant hyperkalemia or renal dysfunction. Aggressive lifestyle modification and discontinuation of contributing medications, such as nonsteroidal anti-inflammatory drugs, are also recommended (Whelton et al., 2018).

Despite these widely available antihypertensive agents, drug-resistant hypertension remains a challenging issue in clinical hypertension care. With the decrease in new antihypertensive medication classes available in the clinic (there have been no additions since direct renin inhibitors in 2007), the search for more effective ways to manage drug-resistant hypertension was shifted to revisiting device-based approaches such as renal denervation (RDN; Rey-García and Townsend, 2022).

Renal Denervation Devices

RDN involves ablating nerves in the renal arteries via a catheter-based radiofrequency or ultrasound procedure. Catheter-based radiofrequency ablation is the most commonly used technique, delivering heat to the intended tissue. Alternatively, intraluminal and extracorporeal high-intensity focused ultrasound delivers high-frequency acoustic energy via a transducer to destroy the tissue; see **Appendix B** for more on the characteristics and operator factors for the devices considered.

There is no evidence of anatomical or functional reinnervation in patients who have undergone catheter-based RDN, but this is an important long-term consideration (Weber et al., 2019). Both functional and anatomical reinnervation of renal nerves has been reported within 12 weeks after surgical RDN in normal rats (Mulder et al., 2013), although renal norepinephrine levels do not return to normal levels by 12 weeks (Rodionova et al., 2016). In normal sheep, both anatomical and functional evidence of afferent and efferent reinnervation was shown at 11 months after

RDN (Symplicity Flex catheter), and there was nearly complete recovery of norepinephrine levels by 11 months (Booth et al., 2015). On the other hand, Sharp et al. (2022) demonstrated sustained reductions in renal norepinephrine, cortical axon density, and downstream axonal loss caused by axonal destruction through 180 days post-RDN using Spyral in normotensive pigs, suggesting that functional nerve regrowth after radiofrequency RDN (rfRDN) is unlikely. These results confirmed similar observations by Rousselle et al. (2015) in a similar model also using rfRDN. These studies, together with the experience from the transplantation field, indicate that at least partial anatomical and functional reinnervation is likely to occur after RDN, but the exact timeframe and relevance to sustained BP control are unclear. Nonetheless, evidence from observational studies suggests that blood pressure reductions may persist beyond four years, and functional reinnervation may not be occurring (Mahfoud F et al., 2025).

Investigators have found that assessing the adequacy or completeness of RDN is challenging. Currently, no simple physiological or biochemical markers can evaluate the extent of RDN at the time of the procedure; thus, there is no confirmation that the procedure has been successful. Several immediate markers have been proposed, including renal blood flow parameters (Tsioufis et al., 2013), blood levels of brain-derived neurotrophic factor (Dörr et al., 2015), renal norepinephrine spillover (Esler et al., 2010), and the BP response to catheter-based renal nerve stimulation (de Jong et al., 2016). However, none of these are currently used clinically, and both technique and operator experience are important.

B. Food and Drug Administration Status

On November 2, 2023, the Food and Drug Administration (FDA) approved Recor Medical's Paradise® Ultrasound Renal Denervation System premarket approval (PMA) application (P220023).

Recor Medical's Paradise ultrasound RDN (uRDN) device utilizes intra-arterial catheters to deliver ultrasound energy through the renal arterial wall to ablate the adjacent sympathetic nerves. The Paradise uRDN System includes the Paradise Catheter with ultrasound transducer, Paradise Generator, Paradise Cartridge, and the Paradise Connection Cable. The Paradise uRDN System is a catheter-based system that delivers ultrasound energy circumferentially to thermally ablate and disrupt renal sympathetic nerve activity to reduce systemic arterial BP.

On November 17, 2023, FDA approved Medtronic's Symplicity Spyral™ Renal Denervation System PMA application (P220026).

The Symplicity Spyral rfRDN System consists of two main components: a single-use, disposable catheter (Symplicity Spyral multielectrode renal denervation catheter, also referred to as Symplicity Spyral catheter) and a reusable radiofrequency (RF) generator (Symplicity G3 Renal Denervation RF generator, also referred to as Symplicity G3 RF generator). The generator includes an optional remote control and power cord.

Medtronic previously studied an earlier version of their RDN device, the Symplicity Flex RDN, in a series of clinical trials: HTN-1 (Esler et al., 2014); HTN-2 (Esler et al., 2010, Esler et al., 2014, Esler et al., 2012); and HTN-3 (Bakris et al., 2015, Bhatt et al., 2014, Bhatt et al., 2022). HTN-3 was a multicenter, sham-controlled trial of 535 patients. It met its primary safety

endpoint, but the primary and secondary effectiveness endpoints (a significant reduction in BP compared to sham controls) were not met. Potential contributors to the nil result in HTN-3 include prescribed medication changes in 39% of patients during the study period, despite the protocol mandating no medication changes, and a larger than expected decrease in office and ambulatory systolic BP in the control group. Additionally, incomplete ablation might result in inadequate denervation and was cited as a potential contributor to the nil result in HTN-3.

Following HTN-3, Medtronic redesigned its RDN device with a spiral configuration of multiple RF electrodes to deliver more effective circumferential RDN. The Symplicity multi-electrode radiofrequency RDN system's safety and performance were tested in a prospective, non-randomized, open-label, feasibility study that enrolled 50 subjects (Whitbourn et al., 2015). The results of this feasibility study indicated that the Symplicity multi-electrode RDN system was associated with a statistically significant, although highly variable, reduction in office SBP (OSBP) from baseline at 12 months post-procedure (-19.2±25.2 mm Hg), with minimal complications.

The indication for both RDN devices is to reduce BP as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control BP.

III. Evidence

This section provides a summary of the evidence we considered during our review. The evidence presented here includes the published medical literature on pertinent clinical research of endovascular RDN (radiofrequency energy or high-focused ultrasound energy) for resistant hypertension. This assessment does not address other methods of RDN, such as surgical renal denervation or chemical ablation using alcohol injections into the perivascular space of the renal artery.

A. Evidence Questions

The following questions guided our clinical literature search, review, and analysis of the evidence on RDN for resistant HTN. We answer these questions in **Section IV.B. 6**. following the CMS coverage analysis.

Q1. Is the evidence sufficient to conclude that RDN for hypertension meaningfully improves health outcomes for Medicare beneficiaries?

Q2. Do specific characteristics or comorbidities make patients more or less likely to benefit from RDN in hypertension management?

Q3. Are specific treatment conditions necessary to achieve outcomes with the use of RDN for hypertension management similar to those demonstrated in the clinical studies reviewed in this analysis?

B. Technology Assessments

CMS did not request an external technology assessment on this topic. Our review did not identify any Cochrane or Evidence-based Practice Center (EPC) reviews of RDN for uncontrolled HTN.

C. Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened on this topic.

D. Clinical Literature Search

A systematic literature review addressed the above evidence questions and focused on RDN for resistant HTN, population risk factors, and endpoints. Literature searches were conducted in PubMed and Embase with search terms related to the following topics: (1) "hypertension," (2) "anti-hypertensive therapy," (3) "kidney denervation system," or (4) "anti-hypertensive devices." The review included all published, peer-reviewed English language clinical studies and systematic reviews from the databases' inception to Oct 10, 2024. We excluded clinical studies with fewer than 30 patients, editorials, and conference abstracts.

Of the references identified in the searches, 26 were deemed eligible for inclusion. These publications reported on a total of seven randomized controlled trials (RCTs), which served as the primary basis for our analysis. We note that additional results were published shortly before publication of this coverage analysis (Kandzari et al., 2025). Although they are not part of the evidence base, we have briefly summarized those results, and the findings in the recent publication do not change our decision.

The primary studies are summarized in **Table 2**.

Table 2. Key Studies[1] for RDN for Hypertension

Study			Patients				Endpoint		
Author	**Year**	**Study design**	**Inclusion**	**N**	**Age (yr)**	**Female (%)**	**Blinding** **Additional AHM allowed**	**Follow-up**	**Primary findings[2]**
Urdn									
On-Medication									
Azizi et al. (RADIANCE-HTN SOLO)	2018	RCT	Mild to moderate	74: 72	54.4; 53.8	30; 46	Blinded No	2 mo	Δ Daytime ASBP: -6.3 (-9.4 to -3.1); p= 0.0001
Azizi et al. (Follow-up of RADIANCE-HTN SOLO)	2019			69: 71	54.1; 53.8	37.7; 45.1	Blinded Yes, Standardized	6 mo	Δ Daytime ASBP: -4.3 (-7.9 to -0.6); p= 0.024
Azizi et al. (Follow-up of RADIANCE-HTN SOLO)	2020			65: 67	54.3; 54.1	33.9; 47.8	Unblinded Yes, Standard of Care	12 mo	Δ Daytime ASBP: -2.3 (-5.9 to 1.3); p=0.201

									Δ OSBP: -6.3 (-11.1 to -1.5); p=0.010
Rader et al, (Follow-up of RADIANCE-HTN SOLO)	2022	Single-arm follow-up		51: n/a	53.9: n/a	33.3:n/a	Unblinded Yes, Standard of Care	36 mo	Δ OSBP from baseline to 36 months: Mean:18; SD:15 mmHg; p< 0.001
Azizi et al. (RADIANCE-II)	2023	RCT	Stage 2 HTN	150: 74	55.1; 54.9	31.3; 23.0	Blinded No	2 mo	Δ Daytime ASBP: -6.3 (-9.3 to -3.2); p<0.001 Δ OSBP: -5.4 (-9.0 to -1.8); p= 0.004
On Medication									
Azizi et al. (RADIANCE-HTN TRIO)	2021	RCT	Resistant	69: 67	52.3; 52·8	19; 21	Blinded Yes, Standardized	2 mo	Δ Daytime ASBP: -4.5 (-8.5 to -0.3); p= 0.022 Δ OSBP: -7.0 (-13.0 to 0.0); p= 0.037
Azizi et al. (Follow-up of RADIANCE-HTN TRIO)	2022	RCT	Resistant	65: 64	51.9; 53.0	18.5; 20.3	Blinded Yes, Standardized	6 mo	Δ Daytime ASBP: -0.0 (-4.6 to 4.5); p= 0.65 Δ OSBP: -0.7 (-5.3 to 6.6); p= 0.93
Bloch et al. (Follow-up of RADIANCE-HTN TRIO)	2024	Single-arm follow-up	Resistant	49: n/a	53.0: n/a	18: n/a	Unblinded Yes	36 mo	Δ OSBP from screening: Mean: -14.5; SD: 26.1; p < 0.001 Δ OSBP from baseline: Mean: -8.0; SD: 24.5; p= 0.007
Kario et al. (REQUIRE)	2022	RCT	Resistant	69: 67	50.7; 55.6	30.4; 20.9	Single-blind Yes, Not standardized	3 mo	Δ 24-hour ASBP: LSMD: -0.1; SEM: 2.1; p=0.971 Δ 24-hour OSBP: LSMD: -2.0; SEM: 3.0; p= 0.511
RfRDN									
Off Medication									
SPYRAL HTN-OFF MED Pivotal Böhm et al.	2020	RCT	Un-controlled	166:165	51.4; 52.5	36.7; 33.3	Blinded No	3 mo	Δ 24-hour SBP: -4.0 (95% BCI -6.2 to -1.8); pps> 0.999

Includes patients enrolled in Townsend et al., 2017									Δ OSBP: -6.6 (95% BCI -9.6 to -3.5); pps> 0.999
On Medication									
Kandzari et al. (SPYRAL HTN-ON MED Expansion) Includes patients enrolled in Kandzari et al. 2018	2023	RCT	Un-controlled	206: 131	55.2; 54.6	19; 21	Blinded Yes	6 mo	Δ 24-hour ASBP: -0.03 (95% BCI: -2.82 to 2.77); pps= 0.51 Δ OSBP: -4.9 (-7.9 to -1.9); p= 0.0015
Kandzari et al. (Follow-up of SPYRAL HTN-ON MED)[3]	2025	RCT	Un-controlled	206: 131[4] (ITT) 187: 35 (Per-protocol)	55.2; 54.6	19; 21	Patients and physicians unblinded Outcome assessors for OSBP blinded Yes	12 mo 24 mo	Δ 24-hour ASBP: -0.6; p=0.71 Δ OSBP: -3.1; p=0.15 Δ 24-hour ASBP: -5.7; p=0.039 Δ OSBP: -8.7; p=0.0034
Mahfoud et al. (SPYRAL HTN-ON MED proof-of-concept)	2022	RCT	Un-controlled	38: 42	53.9; 53.0	13.2; 19	Unblinded Yes	36 mo	Δ 24-hour ASBP: -10.0 (-16.6 to -3.3); p=0.0039 Δ OSBP: -8.2 (-17.1 to 0.8); p= 0.073

[1] There are multiple subtrials and analyses reported within this document. Table 2 reflects the findings of the main trials.

[2] Findings are reported as baseline-adjusted MD in mm Hg (95% CI) unless otherwise indicated.

[3] The 24 month follow-up of SPYRAL HTN-ON MED was published subsequent to the evidence review but is included here for completeness.

[4] Patients were able to cross over to the RDN group (n=66) after the primary endpoint measure at 6-months. Patients in the sham condition who crossed over to RDN were censored, meaning that no data from these patients were carried forward.

AHM: antihypertensive medications; ASBP: ambulatory systolic blood pressure; BCI: Bayesian credible interval; CI: confidence interval; ITT: intention-to-treat population; MD: mean difference; n/a: not applicable; OSBP: office systolic blood pressure; pps: posterior probability of superiority; RCT: randomized controlled trial; rfRDN: radiofrequency renal denervation; SBP: systolic blood pressure; SD: standard deviation; SEM: standard error of the mean; uRDN: ultrasound renal denervation

E. Assessment of Evidence

The seven RCTs considered as evidence consisted of various designs to evaluate renal denervation systems in patients with hypertension. Three trials—RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, and RADIANCE II—were randomized, double-blind, sham-controlled studies conducted at multiple centers across Europe and the United States. The REQUIRE trial, conducted in Japan and South Korea, was a randomized, single-blind, sham-controlled study. Additionally, two multicenter, sham-controlled, single-blind trials, SPYRAL HTN-OFF and SPYRAL HTN-ON, were conducted across the US, Canada, Japan, Europe, and Australia. The RADIOSOUND-HTN trial was a 3-arm study, conducted in Germany, comparing uRDN, and

rfRDN ablation of either the main renal artery or of both the main renal artery, branches, and accessory arteries to each other.

The RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, RADIANCE II, and REQUIRE trials evaluated the safety and efficacy of the uRDN system. These studies were conducted in groups of patients who were either not using (Off Med) or who were using (On Med) antihypertensive drugs.

The SPYRAL HTN-OFF and HTN-ON trials assessed the safety and efficacy of the rfRDN system, incorporating an adaptive Bayesian design with a pilot study followed by an expansion cohort. Like the RADIANCE trials, these studies were conducted in groups of patients who were either not using (Off Med) or who were using (On Med) antihypertensive drugs.

Finally, the RADIOSOUND-HTN trial employed a prospective, randomized design to directly compare the different renal denervation methods in patients with resistant hypertension. Participants who were considered medication-adherent were admitted into the study and continued with their antihypertensive medications during the trial, with therapeutic adjustments as needed.

Study Quality Assessment

Study quality for RCTs was assessed using the US Preventive Services Task Force's (USPSTF) Criteria for Assessing Internal Validity of Individual Studies. We rated the quality of the primary RCTs, and it should be noted that most studies were unblinded during the follow-up period, which could impact the findings. All Radiance trials were sponsored by Recor, and all SPYRAL trials were sponsored by Medtronic. REQUIRE was funded by JIMRO Co. and Korea Otsuka Pharmaceutical. RADIOSOUND-HTN was funded by the Leipzig Heart Institute. All studies except RADIOSOUND-HTN received editorial or trial design input or medical writing support from the manufacturers, and all studies had declarations of support (e.g., receiving speaker or consulting fees) from manufacturers for one or more authors.

uRDN

The RADIANCE trials, including SOLO, TRIO, and RADIANCE II, were rated as "Good." There was adequate randomization and allocation of participants for RADIANCE II, SOLO, and TRIO, adequate blinding of patients (for 6 months), and outcome assessors. Intention-to-treat (ITT) analysis was conducted, and overall attrition was low. Retention in the SOLO trial was 100%, 95%, and 90% at the 2-, 6-, and 12-month follow-up visits, respectively. Retention in the TRIO trial was 100% and 95% at the 2- and 6-month follow-up visits, respectively. RADIANCE II has reported 2-month results with no loss to follow-up at this time.

The REQUIRE trial received a rating of "Poor." The authors reported the possibility of patient sampling error such that a significant number of patients with uncontrolled hypertension and poor drug adherence may have been enrolled in the study and may have improved their drug adherence during the study. Although patients were blinded, clinical staff were not blind to treatment condition, which is a critical study limitation under the USPSTF framework. There was no standardization of AHM. Additionally, authors reported poor drug adherence in nearly half the patients during the study. There were no other major methodological concerns.

Randomization and allocation concealment were adequate, as was the blinding of participants and outcome assessors. No ITT analysis was performed, but attrition was low (~95% retention).

rfRDN
The SPYRAL HTN OFF MED and SPYRAL HTN ON MED trials received ratings of "Good." Randomization and allocation concealment were adequate. There was adequate blinding of participants across studies. In both HTN OFF MED and HTN ON MED, pilot cohort participants remained blinded for 12 months, and expansion cohort participants remained blinded for 6 months. There was adequate blinding of outcome assessors. ITT analyses were performed, and there were no other major methodological concerns.

The RADIOSOUND-HTN was rated “Poor” as only the participants were blinded. Under the USPSTF framework, the lack of blinding of outcome assessors is considered a critical design limitation. Additionally, there was no standardization of AHM, and adherence was not tested. Randomization was adequate, and while no ITT analysis was performed, attrition was low (~95% retention).

Evidence Base and Synthesis of Results

A total of 1,465 patients were enrolled across seven RCTs, with 506 participants in the RADIANCE trials, 366 in the HTN OFF MED trial, 337 in the HTN ON MED trial, 136 in the REQUIRE trial, and 120 in the RADIOSOUND trial. Follow-up periods for participants ranged from 2 to 36 months. Across all trials, the mean age of participants ranged from 51.4 years in the HTN OFF MED trial to 64.6 years in the RADIOSOUND trial. However, the overall proportion of patients aged 65 and older was not reported.

Overall, these seven trials represented a broad spectrum of hypertensive populations, ranging from mild to resistant forms of hypertension. The RADIANCE-HTN trials targeted two distinct patient groups: those with mild to moderate hypertension not on medications at the time of enrollment (SOLO and RADIANCE II) and those with resistant hypertension (TRIO). In contrast, the SPYRAL HTN-OFF and HTN-ON trials focused on patients with mild to moderate hypertension, and HTN-OFF was further limited to patients able to discontinue AHMs, while HTN-ON included patients on stable regimens of 1-3 AHMs. These two trials were conducted in two phases: an initial Pilot Cohort to assess feasibility and an Expansion Cohort utilizing an adaptive Bayesian design. The REQUIRE and RADIOSOUND trials both studied patients with resistant hypertension.

Across all trials, baseline characteristics between the RDN (uRDN or rfRDN) and sham groups were generally well-balanced, with minor variations. Key parameters such as age, sex, BMI, and BP showed close alignment in most studies. For instance, age and BMI were comparable across groups in trials like SOLO, Radiance II, and HTN-OFF. BP, both office and 24-hour measurements, also showed similar baseline levels between the RDN and sham groups, ensuring fair comparisons. Minor differences included slightly higher male representation in the sham groups of some trials, such as Radiance II and REQUIRE. Racial and ethnic status, however, was not always thoroughly reported, and enrollment of different racial and ethnic groups was limited across studies, with most participants being white. In the studies where racial backgrounds were properly reported (RADIANCE SOLO, RADIANCE II, and TRIO), the proportion of African

Americans in these studies was similar to their overall proportion in the general US population. However, resistant hypertension is more prevalent in African Americans (Sarafidis et al., 2013). Hispanics and Asian Americans were generally underrepresented in these studies. Despite this, the racial distribution within each trial (when reported) was generally balanced between the groups. Background medical therapy was not standardized in SPYRAL HTN ON MED, and it was not in the form of single-pill combination therapy in the RADIANCE HTN TRIO trial. This study design left room for adding or withdrawing medications during the studies.

Below, we describe the main outcomes for safety and efficacy as reported in the RCTs investigating RDN. Please refer to the tables in **Appendix C** for baseline characteristics across all trials.

Ultrasound Renal Denervation (uRDN)

Inclusion Criteria and Setting

The RADIANCE studies enrolled individuals aged 18 to 75 years with a documented history of hypertension, suitable renal anatomy for the renal denervation procedure confirmed by recent renal CTA (computed tomography angiography) or MRA (magnetic resonance angiography), and the ability to comply with study procedures. The studies RADIANCE-HTN SOLO (Azizi et al., 2018), RADIANCE-HTN TRIO (Azizi et al., 2021), and RADIANCE II (Azizi et al., 2023) were conducted at multiple centers across Europe and the United States. The REQUIRE trial was conducted in Japan and South Korea (Kario et al., 2022).

Findings

The efficacy of uRDN for lowering BP was mixed between the Off Med (SOLO and RADIANCE II) studies and between the Off Med and On Med (TRIO and REQUIRE) studies. Use of uRDN in the Off Med SOLO and RADIANCE II trials showed consistent reductions in office systolic BP and daytime ASBP compared to the sham intervention at 2 months follow-up in patients with mild-to moderate HTN and patients with Stage 2 HTN, although the evidence is more varied at later time points, and the evidence is limited for durability of effect. In patients with resistant HTN, findings differed between the two On Med trials. In TRIO, uRDN reduced daytime ASBP statistically, but not meaningfully, more than the sham procedure at 2 months but not at 6 months. The smaller REQUIRE trial found no difference in ASBP changes between uRDN and sham at the 3-month follow-up. There were relatively few treatment-related adverse events across studies.

Mild-to-Moderate Hypertension

In patients with mild-to-moderate hypertension (SOLO; Azizi et al., 2018), at 2 months the uRDN group (n=74) achieved a clinically significantly greater reduction in office systolic BP (SBP) relative to the sham group (n=72), with a baseline-adjusted difference (AD) between groups of -6.5 mm Hg (95% CI: -11.3 to -1.8; p=0.007) as well as daytime ASBP (-6.3 mm Hg; 95% CI: -9.4 to -3.1; p=0.0001). At 6 months, patients in the SOLO trial were still blinded to treatment condition (Azizi et al., 2019) and had received recommended and standardized stepped-care antihypertensive treatment since the 2-month follow-up if home BP control did not achieve the target range (home BP ≥135/85 mm Hg). At the 6-month time point, 65.2% of patients in the uRDN group were treated with antihypertensive medications (AHM) versus 84.5% in the sham group (p=0.008), the number of medications used and the defined daily dose (DDD) were lower in the uRDN group relative to the sham group (AHM: 0.9 ± 0.9 vs 1.2 ± 0.9,

p=0.043 and DDD: 1.4 ± 1.5 vs 2.0 ± 1.8, p = 0.018; respectively). Reductions in OSBP did not differ between the groups (AD: -3.7 mm Hg; 95% CI: -8.1 to 0.7 mm Hg; p=0.102; adjusted for baseline value and AHM). However, reductions in ASBP were statistically different between the groups (AD: -4.3 mm Hg; 95% CI: -7.9 to -0.6 mm Hg; p = 0.024; adjusted for baseline value and AHM), but this difference may not be clinically meaningful. At the 12-month follow-up (Azizi et al., 2020), patients were no longer blind to treatment condition and were treated with AHM according to standard-of-care (i.e., not standardized). The number of medications (1.0 vs. 1.4; p=0.015), and DDD (1.4 vs. 2.2; p=0.007) were less with uRDN versus sham. There was no difference in daytime ASBP between the groups (AD: -2.3 mm Hg; 95% CI: -5.9 to 1.3; p=0.201; adjusted for baseline value and AHM), but OSBP was clinically meaningfully decreased (AD: -6.3 mm Hg; 95% CI: -11.1 to -1.5 mmHg; p=0.010).

Regarding safety outcomes, the SOLO trial reported no major adverse events in either group at 30 days or 6 months (Azizi et al., 2019). At the 12-month follow-up, one patient in the sham group died (suicide), and one experienced a cerebrovascular event. Neither group had any other major adverse events (Azizi et al., 2020). Twelve-month imaging was available in 63 RDN patients. One patient underwent renal artery stent placement at 6 months after mild progression of ostial renal artery plaque. No new renal artery stenosis >70% was detected on CTA or MRA of the renal arteries at 12 months, and the calculated eGFR remained stable from baseline to 12 months in the RDN group (Azizi et al., 2020).

Of note, the SOLO trial was not designed or powered to demonstrate a difference in BP between the uRDN and the sham beyond 2 months, and sham patients with persistent uncontrolled hypertension were eligible to crossover and receive uRDN. A single-arm follow-up study of patients who remained in the uRDN arm from randomization reported findings at 36 months (Rader et al., 2022). In patients with uncontrolled BP at screening (n=36), office systolic BP decreased by 10.8 mm Hg (no estimate of variability; p<0.001) at 36 months. This is a small subset of patients, and these findings regarding durability should be interpreted in that context. No new adverse events were deemed related to the procedure at this follow-up.

Stage 2 Hypertension

In patients with stage 2 HTN (RADIANCE II; Azizi et al., 2023) those randomized to uRDN (n=150) versus sham (n=74) demonstrated a clinically meaningful reduction in OSBP with a between-group difference of -5.4 mm Hg (95% CI: -9.0 to -1.8; p=0.004) and in daytime ASBP (AD: -6.3 mm Hg; 95% CI: -9.3 to -3.2; p<0.001) at two months follow-up with no major adverse events in either group. This study's follow-up is short, and planned observational data at 6 and 12 months have yet to be reported.

Resistant Hypertension

The findings in patients with resistant HTN are mixed. Both studies were conducted in patients receiving concomitant antihypertensive drug therapy. In the TRIO trial, patients with resistant hypertension on fixed-dose, triple combination therapy (Azizi et al., 2021), uRDN (n=69) reduced OSBP (unadjusted median difference: -7.0: 95% CI: -13.0 to 0.0; adjusted p=0.037) and daytime ASBP (unadjusted median difference: -4.5 mm Hg; 95% CI -8.5 to -0.3; adjusted p=0.022) more than sham (n=67). These findings are statistically different but may not be clinically meaningful. However, at 6 months, the per-protocol analysis indicated no significant

difference between treatment conditions in either OSBP (AD: 0.7; 95% CI: -5.3 to 6.6; p=0.93) or daytime ASBP (AD: -0.0 mm Hg; 95% CI: -4.6 to 4.5; p = 0.65; Azizi et al., 2022). In REQUIRE, patients with resistant hypertension and standard-of-care medication therapy (Kario et al., 2022), uRDN (n=69) and sham (n=67) treatments did not differ at 3-month follow-up for either OSBP (Least Squares Mean Difference [LSMD]: -2.0; Standard Error of the Mean (SEM): 3.0; 95% CI: not reported; p=0.511) or 24-hour ASBP (LSMD: -0.1, SEM: 2.1; 95% CI: -5.5 to 5.3; p=0.971).

Regarding safety outcomes, three adverse events were reported in the TRIO trial after uRDN within 30 days of the procedure (Azizi et al., 2022). Six other cardiovascular or kidney events through 6 months were reported in four patients in each group, and eGFR decreased slightly and similarly from baseline to 6 months in the 2 groups. No new 50% or greater kidney artery stenosis was detected on non-invasive imaging in either group at 6 months (Azizi et al., 2022). REQUIRE did not report any major procedure- or device-related adverse events. However, vasospastic angina was seen in one patient, and a puncture site hemorrhage occurred in another during the RDN procedure (Kario et al., 2022).

It should be noted that the patient populations differed between TRIO and REQUIRE. Patients enrolled in TRIO were primarily white and residing in Western countries (e.g., the United States, the United Kingdom, Germany, and France), whereas patients enrolled in REQUIRE were Asian and resided in Japan or South Korea. Baseline enrollment criteria differed between the two studies, with TRIO enrolling patients with office BP of at least 140/90 mm Hg despite using three or more medications, including a diuretic. Participants in TRIO received a standardized fixed-dose triple-drug regimen. REQUIRE enrolled patients with a seated office BP of at least 150/90 mm Hg with the same medication treatment requirements. Drug treatment in REQUIRE was defined as standard-of-care (i.e., not standardized). Although the baseline measures of office BP appear similar between the two trials, the concomitant drug therapies differed between the studies, and there may be differences between the two patient populations; the data should be interpreted in this context. Some additional limitations were noted in the REQUIRE trial. First, the patients were blinded, but the physicians were not, and there was no objective assessment of medication adherence, as measured by drug concentrations in blood or urine. The authors suggest that there may have been several patients with poor medication adherence who, during the study, were more compliant with treatment, leading to similar improvements in BP between the two treatment conditions, minimizing the impact of uRDN on BP. Additionally, the mean SBPs in this study were similar for AMBP and OBPM, further suggesting possible sampling error or compliance issues.

Of further note, trial blinding was only maintained for 6 months in the TRIO trial, after which medication changes could be made as needed. Beyond the 12-month follow-up, only OSBP measurements were recorded. A single-arm follow-up study of 49 patients who remained in the uRDN arm from randomization reported findings at 36 months (Bloch et al., 2024). In these patients, OSBP was reduced by an average of -14.5 mm Hg (Standard Deviation [SD]: 26.1) from screening and an average of -8.0 mm Hg (SD: 24.5) from baseline while on an average of 3.7 antihypertensive medications. Like the long-term findings for the SOLO trial, these data are from a small subset of patients, and these results regarding durability should be interpreted in that context. No new adverse events were deemed related to the procedure at this follow-up.

Summary

uRDN effectively reduced BP across all three RADIANCE studies in short-term follow-ups. These reductions exceeded the clinically meaningful threshold of 5 mm Hg (Haberman et al., 2024) and, should the effect be durable, may contribute to a relative risk reduction in cardiovascular events. However, the long-term superiority of the uRDN over sham interventions is not well-established. The SOLO, TRIO, and RADIANCE II trials were not designed or powered to assess differences in BP between uRDN and sham interventions beyond 2 months. As a result, patients on sham intervention with persistent uncontrolled hypertension were eligible to crossover and receive uRDN. Consequently, the long-term treatment durability effects were assessed only in a small subset of patients originally randomized to the uRDN group.

Overall, few serious adverse device/procedure-related events (<3%) have been seen with uRDN, of which all have been transient and resolved with no long-term sequelae. Injury to the renal artery and/or the kidneys is rare. There have been no reports of new-onset clinically significant renal artery stenosis requiring intervention. The totality of evidence from the RADIANCE trials suggests a positive benefit-risk profile of the uRDN. However, the trials' exclusion criteria were strict, omitting patients with renal abnormalities, aneurysmal renal arteries, previous renal stenting, or eGFR below 40 mL/min/1.73 m². Renal anatomy suitability was confirmed via renal CTA or MRA before the procedure and renal angiography during the procedure, ensuring safe RDN application. Notably, medication adherence and eGFR analyses were not protocol-mandated beyond the 12-month follow-up, which raises considerations for long-term kidney function monitoring post-procedure. Safety findings should be considered within the context of this highly selected patient population, and applicability may be limited when considering the broader real-world population of patients with HTN.

Catheter-Based Radiofrequency Renal Denervation (rfRDN)

Inclusion Criteria and Setting

The SPYRAL HTN studies enrolled individuals aged 20-80 with baseline ASBP 140-169 mm Hg and OSBP 150-179 mm Hg. Key exclusion criteria included recent angina or myocardial infarction; heart failure, stroke, transient ischemic attack, or atrial fibrillation; prior renal denervation; untreated secondary causes of HTN; uncontrolled diabetes; and renal anatomy ineligible for treatment. SPYRAL HTN-OFF MED studies (Townsend et al., 2017; Böhm et al., 2020) were further limited to patients able to discontinue antihypertensive medications, while SPYRAL HTN-ON MED studies (Kandzari et al., 2018; Mahfoud et al., 2022; Kandzari et al., 2023; Kario et al., 2023) included patients on stable regimens of 1-3 antihypertensive medications. The SPYRAL HTN studies were conducted across the US, Canada, Japan, Europe, and Australia.

The SPYRAL HTN trials assessed the efficacy of rfRDN in reducing BP in patients with uncontrolled hypertension. The SPYRAL HTN trial began with two international, multicenter, sham-controlled pilot studies exploring the rfRDN catheter system in patients with mild-to-moderate hypertension: SPYRAL HTN-ON MED, involving patients on AHMs, and SPYRAL HTN-OFF MED, involving patients off AHM therapy. Each pilot study included 80 participants and, while not powered for efficacy outcomes, demonstrated significant BP-lowering effects following rfRDN with minimal BP changes in the sham groups (Townsend et al., 2017; Kandzari et al., 2018). Following these pilot studies, two larger prospective trials were launched to detect changes in 24-hour ASBP. These trials included the SPYRAL HTN-OFF MED Pivotal trial (for

patients without AHMs; Böhm, 2020) and the SPYRAL HTN-ON MED Expansion trial (for patients with AHMs; Kandzari et al., 2023; Mahfoud, 2022). Using an adaptive Bayesian design, these studies incorporated data from the pilot trials as informative priors and conducted interim analyses, allowing for early study termination for efficacy or futility.

Findings

Uncontrolled Hypertension

Off Medication

The SPYRAL HTN-OFF Pivotal trial (n=251; Böhm et al., 2020) combined data from this named trial and the HTN-OFF Pilot trial (Townsend et al., 2017) using a Bayesian approach to incorporate data from the pilot (n=80) as an informative prior into the primary analysis (total n=331). Medications were discontinued 3-4 weeks before randomization through 3 months post-procedure unless they met safety escape criteria requiring re-introduction of medications (SBP > 180 mm Hg or BP-related symptoms or complications). After the primary efficacy follow-up visit at 3 months, patients were treated with a guideline-based AHM escalation protocol between 3 and 6 months post-procedure if needed. Crossover to RDN was permitted after 12 months for the Pilot cohort and 6 months for the Pivotal cohort.

In the rfRDN group, there was a greater mean reduction in OSBP (MD: -6.6 mm Hg; 95% Bayesian credible interval [BCI]: -9.6 to -3.5) and 24-hour ASBP (MD: -4.0 mm Hg; 95% BCI: -6.2 to -1.8) at 3 months relative to sham. For both endpoints, rfRDN met the statistical requirement for superiority (>0.975) with a posterior probability of superiority >0.999, and the authors indicate that the differences in SBP measurements were clinically meaningful at 3 months. No major procedural or device-related safety events were reported.

On Medication

SPYRAL HTN-ON MED Expansion trial combined data from this trial (n=257; Kandzari et al., 2023) and the HTN-ON proof-of-concept trial (Kandzari et al., 2018) using a Bayesian approach to incorporate data from the pilot (n=80) as an informative prior into the primary analysis (total randomized n=337). Patients were prescribed 1, 2, or 3 standard AHMs, and the primary efficacy follow-up was at 6 months. At this time point, there were no between-group differences for the primary endpoint of 24-hour ABSP (MD: -0.03 mm Hg; 95% BCI: -2.82 to 2.77 mm Hg). The secondary effectiveness endpoint was the baseline-adjusted change in OSBP from baseline to 6 months post-procedure. In the rfRDN group, there was a greater reduction in OSBP at 6 months vs. the sham group (MD: -4.9 mm Hg; 95% BCI: -7.9 to -1.9), but this may not be clinically meaningful, and the authors note that the study was not powered for this endpoint. The mean number of AHMs at 6 months was lower in the rfRDN group versus in the sham group (1.9 vs. 2.1; p=0.0085); the medication burden (based on number, class, and dosage) at 6 months was 2.9 in the rfRDN group vs. 3.5 in the sham group (p=0.043). One patient in the rfRDN group required pseudoaneurysm repair at the right femoral access site.

A pre-specified win ratio analysis (to address the potentially confounding effect of medication burden) applied a hierarchical composite of outcomes to compare the rfRDN and control groups using two endpoints. The first endpoint was the difference in 24-hour ASBP change from baseline to 6 months using a threshold of 5 mm Hg. Win ratio analysis favored rfRDN treatment versus the sham intervention (1.50; 95% CI: 1.13 to 1.99; p=0.005; Kandzari et al., 2023).

Safety and efficacy follow-up data for SPYRAL HTN-ON MED at 12 and 24 months (Kandzari et al, 2025) were published after our initial analysis of the evidence. Once the primary endpoint data were collected at the 6-month follow-up, patients and clinicians were unblinded, and patients in the sham group were permitted to cross over to the rfRDN group. Half of the control patients elected to receive rfRDN; 54 patients crossed over between the 6- and 12-months visit, and a further 12 patients crossed over between the 12- and 24-months visit. ITT analysis used the last observation carried forward method, and patients who crossed over to the rfRDN group were censored from the dataset at the time of crossover. At 12 months, there were no differences between rfRDN and sham for either 24-hour ASBP (-0.06; p=0.71) or OSBP (-3.1; p=0.15). At 24 months, however, both 24-hour ASBP and OBSP were statistically improved for patients in the rfRDN group (-5.7; p=0.039 and -8.7; p=0.0034, respectively). The authors suggest that, at 12 months, patients in the sham condition were showing decreases in SBP measures with a statistically significantly higher medication burden than those in the rfRDN group. At 24 months, the ambulatory systolic BP change was significantly greater in RDN patients compared with sham control patients (-12.1±15.3 mmHg versus -7.0±13.1 mmHg; treatment difference: -5.7 mmHg; P=0.039) (Kandzari et al., 2025). At this time point, the sham population was half of the enrolled patients at randomization (50% attrition) due to crossover and other loss to follow-up, and there was only 3.4% attrition in the rfRDN group. Analysis of patients who crossed over to rfRDN from sham, there were few differences in baseline characteristics relative to those who did not with the exception of more patients remaining in the sham group being smokers. At 12 months after crossover, patients in this group showed decreases in 24-hour ASBP and OSBP relative to baseline (-14.0±13.3; p<0.0001 and -19.1±16.9, p<0.0001, respectively) and relative to the point of crossover (-4.1±14.1; p=0.027 and -8.5±16.3, p<0.0001, respectively). Adverse events were similar between the two groups, with ~2.5% of patients in each group meeting the composite safety endpoint, which consisted of the following events. At 24 months, there were no renal reinterventions or renal stenosis >70% in the rfRDN group. Two deaths occurred, one in each group, two strokes occurred, one in each group, two patients required treatment for vascular complications in the rfRDN group as did one in the sham group. In the rfRDN group, one patient experienced a significant embolic event resulting in end-organ damage, one required hospitalization for hypertensive crisis with no patients in the sham group experiencing these events.

Long-term safety and efficacy at 36 months were assessed in a very small subset of the initial cohort of the SPYRAL HTN-ON MED proof-of-concept trial (Mahfoud et al., 2022). In patients with uncontrolled hypertension, there were modest BP reductions at 36 months in 24-hour ASBP in the rfRDN group (n=30) compared to sham (n=32), but there were no differences in OSBP (MD: -8.2; 95% CI: -17.1 to 0.8, p=0.073). A second exploratory analysis (Kario et al., 2023) of a subset of these patients taking at least three AHM at 36 months found similar results as the Mahfoud analysis for 24-hour and OSBP outcomes. Their analysis found that 24-hour SBP was controlled to <130 mm Hg in a greater percentage of rfRDN patients both in the morning and at night compared to the sham group (Morning: 40% vs. 6%, p=0.021; Night 80% vs. 39%, p=0.019). The authors suggest that rfRDN may be beneficial at the times of day when cardiovascular risk is elevated, but these findings should be interpreted with consideration for the small sample size and the post hoc nature of the analyses. No further safety concerns were noted at 36 months post-procedure.

Townsend et al. (2024) compared AHM and BP changes among different prespecified patient subgroups based on geography (United States and outside the United States), age, sex, body mass index (BMI), baseline 24-hour and OSBP, and race within the US only (Black versus non-Black). Most patients (n=187; 54%) were enrolled outside the United States, while 156 (46%) US patients were enrolled, including 60 (18%) Black Americans.

Among patients outside the US subgroup (e.g., Europe, Japan, and Australia), both 24-hour ASBP (AD: -4.8 mm Hg; 95% CI: -7.6 to -2.0; p=0.001) and OSBP (AD: -6.7 mm Hg; 95% CI: -10.5 to -2.8; p<0.001) decreased statistically significantly in the rfRDN group compared with the sham group. Within the US subgroup, there were no differences in 24-hour ASBP between rfRDN and sham treatment across all US patients (data shown graphically; p=0.21) and when considering Black Americans (AD: 5.4 mm Hg; 95% CI: -3.4 to 14.1; p=0.22) and non-Black Americans separately (AD: -0.2 mm Hg; 95% CI: -4.8 to 4.3; p=0.92). The authors noted that the treatment effect in Black Americans was slightly greater in sham relative to rfRDN, but this difference was not significant. Similarly, there were no differences between treatment groups for OSBP measures (US Black AD: -3.4 mm Hg; 95% CI -12.5 to 5.7; p=0.46; Non-Black US: AD: -2.4 mm Hg; 95% CI: -8.0 to 3.1; p=0.38). In a newly published paper reporting on available data from the complete cohort (Kandzari et al., 2025), the findings are substantively similar to what was reported in this paper. The authors caution that the study was not adequately powered to rigorously determine any subgroup differences.

There were no differences between prespecified patient groups for either 24-hour ASBP or OSBP across patients younger than 65 or 65 and older (24-hr ASBP: p=0.99; OSBP: p=0.21), sex (24-hr ASBP: p=0.84; OSBP: p=0.18); BMI (24-hr ASBP: p=0.66; OSBP: p=0.49); or baseline SBP (24-hr ASBP: 0.99; OSBP: p=0.37; all data shown graphically; Townsend et al., 2024). Although these findings should be interpreted within the context that subgroup analyses may pose increased risk of Type 1 error (false positives arising from multiple comparisons), reduced statistical power for any observed effects, and potential for misleading interpretations when applied to complex patient characteristics, these data provide some information that may be of relevance to patients eligible for Medicare services.

Summary

While the SPYRAL HTN-OFF MED Pivotal trial demonstrated clinically meaningful reductions in both OSBP and 24-hour ASBP at three months, the SPYRAL HTN-ON MED Expansion trial did not achieve similar results at 6 or 12 months, although a significant between-group difference was seen at 24 months (Kandzari et al., 2025). Notably, differences in HTN medication burden between the groups confound interpretation. At this time point, only 50% of the patients randomized to the sham condition remained in that condition, and between the 12- and 24-month follow-up, BP increased in the sham condition while BP continued to decrease in the rfRDN group. The authors note that most participants in the HTN-ON trial had their 6-month follow-ups scheduled during the COVID-19 pandemic, and there were more protocol deviations during the Expansion study compared to the pilot study. Further, it was proposed in an analysis of pre-specified subgroups (Townsend et al., 2024) that an unexpectedly large BP decrease in the sham group may have been due to, in part, more common increases in AHM in the US patient cohort of Black Americans. This study had a small sample size, which may limit the interpretation and generalizability of the subgroup analysis.

Across the SPYRAL trials, safety remained favorable, with a 0.04% incidence of major adverse events in the first 253 treated patients, which met the predefined safety endpoint performance goal of 7.1% ($p<0.001$). The primary safety endpoint was the rate of major adverse events at 30 days post-procedure and renal artery stenosis at 6 months in RDN-treated subjects pooled from HTN-OFF and HTN-ON studies (Böhm et al., 2020). No device-related adverse events were reported up to 24 months of follow-up (Kandzari et al., 2023; Kandzari et al., 2025).

Head-to-Head Comparison of uRDN and rfRDN

Inclusion Criteria and Setting

RADIOSOUND-HTN was a head-to-head comparison of three different techniques of RDN in patients with resistant hypertension: rfRDN (main artery: RFM-RDN: n=39) as the reference standard, rfRDN (main and branch arteries; RFB-RDN: n=39), and uRDN (USM-RDN: n=42). Key inclusion criteria for the RADIOSOUND-HTN trial were patients diagnosed with resistant hypertension with daytime SBP >135 mm Hg on ABPM, with a renal artery diameter of ≥5.5 mm for at least 1 of the main renal arteries. Use of AHM was required to be stable for at least 4 weeks. Patients then underwent ABPM to exclude those with white-coat hypertension. Exclusion criteria were age ≥75 years, pregnancy, life expectancy <6 months, evidence for secondary hypertension, participation in any other randomized clinical trial, known renal artery stenosis or anatomy unsuitable for interventional RDN, and any main renal artery diameter <4.0 mm. The trial was conducted at a single center in Germany (Fengler et al., 2019).

Findings

RDN lowered BP across all groups at all time points. At 3 months, daytime systolic and diastolic BP decreased significantly in the overall cohort by 9.5 (SD: 12.3) and 6.3 (SD: 7.8) mm Hg, respectively ($p<0.001$ for both) and within each treatment group ($p<0.001$) (Fengler et al., 2019). This effect was maintained at 6- and 12-month follow-up ($p<0.001$) (Fengler et al., 2023).

At 3 months, uRDN was found to be more effective than rfRDN (Daytime ASBP MD: -6.7 mm Hg; 98.3% CI: -13.2 to -0.2, adjusted $p=0.043$). rfRDN did not differ between uRDN (Daytime ASBP MD: -4.9 mm Hg; 98.3% CI: -11.5 to 1.7; $p=0.22$) or by rfRDN approach (Daytime ASBP MD: -1.8 mm Hg; 98.3% CI: -8.5 to 4.9; $p>0.99$). Rates of response to RDN were similar across treatment groups. There were several peri-procedural adverse events, including transient renal artery spasm, a symptomatic groin hematoma, and a pseudoaneurysm. The authors reported that all events were resolved. During the 3-month follow-up period, two patients in the rfRDN group experienced symptomatic hypotension. Three patients (main artery rfRDN: 1; main and branch arteries rfRDN: 2) experienced symptomatic hypertension that required medical treatment. A patient in the rfRDN group experienced acute decompensated heart failure, which required hospitalization. Finally, one patient in the rfRDN group died from acute aortic dissection 2 months post-procedure. Examination of this patient's angiogram suggested no evidence of dissection at the time of the procedure. No adverse events were reported in the uRDN group, and there were no renal vascular complications or instances of renal stenosis.

In a research letter, 6- and 12-month follow-up data were reported for the head-to-head comparisons (Fengler et al., 2023). At 6 months, ASBP reduction from baseline varied across the treatment arms, with uRDN producing a statistically greater effect than rfRDN (uRDN: -12.1 mm Hg; SD: 11.5; main artery rfRDN: -6.0 mm Hg; SD: 11.0; main and branch arteries rfRDN: -

4.8 mm Hg: SD: 12.1; p=0.017 for between-group comparison; Fengler et al., 2023). Given the wide variability around the point estimates for each treatment, this may not be a clinically meaningful difference. At 12 months, there were no longer any between-group differences in ASBP (Fengler et al., 2023). Harms were not reported.

Evidence from observational studies/meta-analyses and relevance to Medicare beneficiaries

In addition to the seven RCTs considered above, a series of observational studies report broadly consistent findings with those from the RCTs, both in terms of enrolled patients and safety and efficacy outcomes. While data on efficacy in these single-arm trials is reported, these findings are limited by the lack of a meaningful comparator, and, while provided for completeness, in this analysis, greater weight is given to data from the RCTs. Observational trials, however, can be useful in identifying safety signals, particularly if longer follow-up times are reported than are available from RCTs.

Controlled Observational Studies

No controlled observational studies met the criteria for inclusion in this analysis.

Uncontrolled Observational Studies

Five uncontrolled observational studies met the criteria for inclusion in this review. Two of these studies were registry-derived (one [Rosch et al., 2023] pooled longer-term data from two of the other included observational studies [Fengler et al., 2017; Fengler et al., 2022]), one was a cohort review, and two were prospective single-arm studies (one a feasibility trial).

Two single-arm uRDN studies reported short-term efficacy follow-up findings for 24-hour systolic ABPM at three months (Fengler et al., 2017; Fengler et al., 2022). Both studies demonstrated a statistical reduction from baseline for 24-hour systolic and diastolic ABPM at 3 months. Fengler et al. (2017) reported very few adverse events, and Fengler et al. (2022) did not report safety outcomes. Of note, 50% of the patients enrolled in the study by Fengler et al. (2017) had previously undergone treatment with rfRDN and did not display a sufficient treatment response. The patient populations differed on important baseline characteristics, and as this study was small (total n=50), interpreting efficacy in these patients would be challenging. Further, 19/31 participants did not show an adequate treatment response (35% of first-treated and 40% of re-treated). Regarding safety, during the procedure, 10% of patients experienced transient vascular spasm, 4% required transient noninvasive ventilation, and 1 patient required single-sided ablation to facilitate balloon catheter placement. No deaths and no new renal artery stenosis were reported. Daemen et al. (2019) reported findings for 24-hour and office BP outcomes at 12 months from a prospective, non-randomized study of 96 patients treated with an uRDN device. The results indicated statistical reductions at 12 months in 24-hour systolic and diastolic ABPM and OBP. There was one patient who experienced a hypertensive crisis requiring hospitalization, and five patients experienced minor groin complications. One patient died (presumed myocardial infarction), but the authors indicated that this patient had a history of coronary heart disease, and the event was not thought to be due to the procedure. No renal artery stenosis was observed.

Whitbourn et al. (2015) conducted a prospective observational, open-label, feasibility study of 50 patients treated with rfRDN (Symplicity Spyral). The authors noted statistical reductions in

office-based systolic and diastolic BP from baseline at 3, 6, and 12 months and 24-hour systolic and diastolic ABPM reductions at 6 and 12 months. At 6 months, 6 adverse events were reported: 1 myocardial infarction, 2 elevated serum creatinine (>50%), and 3 vascular complications. At 12 months, 3 additional adverse events were reported: 1 myocardial infarction, and 2 elevated serum creatinine values (>50%). There were no deaths or reports of renal artery stenosis.

Systematic Reviews and Meta-Analyses

Four meta-analyses were identified, with significant overlap between them and the present analysis (Ogoyama and Kario, 2024; Yang et al., 2022; Stavropoulos et al., 2020; Sardar et al., 2019). The most recent meta-analysis by Ogoyama and Kario (2024) represents the most comprehensive and recent meta-analysis of the data. However, the included trials are already represented in our primary analyses, and we rely on the original RCTs for completeness and for our evidence synthesis.

F. Limitations of Evidence

Our evidence review found relatively few randomized trials (n=7), and most were funded by each device's manufacturer. Only one poor-quality study directly compared uRDN and rfRDN, and the sample sizes in this study were fewer than 50 patients per arm. RCTs were conducted in multiple countries, including the US, the UK, Germany, France, the Netherlands, Poland, Belgium, Japan, and Korea, but detailed analyses of the US data reflective of the US population are lacking. Analyses of the SPYRAL HTN-ON trial reported on the US population subgroup, but the analysis is not comprehensive (Townsend et al., 2024; Kandzari et al., 2025).

Patient selection across all trials was highly selective, with a range of 35% (REQUIRE) to 6% (RADIOSOUND-HTM) of patients who were screened ultimately being enrolled. Overall, sample sizes in the RDN studies were relatively small when considering how common HTN is as a condition. Strict inclusion/exclusion criteria may limit applicability to the Medicare population, particularly older patients, those from different racial and ethnic groups, and those with multiple comorbidities.

Primary endpoints in each trial were assessed at a relatively short follow-up (2-3 months), and most trials did not maintain blinding long-term. Additionally, variations in AHM standardization, differences in medication treatment load, and measures of medication treatment adherence could contribute to the observed variability of the outcome measures across studies.

These studies were not powered to assess long-term health outcomes. Because HTN treatment is often lifelong and BP is a surrogate outcome, long-term follow-up and demonstration of improved health outcomes are very important. These studies only measured BP and were not designed to capture long-term health sequalae of HTN, including preventing hypertension-associated end-organ damage and survival. Since hypertension treatment is usually required for life, long-term studies are needed to demonstrate the durability of treatment and improved health outcomes.

In addition to the above-identified limitations of the reviewed studies, other evidentiary gaps raised in the literature include patient selection and facility/operator experience, which strongly

influence the benefit and utility of RDN. A volume-outcomes association has been demonstrated for most invasive procedures, especially during the earlier stages of technology adoption. Operators should have expertise in renal vascular anatomy (for instance, the presence of accessory or aberrant renal arteries), prompt recognition and management of potential complications, including vascular access complications and renal arterial injuries such as dissection, embolization, or perforation. Careful selection of patients who may benefit from the procedure through a multidisciplinary team approach that includes an HTN expert in a specialized center is also an important consideration. Such centers should be able to thoroughly evaluate patients for secondary causes of hypertension. For instance, up to 10% of patients with stage 1 hypertension and between 20% and 25% with stage 2 or resistant hypertension may have evidence of primary aldosteronism (O'Malley et al., 2023). Some patients may be misdiagnosed (white coat HTN, high-salt diet, incorrect BP recording technique). Such centers should also be proficient in the judicious pursuit and interpretation of 24-hour ambulatory BP recordings. Assessment for medication adherence through direct questioning and biochemical screening of serum or urinary drug levels (now available in clinical practice) may be necessary. The assessment and treatment of obstructive sleep apnea is another important factor in addressing apparent treatment-resistant hypertension.

G. Conclusions

Collectively, these trials demonstrate that second-generation RDN devices are effective for lowering BP in some, but not all, patients with hypertension, achieving modest reductions comparable to those seen with a single antihypertensive medication. The findings also suggest that RDN is safe, with minimal impact on renal function and consistent efficacy across the studied patient populations and device types. The benefit of these devices is mainly that they function as an “always on” treatment, which is useful for patients who may have difficulty adhering to or have contraindications to medical treatment; they do not appear to produce side-effects that challenge some medication options.

However, the current evidence is inadequate to fully assess which patient, practitioner, or facility characteristics predict the most successful patient outcomes from RDN. Studies of RDN with an active comparator or larger studies of head-to-head comparisons of RDN devices are needed. While one study found a greater BP reduction for uRDN at 3 months compared to rfRDN (with and without branch artery treatment), the differences were no longer evident at 12 months (Fengler et al., 2023; Fengler et al., 2019). Additionally, studies enrolling patients that better reflect real-world individuals are needed to understand the risks/benefits of this technology when combined with other AHTs. One recent analysis suggests that BP reductions after RDN may be dependent on baseline BP, with higher baseline BPs associated with larger BP reductions (Ziegler et al., 2024). Even so, many patients with severe, resistant hypertension will continue to require multiple AHTs after RDN. For context, adding one AHT can similarly achieve 4 to 6 mmHg in ambulatory SBP (equivalent to 7-10 mm Hg reduction in OSBP) with RDN. In particular, spironolactone reduced 12-week averaged home SBP by 8.7 mm Hg compared with placebo among patients with treatment-resistant HTN (Williams et al., 2015).

Future studies are needed to better define the most appropriate population(s) for RDN (resistant HTN, isolated systolic HTN, early HTN, high lifetime cardiovascular risk, etc.) and whether this BP reduction translates into improvements in surrogate markers (such as left ventricular

hypertrophy) or hard clinical endpoints (such as major adverse cardiovascular events, stroke, etc.) as has been noted with studies of antihypertensive medications. Patients with features of sympathetic overactivity, including combined systolic-diastolic hypertension, orthostatic hypertension, and elevated renin levels, may benefit more from RDN. In contrast, the procedure may have less effectiveness for the treatment of isolated systolic hypertension because the mechanism of hypertension is mainly driven by aortic stiffening rather than sympathetic overactivity (Vongpatanasin and Addo, 2024). Additionally, given that a significant proportion of patients do not respond to RDN, statistical models are needed to define the predictors of treatment response.

H. Evidence-Based Guidelines

We identified two professional society guidelines relevant to managing resistant HTN with RDN.

2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension (Mancia et al., 2023).

- "RDN can be considered as a treatment option in patients with an Estimated Glomerular Filtration Rate (eGFR) >40 ml/min/1.73 m^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 (Class of recommendation [CoR] II, Level of evidence [LoE] B)."
- "RDN can serve as an additional treatment option for patients with true resistant hypertension if their eGFR is greater than 40 ml/min/1.73 m^2 (CoR II, LoE B)."
- "Patient selection for RDN should involve a shared decision-making process, ensuring that patients receive objective and comprehensive information about the procedure (CoR I, LoE C)."
- "To ensure optimal outcomes, "RDN should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure (CoR I, LoE C)."

2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (Jones et al., 2025).

- "In carefully selected patients with systolic and diastolic hypertension (office SBP 140 – 180 mm Hg and DBP > 90 mm Hg) and eGFR > 40 mL/min/1.73 m2 who have resistant hypertension despite optimal treatment, or intolerable side effects to additional antihypertensive drug therapy, renal denervation (RDN) may be reasonable as an adjunct treatment to BP medications and lifestyle modifications to reduce BP." (CoR 2b, LoE B-R)"All patients with hypertension who are being considered for RDN should be evaluated by a multidisciplinary team with expertise in resistant hypertension and RDN." (CoR I, LoE B-NR)

- "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." (CoR I, LoE C-EO)

I. Professional Society Recommendations / Consensus Statements / Other Expert Opinion

The review identified 15 articles reporting on position statements by national and international specialty societies on patient selection and RDN performance; the five most relevant to the US context are summarized below.

The *Society for Cardiovascular Angiography & Interventions (SCAI)* Position Statement (Swaminathan et al., 2023) provides suggested guidance on standardizing RDN procedures, approaches to selecting patients, and suggested post-procedural follow-up, along with operator and institutional requirements.

The *American Heart Association (AHA)* stated that although further research is needed, RDN presents a novel treatment strategy for patients with uncontrolled BP (Cluett et al., 2024). AHA states that most but not all the new generation of trials reached their primary endpoint, demonstrating modest efficacy of RDN in lowering BP across a spectrum of hypertension, from mild to truly resistant. Individual patient responses vary, and further research is needed to identify those who may benefit most. The initial safety profile appears favorable, and multiple ongoing studies are assessing longer-term efficacy and safety. Multidisciplinary teams that include hypertension specialists and adequately trained proceduralists are crucial to ensure that referrals are made appropriately with full consideration of the potential risks and benefits. Incorporating patient preferences and engaging in shared decision-making conversations will help patients make the best decisions given their individual circumstances (Cluett et al., 2024).

The *European Society of Cardiology (ESC)* and the *European Association of Percutaneous Cardiovascular Interventions (EAPCI)* suggests that RDN is an adjunct treatment option in uncontrolled resistant hypertension, confirmed by ambulatory BP measurements, despite best efforts at lifestyle and pharmacological interventions (Barbato et al., 2023). RDN may also be used in patients who are unable to tolerate AHMs in the long term. A shared decision-making process is a key feature and should take (i) the patient's global cardiovascular (CV) risk and/or (ii) the presence of hypertension-mediated organ damage or CV complications into account. Multidisciplinary hypertension teams involving hypertension experts and interventionalists should assess the patient and facilitate the RDN procedure. The interventionalists require expertise in renal interventions and specific training in RDN procedures (Barbato et al., 2023).

The *European Society of Hypertension (ESH)* states that RDN represents an evidence-based option to treat a variety of hypertensive patients ranging from mild to moderate as well as more severe hypertension, in addition to lifestyle changes and BP-lowering drugs (Schmieder et al., 2021). *ESH* states that RDN is an alternative or additive, not a competitive treatment strategy, and recommends a structured pathway for its clinical use in daily practice. Patients' perspectives

and preferences, 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 considers the various treatment options, including RDN (Schmieder et al., 2021).

J. Appropriate Use Criteria

There are no relevant, published appropriate use criteria.

K. Public Comment

CMS uses the initial public comments to inform its proposed decision. Public comments that cite published clinical evidence give CMS useful information. Public comments that contain information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

First Comment Period: January 13, 2025 – February 12, 2025

During the first 30-day public comment period CMS received 81 comments. Of these comments, three were omitted from publication on the CMS website due to excessive personal health information content, for a total of 78 comments posted to the CMS website. The majority of commenters (76) spoke positively of the use of RDN. One comment was mixed and one did not support coverage of RDN citing limited evidence. All comments that were submitted during the comment period without personal health information may be viewed by using the following link: https://www.cms.gov/medicare-coverage-database/view/ncacal-public-comments.aspx?ncaid=314

The majority of comments were anecdotes provided by physicians who utilized RDN among their patients. These physicians represented a range of specialties, including interventionalists and physicians who manage hypertension. We also received comments from medical technology manufacturers, including Boston Scientific, Medtronic, and Recor Medical, and from industry organizations, including AdvaMed and the Medical Device Manufacturers Association (MDMA). We received a joint comment from The Partnership to Advance Cardiovascular Health, The National Kidney Foundation, The American Society of Nephrology, and The American Association of Nurse Practitioners. We also received a joint comment from the American College of Cardiology, the Society for Cardiovascular Angiography and Intervention, and the Society for Vascular Medicine. The Association of Black Cardiologists submitted two comments. One comment was received from the American Society for Preventive Cardiology. The National Forum for Heart Disease and Stroke Prevention also submitted a comment. One comment was received from a patient advocacy organization, Mended Hearts.

Second Comment Period: July 10, 2025 – August 9, 2025

During the second 30-day public comment period, CMS received 110 comments. Of these comments, one was omitted from publication on the CMS website due to excessive personal health information content, for a total of 109 comments posted to the CMS website. Similar to the initial public comment period, the comments received were overwhelmingly positive. All commenters supported the use of RDN for uncontrolled hypertension, citing clinical promise and

unmet clinical needs in hypertension management and the proposed coverage through CED. All pertinent comments that were submitted during the comment period without personal health information may be viewed by using the following link: https://www.cms.gov/medicare-coverage-database/view/ncacal-public-comments.aspx?ncaId=318&fromTracking=Y&

The majority of comments were provided by physicians, many of whom utilized RDN among their patients, and other health care professionals. Comments were also received from four medical technology manufacturers, including Ablative Solutions, Inc., Boston Scientific, Medtronic and Recor Medical. Three industry organizations submitted comments, including AdvaMed, the Medical Device Manufacturers Association (MDMA), and The Federation of American Hospitals. Seven comments were from professional organizations, including: a joint comment from The Partnership to Advance Cardiovascular Health, The National Kidney Foundation, and The American Society of Nephrology; a joint comment submitted by The American College of Cardiology, The Society for Cardiovascular Angiography and Intervention and The Society for Vascular Medicine; The Society of Interventional Radiology; Preventive Cardiovascular Nurses Association; American Heart Association; The Association of Black Cardiologists; and The American Society for Preventive Cardiology. Advocacy organizations submitting comments included the National Forum for Heart Disease and Stroke Prevention; The Mended Hearts, Inc. and WomenHeart. One comment was from an insurer, Blue Cross Blue Shield of Michigan.

1. Support for Medicare Coverage for RDN

Comment: The overwhelming majority of commenters supported coverage of RDN for uncontrolled hypertension, though many commenters suggested modifications to individual criteria as detailed below.

Response: We thank commenters for their support.

Comment: Several comments saw the proposed national coverage determination as an opportunity to improve patient outcomes by expanding access to RDN into the community.

Response: We thank commenters for their support.

2. Patient Criteria

Comment: One commenter requested that CMS clarify the definitions of uncontrolled and resistant hypertension.

Response: The 2025 Multispecialty Guideline for the Prevention, Detection, and Evaluation of High Blood Pressure in adults definition of Stage 2 hypertension is SBP > 140 mm Hg or a DBP > 90 mm Hg (Jones et al., 2025). Additionally, the 2025 multispecialty guideline defines resistant hypertension as BP above goal despite treatment with 3 antihypertensive medications with complementary mechanisms of action, including a diuretic at maximally tolerated doses or BP at goal but requiring >4 medications (Jones et al., 2025). Consistent with this CMS national coverage analysis, a diagnosis of uncontrolled hypertension requires a SBP > 140 mm Hg and a

DBP > 90 mm Hg despite active management with lifestyle changes and stable doses of maximally tolerated GDMT (with assessment of the level of adherence to the prescribed regimen).

Comment: Some commenters supported the systolic blood pressure cutoff of 140 mmHg for RDN treatment. Other commenters expressed the position that despite promising evidence of clinically meaningful blood pressure reduction and the low risk of complications in clinical studies, RDN should not be considered a first-line treatment for hypertension. Thirty-five commenters recommended that CMS expand RDN coverage to Stage I hypertension (SBP 130-139 mm Hg or DBP 80-89 mm Hg). These commenters stated that Stage 1 hypertension patients are also at increased risk, and RDN should be covered.

Response: Many safe and effective anti-hypertensive medications from multiple drug classes are well-established and widely available. The blood pressure cutoffs of $\geq$ 140 mmHg and $\geq$ 90 mmHg align with the inclusion criteria in the pivotal clinical trials for rfRDN and uRDN. While complication risks from RDN are low, it is an invasive treatment, durability is insufficiently established, and approximately one-third of patients do not benefit. Given the currently available evidence, CMS agrees that RDN should not be a first-line treatment for hypertension and should be limited to patients who remain uncontrolled ($\geq$ 140 mm Hg and $\geq$ 90 mm Hg) despite active management with lifestyle and maximally tolerated GDMT for hypertension.

Comment: Several commenters expressed the position that CMS should not limit coverage to resistant hypertension.

Response: Coverage of RDN is not limited to patients with resistant hypertension. Rather, coverage is available for patients who remain uncontrolled ($\geq$ 140 mm Hg and $\geq$ 90 mm Hg) despite attempted lifestyle changes and maximally tolerated doses of GDMT for hypertension (with assessment of the level of adherence to the prescribed regimen).

Comment: Fifteen commenters expressed concern that the proposed coverage criteria might inadvertently exclude patients with isolated systolic hypertension. They stated that patients with isolated systolic hypertension are more common in the Medicare beneficiary population and carry a higher cardiovascular risk.

Response: We appreciate these comments. We note that the 2025 Multispecialty Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults does not recommend RDN for isolated systolic hypertension (ISH) because RDN has not been adequately studied in that population (Jones et al., 2025). Furthermore, the Society for Cardiovascular Angiography and Interventions (SCAI) notes that isolated systolic hypertension is phenotypically distinct and is believed to be caused by arterial stiffness, which may not respond well to RDN (Swaminathan et al., 2023). Therefore, CMS has aligned with the 2025 multispecialty recommendation, and patients must meet both systolic and diastolic blood pressure requirements to be eligible for RDN (Jones et al., 2025).

Comment: Five commenters noted that office blood pressure readings should be confirmed with either ambulatory blood pressure readings or home blood pressure readings. One commenter

stated that ambulatory blood pressure readings are restrictive and impractical and should be removed from the coverage criteria.

Response: We agree that office blood pressure readings should be confirmed by either ambulatory blood pressure readings or home blood pressure readings. Confirmation of persistently elevated blood pressure is necessary to exclude white coat hypertension, which occurs when office blood pressure is elevated, while out-of-office blood pressure (as measured by ambulatory blood pressure or home blood pressure) is normal. The final NCD does not require the use of ambulatory blood pressure measurements, but if they are available, they are sufficient to confirm elevated office blood pressure readings.

Comment: One commenter asked CMS to clarify that office blood pressure readings are different than home blood pressure readings. They expressed the position that home blood pressure readings should be performed using a validated device, using an appropriate technique, and that a standardized reading protocol should be followed.

Response: We agree that office, ambulatory, and home blood pressure readings systematically differ. We also agree that home blood pressure readings should be appropriately performed. Nonetheless, we leave the performance of hypertension measurement to the clinician's discretion and have not added these home blood pressure reading requirements in the final policy. While clinicians may use ambulatory blood pressure measurements to confirm elevated office blood pressure readings, clinicians may also use home blood pressure readings for this purpose in the final policy. We have finalized criteria (b) as proposed.

Comment: Thirteen commenters sought greater clarity regarding what is meant by ‘stable doses’ of maximally tolerated guideline-directed medical therapy (GDMT), including lifestyle modifications. One commenter recommended that patients be on at least three medications, including a diuretic, and confirmed by pharmacy dispensing. Another supported no minimum medication requirement in the definitions. Thirteen commenters requested that CMS acknowledge that many patients may have contraindications, may be intolerant of, or may be non-adherent to certain medications. Several noted that there are often unrecognized socioeconomic barriers to access to hypertension therapies that might make a rigid policy untenable. One commenter stated that lifestyle changes play a crucial role. Several commenters suggested that CMS change the language from "maximally tolerated GDMT" to "optimally tolerated GDMT," claiming that the latter was a more patient-centered standard.

Response: CMS expects physicians to make a good-faith attempt at managing hypertension with lifestyle changes and available hypertension medications before referring patients to RDN. Given the currently available evidence, CMS concludes that RDN should not be a first-line treatment for hypertension and should be limited to patients who remain uncontrolled ($\geq$ 140 mm Hg and $\geq$ 90 mm Hg) despite active management with lifestyle changes and maximally tolerated GDMT for hypertension. CMS concurs with the multispecialty guideline that lifestyle changes may include weight loss, a heart-healthy eating pattern, reduced sodium intake, the use of salt substitutes, moderate potassium supplementation, abstinence from or reduced alcohol intake, and increased physical activity (Jones et al., 2025). CMS also recognizes that non-adherence to medications is prevalent among hypertensive patients, affecting between 27% and 40% globally.

The diagnosis of resistant hypertension is predicated on the patient's adherence to the prescribed regimen, and failure to identify inadequate adherence contributes to overestimation of the prevalence of "true" resistant hypertension (Carey et al., 2018). Medication adherence assessment involves frank and nonjudgmental clinician-patient discussions, monitoring of prescription refills and pill counts, and, if available, biochemical assays of drugs or their metabolites in urine or plasma (Jones et al., 2025).

Nonetheless, CMS recognizes that many patients may face challenges in taking the maximum doses of three or more antihypertensive medications, and that implementing and sustaining lifestyle changes may be difficult. Furthermore, most patients require long-term hypertension management, and patient quality of life is an important consideration. Therefore, CMS is not mandating a minimum number of medications or that medication doses be at the top of the maximum dosing range before referral for RDN but expects that patients and clinicians make a concerted and sustained effort to achieve control with maximally tolerated doses of medications and lifestyle changes before considering RDN. CMS has finalized the "maximally tolerated GDMT" language because it is more commonly used and because we believe that these clarifications sufficiently address commenters' concerns. CMS has added "assessment of adherence to the prescribed regimen" to the final decision.

Comment: We received nineteen comments regarding the three-month medication stability period. Three commenters supported the three-month criteria. Three commenters objected to the three-month stability requirement without proposing an alternative timeframe. One commenter recommended increasing the time to six months to align with patient criteria (f). Eight commenters recommended shortening the stability requirement to 4–6 weeks to better align with expected responses to changes in medication therapy. One commenter recommended shortening the stability requirement to four weeks to align with the RADIANCE HTN-TRIO clinical trial. Seven commenters recommended leaving an assessment of medication stability to clinician judgment, particularly in cases where the patient experienced hypertensive urgency or emergency.

Response: Given the currently available evidence, CMS concludes that RDN should not be a first-line treatment for hypertension and should be limited to patients who remain uncontrolled ($\geq$ 140 mm Hg and $\geq$ 90 mm Hg) despite active management with lifestyle changes and maximally tolerated GDMT for hypertension. Within the six-month period of active management, CMS believes that the patient must be on a steady state of their maximally tolerated drug regimen before their treatment response to medication and lifestyle changes may be reliably assessed. Clinicians should not conclude that the patient is uncontrolled despite maximally tolerated doses of GDMT while they continue to adjust medication doses. After thoughtful consideration of public comments, the final NCD reflects a shortened stability period of at least six weeks: "On lifestyle modifications and stable doses of maximally tolerated guideline-directed medical therapy (GDMT), with assessment of adherence to the prescribed regimen, for at least six weeks before referral for RDN."

Comment: Eight commenters expressed support for a requirement to exclude secondary causes of hypertension before considering RDN. One commenter requested clarification on the criteria. Two commenters suggested strengthening the requirement to align with a recently published

multispecialty guideline. Four commenters recommended that the policy specifically require screening for primary aldosteronism before consideration of RDN.

Response: CMS appreciates these comments. Consistent with the published multispecialty Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, we agree that screening for secondary causes of hypertension should be completed before considering RDN, as targeted, effective treatment is available (Jones et al., 2025). We have strengthened this criterion in the final NCD by adding: "At a minimum, patients must be screened for primary aldosteronism, obstructive sleep apnea, and drug or alcohol induced hypertension before referral to RDN." These secondary causes of hypertension are required explicitly because they are common in patients with uncontrolled and resistant hypertension (Jones et al., 2025).

Comment: Seventeen commenters raised concerns regarding the proposed exclusion of patients with an eGFR < 40 mL/min/1.73m2 as a contraindication. One commenter suggested that the eGFR should be increased to an eGFR $\geq$ 45. Multiple commenters noted that eGFR < 40 is not listed as a contraindication in the FDA indications for use for either of the current market-authorized RDN devices. Instead, eGFRs < 40 are considered a special population that was incompletely addressed in existing clinical trials. Many of these commenters claimed that the eGFR $\geq$ 40 requirement is overly restrictive, does not reflect an evolving evidence base, and excludes patients with elevated risk for cardiovascular complications. Several commenters stated that clinical trials are underway that include patients with lower eGFRs, and restricting coverage criteria to an eGFR $\geq$ 40 could complicate clinical trial enrollment. Lastly, several commenters recommended that the final decision align with FDA indications for use (IFU) to avoid the need for policy adjustments over time.

Response: We thank commenters for noting that an eGFR < 40 is not currently listed as a contraindication for the two FDA market-authorized RDN devices. We recognize that patients with chronic kidney disease experience increased cardiovascular risk and may particularly benefit from good blood pressure control. In response to these comments, we have removed a reference to eGFR < 40 as a contraindication and have further simplified the criteria to read "Patient has no contraindication to RDN, consistent with the FDA labeling of authorized devices."

Comment: Several commenters asked for clarification of what CMS meant by primary clinician or hypertension clinician.

Response: CMS intends that the primary clinician has primary responsibility for determining that the patient remains uncontrolled despite attempted lifestyle changes and maximally tolerated doses of GDMT for hypertension. The primary clinician should have expertise and experience in managing complex hypertension. For example, that clinician could be a primary care provider with an interest and additional training in hypertension management, or it could be a cardiologist or nephrologist without further training. CMS clarifies that primary clinicians must coordinate the active management of GDMT for hypertension; however, other members of the multidisciplinary care team may appropriately conduct some visits.

Comment: Multiple commenters stated that many patients with uncontrolled hypertension have been treated for years by multiple specialists in a multidisciplinary team. Several comments expressed that hypertension management is complex, with multiple clinicians participating in management, and that documentation is "fragmented." Several other commenters claimed that six months of management by a single clinician is overly rigid. They noted that the six-month requirement needlessly "resets" the clock on hypertension management and imposes delays in accessing RDN therapy.

Response: CMS agrees that many patients with uncontrolled hypertension have had long-standing hypertension and have been seen by multiple clinicians, including specialists, over time. CMS does not require that a single clinician conduct all visits. Rather, CMS intends that there be a single provider accountable for managing the multidisciplinary team, as managing uncontrolled hypertension is complex and often not well-coordinated. CMS concludes that RDN is not currently a first-line treatment for hypertension and has finalized the policy that six months of active management coordinated by a primary clinician is appropriate before concluding that the patient remains uncontrolled despite attempted lifestyle changes and maximally tolerated doses of GDMT for hypertension.

Comment: Several commenters supported a requirement for longitudinal care as an essential criterion before referral to RDN. Several commenters agreed that at least six months is an appropriate timeframe. A few commenters recommended at least three months of longitudinal follow-up. Other commenters recommended flexibility, particularly if there is a well-documented evaluation and treatment history before referral to a primary clinician or if the patient is already on maximally tolerated GDMT for hypertension.

Response: CMS agrees that longitudinal management by a primary clinician accountable for hypertension is essential before concluding that blood pressure is uncontrolled despite attempted lifestyle changes and maximally tolerated GDMT for hypertension. CMS notes that several factors must be assessed during longitudinal care, including outpatient verification of office blood pressure readings, exclusion of secondary causes of hypertension, the impact of lifestyle changes, multiple medication adjustments, and a period of six weeks of stability on the patient's medication regimen. Furthermore, RDN contraindications must be excluded, and the patient should engage in shared decision-making after uncontrolled hypertension is confirmed. Therefore, CMS has finalized the policy that at least six months of active management coordinated by the primary clinician is appropriate before concluding that the patient remains uncontrolled despite attempted lifestyle changes and maximally tolerated doses of GDMT for hypertension.

Comment: Thirteen commenters made recommendations related to the three-visit requirement. Several commenters supported a three-visit requirement. One commenter stated that many patients already struggle to see their primary care provider more than twice a year. Others expressed the position that the requirement of three visits within six months might be challenging to satisfy. Some commenters suggested that only two visits should be required or that the language should reflect "multiple" visits rather than a specific number.

Response: CMS clarifies the requirement that patients should be actively managed before concluding that they are uncontrolled despite attempted lifestyle changes and maximally tolerated doses of GDMT for hypertension. Active management requires multiple patient-clinician interactions. CMS notes that several factors must be assessed during longitudinal care, including outpatient verification of office blood pressure readings, exclusion of secondary causes of hypertension, the impact of lifestyle changes, multiple medication adjustments, and a period of six weeks of stability on the patient's medication regimen. Furthermore, RDN contraindications must be excluded, and the patient must engage in shared decision-making after uncontrolled hypertension is confirmed. CMS clarifies that the primary clinicians must coordinate management of the patient for a minimum of six months, during which there must be at least three visits.

Comment: Twenty-five commenters addressed the issue of virtual care delivery. Many of these comments emphasized that telehealth visits play a crucial role in managing patients with hypertension. Several commenters stated that in-person visits are inefficient and may impose burdens on patients and practices, particularly in rural and underserved areas. Several commenters recommended that the policy be changed to allow two of the three required visits to be conducted virtually.

Response: CMS agrees that telehealth visits play a crucial role in hypertension management. We note that at least one visit must be in person so that the patient's blood pressure can be assessed in the office and the patient's home blood pressure cuff readings can be validated. CMS also agrees that, in many cases, patient responses to medication adjustments can be accomplished virtually, and that allowing virtual visits for hypertension management may reduce barriers to accessing medical care. Therefore, we have revised the final decision language to reflect that two of the three required visits may be conducted virtually.

Comment: Three commenters disagreed with the proposed patient criteria limiting RDN to patients who had not previously undergone an RDN procedure. One commenter suggested that the language be changed to reflect that the patient had not received RDN in the preceding two years. One manufacturer stated that because RDN devices are improving, this restriction may be unreasonable. One commenter suggested that if a patient cannot be successfully treated with one device due to their anatomy, they should not be precluded from pursuing treatment with a different device.

Response: CMS concludes that the available evidence does not support repeated RDN treatment. We clarify that if a procedure is attempted with one device but aborted due to incompatible patient anatomy, we do not consider the patient to have undergone RDN, and the patient may still be eligible for RDN using an alternative device.

3. Physician Criteria

Comment: Fourteen commenters submitted comments regarding the physician criteria, with most expressing general support for the physician training requirements. One commenter recommended adding that RDN operators must have interventional and endovascular credentials at the facility where they perform the procedure. One commenter expressed concern that the

physician training requirements as outlined were insufficiently rigorous. One commenter recommended that operators furnishing RDN should have advanced training in interventional cardiology, interventional radiology, or vascular surgery. Several commenters recommended replacing the proctoring criteria with a requirement to be credentialed as an RDN operator at the facility where it is furnished. Some commenters recommended replacing proctoring requirements with manufacturer-recommended training standards. One commenter noted that the criteria were too lenient and that "at least ten supervised cases of diagnostic/therapeutic renovascular procedures, half as primary operator" is insufficient. Three commenters recommended that CMS clarify that physicians furnishing RDN services only need training on the RDN devices that they intend to use in their practice.

Response: We appreciate these comments and agree that training requirements are necessary to achieve optimal RDN outcomes. The training requirements outlined in our decision align with the Society for Cardiovascular Angiography and Interventions Position Statement on Renal Denervation for Hypertension (Swaminathan et al., 2023). CMS does not believe the training requirements are unduly burdensome and considers it essential to have a consistent national standard. As such, we are finalizing the physician criteria as proposed, but provide clarification that physicians performing RDN only require device-specific training for the specific device(s) they intend to use in their clinical practice.

4. Facility Criteria

Comment: While many commenters supported the need for multidisciplinary care, a large number opposed a requirement for a rigid, formal hypertension program. These commenters stated that a rigid hypertension program requirement would limit access for patients in rural and traditionally underserved areas.

Response: We appreciate these comments. CMS reiterates its conclusion that RDN is not a first-line therapy for hypertension. CMS expects physicians to demonstrate a good-faith attempt at management through lifestyle modifications and maximally tolerated guideline-directed medical therapy (GDMT) before referring a patient for RDN.

CMS believes a structured hypertension program is essential to ensure that (1) the diagnosis of uncontrolled hypertension has been confirmed, (2) patients have undergone an adequate attempt at lifestyle changes and maximally tolerated doses of GDMT for hypertension, (3) secondary causes of hypertension have been appropriately excluded, (4) contraindications to RDN have been assessed, (5) patients are referred for this invasive procedure following a process of shared decision-making, and (6) patients have adequate post-procedure follow up.

While not all facilities will have access to a formal multidisciplinary program, we do not believe that requiring a hypertension clinician with longitudinal care responsibility, supported by a hypertension navigator, is excessively burdensome. The hypertension navigator plays a critical role in extending the hypertension clinician by facilitating intermittent reviews of patient home blood pressure measurements and enabling timely adjustments to medical therapy.

CMS does not intend for RDN access to be limited to tertiary academic medical centers or large, multidisciplinary practices; therefore, we are not requiring formal accreditation. While the formal participation of multiple specialists is not mandated, CMS expects the hypertension clinician overseeing longitudinal care to have access to relevant specialty support as needed (e.g., internal medicine, endocrinology, sleep medicine, cardiology and nephrology). Furthermore, CMS intends that the hypertension clinician supervises the patient's hypertension management, including coordination with relevant specialists, as required.

Comment: Many commenters requested clarification of what constitutes a hypertension clinician. Some commenters stated that there are severe limits to the number of certified hypertension specialists and noted that cardiologists and nephrologists direct the vast majority of complex hypertension management.

Response: CMS intends that a hypertension clinician has a special interest and training in hypertension. The hypertension clinician should also have expertise in evaluating primary aldosteronism. CMS does not intend the term hypertension clinician to be limited to certified hypertension specialists and recognizes that cardiologists and nephrologists have the requisite training without the need for further certification.

Comment: While a number of commenters expressed support for a hypertension navigator to support a hypertension program, several commenters noted that a dedicated hypertension navigator may be prohibitively costly and limit RDN access in smaller facilities.

Response: The hypertension navigator requirement intends to ensure that hypertension programs have sufficient support to coordinate the care of patients with complex hypertension. We note the Society for Cardiovascular Angiography and Interventions Position Statement on Renal Denervation for Hypertension (Swaminathan et al., 2023) states that a hypertension navigator could be a physician, advanced practice provider, or registered nurse trained in program management. CMS does not mandate that the hypertension navigator exclusively perform this function, but rather that a hypertension program have a person responsible for care coordination of hypertension management under the supervision of a hypertension clinician as defined above. CMS believes that this coordination function is essential to ensure that patients are appropriately selected for RDN.

Comment: One commenter asserted that the requirement for RDN to be performed in facilities with an appropriate interventional cardiology or radiology suite is overly rigid because RDN may be safely accomplished at ASCs and in vascular operating rooms.

Response: We appreciate this comment and note that dedicated interventional cardiology and radiology suites generally have higher-quality imaging equipment, and staff are generally more experienced with procedures like RDN. We are finalizing this requirement as proposed.

5. CED Criteria for RDN

Comment: Twelve commenters articulated the importance of an NCD with evidence development requirements. Commenters suggested that additional evidence generation would

help identify patients most likely to benefit from RDN and better assess long-term outcomes after RDN. Several commenters emphasized the need for subgroup analyses within a larger cohort of hypertensive patients. One commenter noted that additional evidence would help refine treatment algorithms. No commenters expressed opposition to CED.

Response: We appreciate commenters' support for CED. We agree that while the evidence for RDN is promising, it does not yet satisfy the reasonable and necessary standard required for coverage under Section 1862(a)(1)(A) of the Social Security Act. CED requirements balance the desire for early beneficiary access to promising treatments with the need to ensure further evidence generation.

Comment: Two commenters stated that the CED study requirements are stringent and that funding is necessary to support investigators and data collection. Multiple specialty societies claimed that registry-based data collection would streamline data collection while minimizing the burden on hospitals.

Response: In our CMS National Coverage Analysis Evidence Review[1] and Coverage with Evidence Development[2] guidance documents, CMS endorses the concept that studies should be fit-for-purpose (FFP). That is, the study design, analysis plan, and data source(s) should be sufficient to credibly answer the question(s) it intends to answer. Manufacturers may submit the least burdensome study design that credibly addresses the questions posed in this national coverage analysis. CMS anticipates that manufacturers will submit study designs that rely on real-world data to satisfy CED requirements. Real-world data studies that rely principally on data from administrative claims and electronic medical records will not limit Medicare beneficiary access to RDN and will not impose a burden on Medicare beneficiaries, clinicians, or facilities that furnish RDN. However, while manufacturers are welcome to include registry-based data collection in their evidence development plan, CMS is not requiring registry participation as a coverage condition. CMS anticipates that all Medicare beneficiaries who receive RDN will be studied through a manufacturer-sponsored CED or continued access study.

Comment: Two commenters encouraged CMS to expeditiously review and approve RDN CED study protocols.

Response: CMS will review RDN study protocols as efficiently as possible so they may be approved upon finalization of the NCD.

Comment: One commenter recommended that CMS require a subgroup analysis of patients who require re-treatment with RDN.

Response: CMS has not found compelling evidence that repeated RDN procedures provide additional benefits. There are also no available data on the feasibility or challenges of repeated RDN, such as renal artery scarring. Therefore, we are finalizing our decision to non-cover re-treatment with RDN.

[1] https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=37
[2] https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?mcdid=38

6. Miscellaneous Comments

Comment: One commenter expressed support for the proposed decision to cover renal denervation broadly, stating that the final decision should extend to any technology, regardless of modality.

Response: We appreciate this comment. CMS clarifies that the scope of this final NCD is limited to the evidence reviewed for catheter-based renal denervation devices that deliver either radiofrequency or ultrasound energy. Accordingly, the coverage determination applies only to transcatheter radiofrequency or ultrasound-based renal denervation devices that have received FDA marketing authorization.

Comment: Nine commenters expressed support for a requirement for shared decision-making, particularly for RDN, which has an evolving evidence base. One commenter stated they have developed a patient-facing infographic and intend to publish a comprehensive decision aid.

Response: CMS supports clinician-patient shared decision-making for RDN in hypertension management, but recognizes that no fully developed tool is currently available. We are pleased to hear that an instrument is under development for this purpose.

IV. CMS Coverage Analysis

A. CMS Coverage Authority

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§ 1869(f)(1)(B) of the Social Security Act (the Act)). In general, to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§ 1862(a)(1)(A) of the Act).

When the available evidence is insufficient to demonstrate that the items and services are reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member under section 1862(a)(1)(A) of the Act, coverage with evidence development (CED) has been used to support evidence development for certain items and services that are likely to show benefit for the Medicare population. CED has been a pathway whereby, after a CMS and AHRQ review, Medicare covers items and services on the condition that they are furnished in the context of clinical studies or with the collection of additional clinical data (See CMS' CED Guidance Document) CED relies primarily on the statutory exception in section 1862(a)(1)(E) of the Act, which effectively permits Medicare payment for items and services that are reasonable and necessary to carry out research conducted pursuant to section 1142 of the Act.

Section 1142 of the Act describes the authority of AHRQ to conduct and support research that appropriately reflects the needs and priorities of the Medicare program.

B. CMS Analysis for Coverage of RDN for Hypertension Management

This section includes CMS' analysis of the evidence related to RDN for hypertension treatment. Relevant details from studies listed in **Table 2: Key Studies for RDN for Hypertension Management** above are provided in context when key study findings or limitations are discussed with respect to coverage.

The evidence in **Section III.D-E.** indicates that there is some benefit for some hypertension patients for RDN in defined clinical study conditions. However, as identified in **Section III.F**. Limitations of Evidence, there are crucial limitations to the evidence base for RDN for hypertension management and questions relating to appropriateness for Medicare patients that need to be answered before CMS would be able to determine if coverage is reasonable and necessary under § 1861(a)(1)(A) of the Act.

As further discussed below in the analysis, we propose CED for RDN for hypertension. In **Section IV.B.1-4** below, we analyze key findings and shortcomings of the evidence, and in **Section IV.B.5** below, we describe how those elements translate into the evidence-based rationale for each of the CED study parameters (e.g., patient, physician, facility, and study criteria) that aim to fill the evidence gaps.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that the specific assessment questions raised in a National Coverage Analysis (NCA) can be answered conclusively. When conducting NCAs for an item or service under the reasonable and necessary statute, CMS generally makes three kinds of assessments: (1) The quality of relevant individual studies; (2) What conclusions can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential harms and benefits; and (3) The generalizability of findings from relevant studies to the Medicare beneficiary population. (See CMS' Evidence Review Guidance Document).

CMS coverage determinations for items and services assess whether they lead to meaningful improvement in health outcomes for Medicare beneficiaries, as demonstrated in peer-reviewed publications of clinical studies. Through this construct, we assess the totality of the evidence for FDA market-authorized RDN for the treatment of Medicare beneficiaries with hypertension. The relevant outcome may depend on the disease and the patient's clinical scenario, pathophysiology, and preferences. Patient-centered primary outcomes for hypertension trials have included office systolic blood pressure, office diastolic blood pressure, home systolic blood pressure, home diastolic blood pressure, ambulatory systolic blood pressure, and ambulatory diastolic blood pressure. However, they may also include downstream consequences of inadequately controlled blood pressure. For example, hospitalizations for hypertensive crises, end-organ damage, and mortality. These patient health outcomes are central for determining whether RDN for hypertension management is reasonable and necessary.

1. Analysis of Key Evidence for uRDN

The evidence presented in **Section III. E.** identified four key, contemporary RCTs and numerous other studies evaluating the impact of uRDN on hypertension control.

RADIANCE-HTN SOLO (Azizi et al., 2018; Azizi et al., 2019; Azizi et al., 2020): The studies reported uRDN efficacy in patients without antihypertensive drugs with mild-to-moderate hypertension (SOLO: Azizi et al., 2018; Azizi et al., 2019; Azizi et al., 2020) and Stage II hypertensive patients (RADIANCE II: Azizi et al., 2023). The SOLO trial reported significant daytime ASBP reductions of 6.3 mm Hg at 2 months versus sham (Azizi et al., 2018), and the effect persisted for up to 6 months (Azizi et al., 2019). After the first 2 months of follow-up, the participants were allowed to receive antihypertensive drugs if home BP control did not achieve the target range (home BP ≥135/85 mm Hg) according to the antihypertensive treatment escalation protocol. By 12 months, the differences were no longer significant (Azizi et al., 2020).

RADIANCE II (Azizi et al., 2023): The study had similar findings with a reduction in daytime ASBP in the RDN group versus sham (baseline-adjusted between-group difference, -6.3 mm Hg [95% CI: -9.3 to -3.2 mm Hg], $p < 0.001$) in Stage II hypertensive patients at two months. Unlike RADIANCE-HTN SOLO and TRIO trials, blinding was maintained until 12 months post-randomization, after which AHM was prescribed per community standard of care.

RADIANCE-HTN TRIO (Azizi et al., 2021; Azizi et al., 2022): This trial reported uRDN efficacy in patients on antihypertensive drugs with resistant hypertension and reported the mean difference in daytime ambulatory systolic pressure between uRDN and sham group of 4.5 mm Hg (95% CI: -8.5 to -0.3) at 2 months (Azizi et al., 2021). However, no significant reduction was noted in daytime ASBP at 6 months follow-up (baseline-adjusted mean difference between groups was 0.0 mm Hg (95% CI: -4.6 to 4.5; $p = 0.65$ in the per-protocol analysis; Azizi et al., 2022). Notably, from two to five months, if monthly home BP was ≥135/85 mm Hg, prespecified standardized stepped-care antihypertensive treatment, including an aldosterone antagonist, was started under blinding to the original treatment assignment.

REQUIRE (Kario et al., 2022): The trial in Japan and South Korea also focused on resistant hypertension patients undergoing uRDN or a sham procedure. At 3 months, there was no significant difference in BP reduction between the uRDN and the sham group, with both groups experiencing similar reductions in ambulatory, home, and office BP ($p=0.971$). This study highlighted the variability in response to uRDN and a greater-than-expected BP reduction in the sham group (Kario et al., 2022).

Based on this secondary analysis (and others), we conclude that the evidence for improved health outcomes in patients with hypertension is hypothesis-generating rather than definitive, and thus, this remains an important evidence gap for CED studies to address.

2. Analysis of Key Evidence for rfRDN

The evidence presented in **Section III. E.** identified two key, contemporary RCTs and numerous other studies evaluating the impact of rfRDN on hypertension control.

SPYRAL HTN-OFF MED (Böhm et al., 2020): This trial assessed whether rfRDN performed with the Symplicity Spyral catheter reduces blood pressure in patients not taking antihypertensive medication. At three months, the primary efficacy endpoint of change in average 24-hour SBP, adjusted for SBP at study entry, was -3.9 mm Hg (95% BCI: -6.2 to -1.6), and the secondary efficacy endpoint of change in average office BP, adjusted for office blood

pressure at study entry, was -6.5 mm Hg (95% BCI: -9.6 to -3.5), with a 99.9% probability that rfRDN was superior to the sham procedure. This study does not reflect the real-world intended use of RDN because most patients will require AHMs despite rfRDN. The number of patients included in the study was small, and the average age was 52.5. Additionally, hypertension is a lifelong condition, and the follow-up period was very short due to safety and ethical concerns.

SPYRAL HTN-ON MED (Kandzari et al., 2023): This trial assessed whether rfRDN performed with the Symplicity Spyral catheter reduces blood pressure in patients taking antihypertensive medications. At six months (Kandzari et al., 2023), no between-group differences existed for the primary endpoint of 24-hour ABSP (MD: -0.03 mm Hg; 95% BCI: -2.82 to 2.77 mm Hg). The secondary effectiveness endpoint was the baseline-adjusted change in OSBP from baseline to 6 months post-procedure. In the rfRDN group, there was a greater reduction in OSBP at 6 months vs. the sham group (MD: -4.9 mm Hg; 95% BCI: -7.9 to -1.9), but this reduction is just below what is considered clinically meaningful. In a small subset of the original study (Mahfoud et al., 2022), there were modest BP reductions at 36 months in 24-hour ASBP in the rfRDN group (n=30) compared to sham (n=32), but there were no differences in OSBP (MD: -8.2; 95% CI: -17.1 to 0.8, p=0.073). While this on-medication trial better reflects real-world differences, the study did not meet its primary endpoint at six months and marginally met it at six months in an underpowered study. AHM changes during the final three months of the six-month pivotal study complicate the interpretation of the results. Like the SPYRAL HTN-OFF MED study, the follow-up of the full cohort was brief, and longer-term outcomes were examined in a small patient cohort.

Based on this secondary analysis (and others), we conclude that the evidence for improved health outcomes for patients with hypertension is hypothesis-generating, not definitive, and so this remains an important evidence gap for CED studies to address.

3. Meta-analyses

While the above RCTs represent the primary evidence, meta-analyses of combined data from multiple trials provide additional insights. Four meta-analyses were identified, with significant overlap with the studies reported above and with each other. The findings of this meta-analysis confirm that renal denervation is associated with a statistically significant and clinically meaningful reduction in ambulatory and office blood pressure levels. Blood pressure reductions are relatively small and consistent with adding a single anti-hypertensive drug. These meta-analyses find that second-generation devices demonstrated blood pressure reductions while first-generation devices did not (Sardar et al., 2019; Stavropoulos et al., 2020; Yang et al., 2022; Ogoyama & Karlo, 2024).

These analyses demonstrate a substantial variation in treatment responses to RDN; approximately one-third of patients do not respond to RDN (Yang et al., 2022). These meta-analyses have important limitations. Notably, they did not analyze primary data and included a relatively small number of patients with a short follow-up period. They also combine data from trials with different study protocols and patient characteristics. The completeness of renal denervation achieved by the various devices is uncertain, and patient adherence with antihypertensive medication was not always objectively tested.

4. Conclusions

We considered the strengths and limitations of key contemporary trials, secondary- and meta-analyses of their data, follow-up and other longitudinal (including FDA post-approval) studies, society guidelines, independent expert opinion, and public comments. We conclude that the totality of the evidence supports that RDN devices are a promising therapeutic technology that, combined with lifestyle changes and anti-hypertensive medications, could lead to meaningful improvement of health outcomes for certain Medicare beneficiaries with hypertension.

However, important questions remain, such as:
Question 1: Can the improved blood pressure control seen in trials be replicated in the real world with community-based physicians treating patients with uncontrolled hypertension?

Question 2: Which patient subgroups are most likely to benefit from RDN?

Question 3: Can all populations demonstrate benefit over a longer time? This is an important consideration as RDN is a permanent procedure.

We believe CED is the most appropriate NCD policy for RDN devices because it simultaneously covers these technologies while collecting and analyzing more data to fill evidence gaps to answer key questions. In the past, CMS developed overarching CED study questions to guide CED study protocol development. For this final decision, we provide specific CED study protocol criteria (i.e., Section I B 5 Patient, Physician, Facility, and CED Study criteria) that guide how we expect protocols to address the remaining questions in the evidence base.

5. Rationale for Coverage Requirements for RDN (Patient, Physician, Facility and CED Study criteria)

We cover RDN under CED for FDA market-authorized indications, with the following criteria for patients, physicians, facilities, and CMS-approved study protocols.

General Rationale: The criteria below are derived from trials, expert opinion, and public comments. Based on the totality of the evidence reviewed in this NCD analysis, we believe all of these criteria are necessary in CED studies to confidently answer whether Medicare beneficiaries can achieve improved health outcomes using RDN devices.

Patient Criteria

Patients enrolled in a CMS-approved CED study must meet all of the following:

(a) Diagnosis of uncontrolled hypertension ($\geq$ 140 mm Hg systolic blood pressure and > 90 mm Hg diastolic blood pressure) despite active management by a clinician with primary responsibility for blood pressure management.
(b) Uncontrolled hypertension diagnosed using either ambulatory blood pressure monitoring or serial home blood pressure readings.
(c) On lifestyle modifications and stable doses of maximally tolerated guideline-directed medical therapy (GDMT), with assessment of adherence to the prescribed regimen, for at least six weeks before referral for RDN.

Rationale for (a - c): Clinicians and patients should make a good-faith effort to achieve adequate blood pressure control through lifestyle changes and available AHMs before considering RDN. Because "White Coat Hypertension" is common, the diagnosis of uncontrolled hypertension should be confirmed using either ambulatory blood pressure monitoring or serial home blood pressure readings (Swaminathan et al., 2023; Cluett et al., 2024; Jones et al., 2025). The benefits of existing antihypertensive medications are well-established, and multiple drug classes with distinct profiles, clinical advantages/disadvantages, and side-effect profiles are widely available (Jones et al., 2025). Many anti-hypertensive medications offer benefits beyond blood pressure reduction, and many Medicare beneficiaries have comorbidities that may provide additional compelling indications for the use of specific anti-hypertensive drugs. By contrast, the available RDN studies have focused on short-term blood pressure reduction and have often excluded patients with comorbidities commonly present in the Medicare beneficiary population. Clinicians cannot reasonably conclude that a patient's blood pressure remains uncontrolled while continuing to adjust medication doses, and therefore, we require that patients be on lifestyle changes and stable doses of AHMs for at least six weeks before referral for RDN.

(d) As clinically appropriate, secondary hypertension must be evaluated and treated before determining that blood pressure remains uncontrolled. At a minimum, patients must be screened for primary aldosteronism, obstructive sleep apnea, and drug or alcohol induced hypertension before referral to RDN.

Rationale for (d): Because targeted treatments are available, clinicians and patients should address the secondary cause of hypertension and institute maximally tolerated GDMT before concluding that hypertension is uncontrolled. At a minimum, patients must be screened for primary aldosteronism, obstructive sleep apnea, and drug or alcohol induced hypertension before referral to RDN because these are prevalent in patients with uncontrolled hypertension (Jones et al., 2025). Other secondary causes of hypertension should be evaluated if clinically suspected. These include Cushing's syndrome, pheochromocytoma, thyroid disease, hyperparathyroidism, atherosclerotic renal artery stenosis, fibromuscular dysplasia, and coarctation of the aorta (Barbato et al., 2023).

(e) The patient has no contraindications to RDN, consistent with the FDA labeling of the device used.

Rationale for (e): RDN contraindications are detailed in the FDA labeling and are supported by position statements from the American Heart Association, the Society of Cardiovascular Angiography and Intervention, and the National Kidney Foundation (Kandzari et al., 2022; Swaminathan et al., 2023; Cluett et al., 2024; Jones et al., 2025).

(f) The primary clinicians must coordinate management of the patient for a minimum of six months before referral for RDN, during which the patient had at least three encounters, with no more than two of the three encounters being virtual.

Rationale for (f): Blood pressure fluctuates due to several factors, and it is not feasible to determine if it is uncontrolled based on a single clinical encounter. Additionally, many

antihypertensive medications do not achieve their maximal effect immediately, necessitating multiple incremental adjustments after evaluating the patient's blood pressure response, potential side effects, and laboratory testing. Face-to-face encounters are essential for correlating office and home blood pressure readings, and they offer an opportunity to assess electrolytes and renal function. Subsequent visits may often be conducted virtually and may reduce the burden on patients and clinic staff, while ensuring that practices make a good-faith effort to control blood pressure with lifestyle changes and maximally tolerated doses of AHMs.

(g) No prior RDN procedure.

Rationale for (g): CMS does not find compelling evidence that repeated RDN procedures provide additional benefits. There are also no available data on the feasibility or challenges of repeated RDN, such as renal artery scarring.

Physician Criteria

(a) Clinicians referring Medicare beneficiaries must have longitudinal responsibility for hypertension management.

Rationale for (a): The referring clinician should take primary responsibility for hypertension management to prioritize effective blood pressure control.

(b) Physicians performing RDN must have interventional and endovascular skills to perform effective RDN treatments. Additionally, they must be able to manage potential complications either themselves or with institutional support from colleagues who are immediately available to assist in emergency management.
(c) Physicians performing RDN without prior endovascular training or renovascular expertise must complete at least ten supervised cases of diagnostic/therapeutic renovascular procedures, half as primary operator. Additionally, they must complete at least five proctored RDN cases with each approved device used in their practice.
(d) Physicians performing RDN with prior endovascular training and active endovascular experience must complete at least five proctored RDN cases with each approved device used in their practice.

Rationale for (b - d): Operator experience is essential for optimizing outcomes from RDN because patient selection for renal denervation is critical, and there is currently no reliable method to determine the completeness of RDN during the procedure. These criteria reflect the Society of Angiography and Intervention position statement on patient selection, operator competence, training, and techniques, and organizational recommendations for RDN (Swaminathan et al., 2023). Physicians performing RDN must have adequate training for each approved device used in their practice.

Facility Criteria

(a) Facilities performing RDN must have a hypertension program with contributions from a hypertension clinician with longitudinal patient management responsibility, a

hypertension navigator, and access to relevant medical specialties (e.g., internal medicine, endocrinology, sleep medicine, cardiology, and nephrology) as appropriate.

(b) Preprocedural imaging capabilities (e.g., ultrasound, Computed Tomography Angiography, Magnetic Resonance Angiography).

(c) An appropriate interventional cardiology or radiology suite.

Rationale for (a - c): Institutional characteristics are important for achieving optimal RDN outcomes, which include a hypertension program that focuses on screening, testing, and treating complex hypertension. A hypertension program enables timely follow-up, serial office, home, or ambulatory blood pressure measurements, titration of AHMs, and coordination of serologic and imaging tests. A HTN navigator is central to a hypertension program and may be a physician, advanced practice provider, or registered nurse trained in program management. Hypertension programs should include a clinician trained in hypertension through a certificate program, fellowship, or advanced subspecialty training (e.g., cardiology or nephrology). Noninvasive imaging is essential for excluding secondary causes of HTN, assessing RDN appropriateness, and potentially monitoring for RDN complications. An interventional cardiology or radiology suite is required to perform RDN (Swaminathan et al., 2023).

CED Study Criteria

All CMS-approved CED studies must meet the patient, physician, and facility criteria above and include:

(a) One or more primary outcomes of ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP), home systolic blood pressure (HSBP), home diastolic blood pressure (HDBP), office systolic blood pressure (OSBP), office diastolic blood pressure (ODBP), worsening renal function, cerebrovascular accident, acute myocardial infarction, incidence of new-onset heart failure, cardiovascular mortality, all-cause mortality, or a composite of these, through a minimum of 24 months. Each component of a composite outcome must be individually reported.

Rationale for (a): Blood pressure lowering is a well-established surrogate marker for the reduction of cardiovascular morbidity and mortality (Williams et al., 2018; Rahimi et al., 2021). Poorly controlled blood pressure is a strong risk factor for deterioration in renal function, stroke, heart attack, and heart failure.) All-cause mortality is a core patient-centered outcome that accounts for competing causes of death without further adjudication. The 24-month minimum period for CED studies expands evidence for the durability of outcomes beyond past trials. The 24-month timeframe strikes a balance between the need to establish greater durability for RDN and timely evidence generation within CED studies. Each component of a composite outcome must be individually reported to assess which component(s) is(are) driving the outcome. Finally, we do not require specific secondary outcomes, with the expectation that a number of these will be inherently included in CED study protocols.

(b) An active comparator.

Rationale for (b): Benefits and harms cannot be assessed without a comparator. An "active comparator" is inherent in RCTs that prospectively compare randomized intervention and control groups, but may be seen in other study designs, such as those employing propensity-score matching or regression discontinuity study designs. The latter studies can be many times larger than RCTs, and we believe they can help fill in evidence gaps, especially for subgroups commonly seen in the Medicare beneficiary population.

(c) Design sufficient for subgroup analyses by:

- Age (Stratify <65, 65-74, 75+);
- Other clinically important patient demographic factors;
- Chronic kidney disease (Stratify by CKD Stages);
- Progression of CKD;
- Hypertension phenotype (e.g., resistant hypertension vs. uncontrolled for any reason);
- Medication adherence.

Rationale for (c): Approximately one-third of patients who received RDN in premarket clinical trials did not benefit (Yang et al., 2022). More evidence about the above subgroups is needed to determine which patients will clinically benefit from RDN. Note that patients with advanced renal disease, including those on dialysis, were excluded from trials. Many patients without renal failure who will receive RDN (which permanently alters the renal anatomy) will progress to renal failure. This CED study will give physicians more data to guide their appropriate management. Likewise, we expect many patients to advance to Class IV and do not want to exclude these patients from monitoring if they have already received RDN. In this instance, we anticipate studies would capture the impact of RDN on this subgroup.

A CED study would be considered successful if it demonstrated:

- That patients receiving RDN achieve a meaningful and durable reduction in blood pressure relative to matched patients who did not undergo RDN. We define a reduction in office systolic blood pressure or daytime ambulatory SBP of at least 5 mm Hg as clinically meaningful; and
- A clinically meaningful improvement of the primary outcome in patients who underwent RDN compared to similar patients treated without RDN.
- A meaningful reduction in progression of renal dysfunction, stroke, heart attack, heart failure, or death.

6. Evidence Questions – Answered

Our initial literature search and review of the evidence on RDN for Medicare beneficiaries with hypertension were guided by three general questions. Answers to these questions inform the overarching question of whether RDN meets the reasonable and necessary standard under § 1862(a)(1)(A) of the Act.

Q1. Is the evidence sufficient to conclude that RDN for hypertension meaningfully improves health outcomes for Medicare beneficiaries?

A1: No. The quality and strength of the evidence are insufficient to make this determination, and RDN for hypertension management in this population is not reasonable and necessary under §1862(a)(1)(A) of the Act, as critical evidentiary gaps remain. The key RCTs and other studies provide evidence that an RDN may significantly reduce blood pressure in carefully selected patients over a short-term follow-up period. However, due to the limitations in RDN trials to date (as discussed in the Evidence Review and CMS Coverage Analysis sections above), the evidence that RDN causes a meaningful reduction in blood pressure in Medicare beneficiaries is suggestive, but not definitive.

Q2. Do specific characteristics or comorbidities make patients more or less likely to benefit from RDN in hypertension management?

A2: No. Approximately one-third of patients who undergo RDN do not respond (Yang et al., 2022). There is no clear evidence to predict which patients are likely to benefit. There is a great deal of uncertainty, due in part to small numbers of patients and wide confidence intervals surrounding their trial outcomes, as to whether use of RDN improves health outcomes for the subgroups of Medicare beneficiaries listed above. Based on the lack of evidence of a benefit for patients with co-morbidities and patient sub-groups, CED under § 1862(a)(1)(E), is appropriate for RDN for hypertension management. We believe CMS-approved clinical studies could fill these gaps in the existing evidence base.

Q3. Are specific treatment conditions necessary to achieve outcomes with the use of RDN for hypertension management similar to those demonstrated in the clinical studies reviewed in this analysis?

A3: Uncertain. There is little evidence that outcomes achieved in rigorous trials at highly selective sites can be replicated in the real world, with a community-based, clinician team managing patients reflective of the Medicare population. Based on the totality of the evidence, CMS finds further justification that coverage under CED is appropriate. We believe that CMS-approved clinical studies could fill these gaps.

C. Benefit Category

For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in § 1812 (Scope of Part A); § 1832 (Scope of Part B); or § 1861(s) (Definition of Medical and Other Health Services) of the Act.

RDN qualifies as:

- Inpatient hospital services
- Outpatient hospital services
- Physicians' services

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

D. Patient Evaluation

CMS will carefully monitor treated patients for adherence to these criteria and assess patient outcomes using evidence published in the peer-reviewed medical literature. CMS will consider modifying this NCD contingent upon a real-world demonstration of improved health outcomes for Medicare beneficiaries with hypertension, as described above.

E. Shared Decision Making

CMS recognizes the importance of shared decision making in many clinical scenarios and has required it in other NCDs, such as implantable cardiac defibrillators. CMS supports clinician-patient shared decision making for RDN in hypertension management, but recognizes that no fully developed tool is currently available. CMS strongly encourages the use of standardized decision aids or tools. The National Quality Forum has published standards for decision aids to facilitate the decision making process between patients and clinicians and will be monitoring this space closely. CMS is pleased to learn that the American College of Cardiology is developing a patient-facing infographic and intends to publish a comprehensive decision aid.

V. History of Medicare Coverage

A. Current National Coverage Request

Prior to this final NCD, Medicare Administrative Contractors (MACs) had discretion to determine whether to cover RDN for the treatment of uncontrolled hypertension.

This is CMS' first NCA on RDN for the treatment of uncontrolled hypertension. This request for coverage was initiated externally. CMS received a complete, formal request from Medtronic to open an NCA on the topic of RDN for the management of uncontrolled hypertension. The request letter is available at https://www.cms.gov/files/document/id318.pdf

B. Timeline of NCA Milestones

Date	Milestone
Jan. 13, 2025	CMS posts a tracking sheet announcing the opening of the NCA. The first 30-day public comment period begins.
Feb 12, 2025	First public comment period ends. CMS receives 81 comments.
Jul. 10, 2025	CMS posts proposed Decision Memorandum. The second 30-day public comment period begins.
Aug. 09, 2025	The second public comment period ends. CMS receives 110 comments.
Oct. 28, 2025	CMS posts the final Decision Memorandum.

VI. Appendices

Appendix A. Proposed Medicare National Coverage Determinations Manual Language

Medicare National Coverage Determinations Manual
Draft

This draft NCD is subject to formal revisions and formatting changes prior to the release of the final NCD, contractor instructions, and publication in the Medicare National Coverage Determinations Manual.

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(Rev.)

NCD XXX – Renal Denervation for Uncontrolled Hypertension

A. General

Renal Denervation (RDN) is used in the treatment of uncontrolled hypertension.

B. Coverage Criteria
The Centers for Medicare & Medicaid Services (CMS) covers radiofrequency renal denervation (rfRDN) and ultrasound renal denervation (uRDN) (collectively RDN) for uncontrolled hypertension when furnished according to a Food and Drug Administration (FDA) market-authorized indication and all the following conditions are met:

1. Patient Criteria
The patient meets all the following criteria:

(a) Diagnosis of uncontrolled hypertension ($\geq$ 140 mm Hg systolic blood pressure and > 90 mm Hg diastolic blood pressure) despite active management by a clinician with primary responsibility for blood pressure management.

(b) Uncontrolled hypertension diagnosed using either ambulatory blood pressure monitoring or serial home blood pressure readings.

(c) On lifestyle modifications and stable doses of maximally tolerated guideline-directed medical therapy (GDMT), with assessment of adherence to the prescribed regimen, for at least six weeks before referral for RDN.

(d) As clinically appropriate, secondary hypertension must be evaluated and treated before determining that blood pressure remains uncontrolled. At a minimum, patients must be screened for primary aldosteronism, obstructive sleep apnea, and drug or alcohol induced hypertension before referral to RDN.

(e) The patient has no contraindications to RDN, consistent with the FDA labeling of the device used.

(f) The primary clinicians must coordinate management of the patient for a minimum of six months before referral for RDN, during which the patient had at least three encounters, with no more than two of the three encounters being virtual.

(g) No prior RDN procedure.

2. Physician Criteria
RDN is furnished by clinicians who meet the following criteria, as applicable:

(a) Clinicians referring Medicare beneficiaries must have longitudinal responsibility for hypertension management.

(b) Physicians performing RDN must have interventional and endovascular skills to perform effective RDN treatments. Additionally, they must be able to manage potential complications either themselves or with institutional support from colleagues who are immediately available to assist in emergency management.

(c) Physicians performing RDN without prior endovascular training or renovascular expertise must complete at least ten supervised cases of diagnostic/therapeutic renovascular procedures, half as primary operator. Additionally, they must complete at least five proctored RDN cases with each approved device used in their practice.

(d) Physicians performing RDN with prior endovascular training and active endovascular experience must complete at least five proctored RDN cases with each approved device used in their practice.

3. Facility Criteria
The RDN device and related items and services are furnished at facilities meeting the following criteria:

(a) Facilities performing RDN must have a hypertension program with contributions from a hypertension clinician with longitudinal patient management responsibility, a hypertension navigator, and access to relevant medical specialties (e.g., internal medicine, endocrinology, sleep medicine, cardiology, and nephrology) as appropriate.

(b) Preprocedural imaging capabilities (e.g., ultrasound, Computed Tomography Angiography, Magnetic Resonance Angiography).

(c) An appropriate interventional cardiology or radiology suite.

4. CED Study Criteria
The RDN device and related items and services are furnished in the context of a CMS-approved CED study. CMS-approved CED study protocols must: include only those patients who meet the criteria in section B.1; furnish items and services only through practitioners who meet the criteria in section B.2; furnish items and services at facilities meeting the criteria in section B.3; and include all of the following:

(a) One or more primary outcomes of ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP), home systolic blood pressure (HSBP), home diastolic blood pressure (HDBP), office systolic blood pressure (OSBP), office diastolic blood pressure (ODBP), worsening renal function, cerebrovascular accident, acute myocardial infarction, incidence of new-onset heart failure, cardiovascular mortality, all-cause mortality, or a composite of these, through a minimum of 24 months. Each component of a composite outcome must be individually reported.

(b) An active comparator.

(c) Design sufficient for subgroup analyses by:

- Age (Stratify <65, 65-74, 75+);
- Other clinically important patient demographic factors;
- Chronic kidney disease (Stratify by CKD Stages);
- Progression of CKD;
- Hypertension phenotype (e.g., resistant hypertension vs. uncontrolled for any reason);
- Medication adherence.

(d) In addition, CMS-approved CED studies must adhere to the scientific standards (criteria 1-17 below) that have been identified by the Agency for Healthcare Research and Quality (AHRQ) as set forth in Section VI. of CMS' Coverage with Evidence Development Guidance Document, published August 7, 2024 (the "CED Guidance Document").

1. Sponsor/Investigator: The study is conducted by sponsors/investigators with the resources and skills to complete it successfully.
2. Milestones: A written plan is in place that describes a detailed schedule for completion of key study milestones, including study initiation, enrollment progress, interim results reporting, and results reporting, to ensure timely completion of the CED process.
3. Study Protocol: The CED study is registered with ClinicalTrials.gov and a complete final protocol, including the statistical analysis plan, is delivered to CMS prior to study initiation. The published protocol includes sufficient detail to allow a judgment of whether the study is fit-for-purpose and whether reasonable efforts will be taken to minimize the risk of bias. Any changes to approved study protocols should be explained and publicly reported.
4. Study Context: The rationale for the study is supported by scientific evidence and study results are expected to fill the specified CMS-identified evidence deficiency and provide evidence sufficient to assess health outcomes.
5. Study Design: The study design is selected to safely and efficiently generate valid evidence of health outcomes. The sponsors/investigators minimize the impact of confounding and biases on inferences through rigorous design and appropriate statistical techniques. If a contemporaneous comparison group is not included, this choice should be justified, and the sponsors/investigators discuss in detail how the design contributes useful information on issues such as durability or adverse event frequency that are not clearly answered in comparative studies.

6. Study Population: The study population reflects the demographic and clinical diversity among the Medicare beneficiaries who are the intended population of the intervention, particularly when there is good clinical or scientific reason to expect that the results observed in premarket studies might not be observed in older adults or subpopulations identified by other clinical or demographic factors.
7. Subgroup Analyses: The study protocol explicitly discusses beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion requirements effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. In the protocol, the sponsors/investigators describe plans for analyzing demographic subpopulations as well as clinically-relevant subgroups as identified in existing evidence. Description of plans for exploratory analyses, as relevant subgroups emerge, are also included.
8. Care Setting: When feasible and appropriate for answering the CED question, data for the study should come from beneficiaries in their expected sites of care.
9. Health Outcomes: The primary health outcome(s) for the study are those important to patients and their caregivers and that are clinically meaningful. A validated surrogate outcome that reliably predicts these outcomes may be appropriate for some questions. Generally, when study sponsors propose using surrogate endpoints to measure outcomes, they should cite validation studies published in peer-reviewed journals to provide a rationale for assuming these endpoints predict the health outcomes of interest. The cited validation studies should be longitudinal and demonstrate a statistical association between the surrogate endpoint and the health outcomes it is thought to predict.
10. Objective Success Criteria: In consultation with CMS and AHRQ, sponsors/investigators establish an evidentiary threshold for the primary health outcome(s) so as to demonstrate clinically meaningful differences with sufficient precision.
11. Data Quality: The data are generated or selected with attention to provenance, bias, completeness, accuracy, sufficiency of duration of observation to demonstrate durability of health outcomes, and sufficiency of sample size as required by the question.
12. Construct Validity: Sponsors/investigators provide information about the validity of drawing warranted conclusions about the study population, primary exposure(s) (intervention, control), health outcome measures, and core covariates when using either primary data collected for the study about individuals or proxies of the variables of interest, or existing (secondary) data about individuals or proxies of the variables of interest.
13. Sensitivity Analyses: Sponsors/investigators will demonstrate robustness of results by conducting pre-specified sensitivity testing using alternative variable or model specifications as appropriate.
14. Reporting: Final results are provided to CMS and submitted for publication or reported in a publicly accessible manner within 12 months of the study's primary completion date. Wherever possible, the study is submitted for peer review with the goal of publication using a reporting guideline appropriate for the study design and structured to enable replication. If peer-reviewed publication is not possible, results may also be published in an online publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with incomplete results).

15. Sharing: The sponsors/investigators commit to making study data publicly available by sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party. The study should comply with all applicable laws regarding subject privacy, including 45 CFR § 164.514 within the regulations promulgated under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.
16. Governance: The protocol describes the information governance and data security provisions that have been established to satisfy Federal security regulations issued pursuant to HIPAA and codified at 45 CFR Parts 160 and 164 (Subparts A & C), United States Department of Health and Human Services (HHS) regulations at 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient and HHS regulations at 45 CFR Part 46, regarding informed consent for clinical study involving human subjects. In addition to the requirements under 42 CFR and 45 CFR, studies that are subject to FDA regulation must also comply with regulations at 21 CFR Parts 50 and 56 regarding the protection of human subjects and institutional review boards, respectively.
17. Legal: The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals, although it is acceptable for a study to test a reduction in toxicity of a product relative to standard of care or an appropriate comparator. For studies that involve researching the safety and effectiveness of new drugs and biological products aimed at treating life-threatening or severely-debilitating diseases, refer to additional requirements set forth in 21 CFR § 312.81(a).

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet all the criteria and standards identified above.

C. National Non-Covered Indications

RDN is not covered for patients outside of a CMS-approved study.

D. Other

Nothing in this NCD would preclude coverage of RDN through NCD 310.1 (Clinical Trial Policy) or through the Investigational Device Exemption (IDE) Policy.

Appendix B. RDN Device Characteristics and Operator Factors

Table B1: Characteristics of the Symplicity and Paradise RDN catheter systems

Catheter	RDN Platform	Design	Ablation	Contraindications
Symplicity Spyral (Medtronic)	Radiofrequency	Multielectrode (4 1.5 mm in length monopolar gold electrodes 5 mm apart), helical design, rapid exchange monorail catheter. Femoral access: 4 Fr. catheter, compatible with 6 Fr. guide catheter, 0.014" guidewire	Main and accessory arteries, including branches (diameter 3-8 mm); 60 seconds per ablation cycle	Renal artery diameter < 3 mm or > 8 mm Renal artery fibromuscular dysplasia Stented renal artery (< 3 months prior to RDN procedure) Renal artery aneurysm Renal artery diameter stenosis > 50% Pregnancy Presence of abnormal kidney (or secreting adrenal) tumor Iliac/femoral artery stenosis precluding insertion of the catheter
Paradise (Recor Medical)	Ultrasound	Piezoelectric ceramic transducer within a fluid-cooled, low-pressure balloon, over-the-wire. Femoral access: 7 Fr., 0.014" guidewire	Main and accessory arteries (branch vessel ablation not necessary; different catheter sizes for diameters of 3-8 mm); 7 seconds per emission; 2-3 treatments per main renal artery	Renal arteries diameter <3 mm and >8 mm Renal artery Fibromuscular disease Stented renal artery Renal artery aneurysm Renal artery diameter stenosis >30% Pregnancy Presence of abnormal kidney (or secreting adrenal) tumors Iliac/femoral artery stenosis precluding insertion of the catheter

Sources: Medtronic, Recor Medical
Fr.: French unit (1 Fr.=0.33mm); mm: millimeter; RDN: renal denervation;

Renal denervation (RDN) operator factors: A standard interventional technique is used to access the femoral artery, place the indicated-sized and-shaped guide catheter, and advance into the left or right renal artery under fluoroscopic guidance.

Radiofrequency (RF) RDN: The Symplicity Spyral RF one-size-fits-all catheter is positioned in the renal artery, and the guidewire is retracted proximal to the most proximal RF ablation electrode prior to delivering treatment. Hence, the catheter relaxes into a helical shape to make adequate vessel wall contact. The system requires the operator to monitor the high-frequency electric energy conduction impedance and arterial wall temperature measurements at each of the four electrodes during RF wave emission (≤ 4 ablations simultaneously). These measurements allow the operator to determine whether there is adequate vessel wall apposition during a respiratory cycle. The radiofrequency treatment is delivered from the attached generator when the operator selects a generator screen button, remote, or foot pedal. The generator delivers radiofrequency power for 60 seconds using an automated algorithm. If multiple treatments are

administered in one artery, the catheter should be pulled back at least 5 millimeters (mm) proximal to the treated artery location. To move the catheter to another side, the wire is advanced distally out of the catheter tip to straighten the catheter (from the helical shape), the catheter is retracted back into the guide catheter, and arterial imagery is obtained. Fulton and colleagues (2023) have reported that most operators treat branch vessels before the main renal artery due to investigational trial protocol requirements (angiography helps identify suitable-sized vessels). rfRDN requires more procedure time and contrast volume than ultrasound ablation due to the treatment of arterial branches (Ogoyama et al., 2024).

Ultrasound RDN: The Paradise ultrasound system requires angiogram measurement of the distal, mid, and proximal artery diameters to select the appropriate Paradise catheter balloon sizing using a size recommendation table (selecting the smallest measured diameter of the artery).

The Paradise catheter deflated treatment balloon is advanced over a guidewire into the renal artery. The connected Paradise generator is used to administer 2-3 sonications (fully circumferential thermal ablation using acoustic energy) in each of the left and right renal arteries once the automatic low-pressure balloon inflation is triggered by the operator and the position of occlusive balloon/transducer is verified via fluoroscopy. Each treatment is delivered for 7 seconds distal to proximal, in non-overlapping target arterial zones, while the balloon is simultaneously cooled with sterile water. A treated location is never crossed to perform additional treatments, and at least 5 mm is maintained between a sonication of both the kidney parenchyma and the renal artery/aorta ostium. Emission zones should not overlap between adjacent vessels, maintaining a minimum of 10 mm apart or a staggering of sonications. The Paradise Catheter is retracted back into the guide catheter prior to moving the device into an alternate artery or accessory vessel for treatment.

Appendix C. Referenced Materials

Table C1. Comparison of baseline patient characteristics in the trials with the absence of antihypertensive medications RADIANCE SOLO, Radiance II and SPYRAL HTN-OFF trials.

	SOLO (Azizi 2018)		**Radiance II (Azizi 2023)**		**SPYRAL HTN OFF (Böhm 2020)**	
Characteristics	**uRDN (n=74)**	**Sham (n=72)**	**uRDN (n=150)**	**Sham (n=74)**	**rfRDN (n= 166)**	**Sham (n= 165)**
Sex, Male, % (n)	62.1% (46/74)	54.1% (39/72)	68.6% (103/150)	77% (57/74)	64% (107/166)	68% (113/165)
Age (mean ± SD, year)	54.4 ± 10.2	53.8 ± 10.0	55.1 ± 9.9	54.9 ± 7.9	52.4 ± 10.9	52.6 ± 10.4
Race, % (n)						
Caucasian	81.0% (60/74)	72.2% (52/72)	76.0% (114/150)	75.6% (56/74)	28% (47/166)	30% (50/165)
Black	16.2% (12/74)	18.0% (13/72)	14.0% (21/150)	20.2% (15/74)	22% (36/166)	22% (36/165)
American Indian or Alaska Native	0.0% (0/74)	0.0% (0/72)	0.0% (0/150)	0.0% (0/74)	NR	NR
Asian/Japanese from Japan	1.3% (1/74)	0.0% (0/72)	0.0% (0/150)	1.3% (1/74)	5% (9/166)	2% (4/165)
Hispanic or Latino	1.3% (1/74)	5.5% (4/72)	10.0% (15/150)	2.7% (2/74)	NR	NR
Native Hawaiian or Pacific Islander	0.0% (0/74)	0.0% (0/72)	0.0% (0/150)	0.0% (0/74)	NR	NR
Other/Mixed Race	0.0% (0/74)	4.2% (3/72)	10.0% (15/150)	2.7% (2/74)	1% (1)	1% (1/165)
Not reported	-	-	-	-	44% (73/166)	48% (79/165)
BMI, mean ± SD	29.9 ± 5.9	29.0 ± 5.0	30.1 ± 5.2	30.6 ± 5.2	31.1 ± 6.0	30.9 ± 5.5
Abdominal circumference (cm)	101.5 ± 14.2	98.5 ± 15.1	102.4 ± 12.3	104.3 ± 13.1	NR	NR
Comorbidities, % (n)						
Type 2 DM	2.7% (2/ 74)	6.9% (5/72)	6.0% (9/150)	6.8% (5/74)	4% (6/166)	5% (9/165)
Current Smoker	NR	NR	NR	NR	17% (28/166)	6% (27/165)
Obstructive sleep apnea	8.1% (6/74)	11.1% (8/72)	14.0% (21/150)	17.6% (13/74	8% (14/166)	7% (12/165)
History of coronary artery disease	0.00% (0/74)	0.00% (0/72)	0.00% (0/150)	0.00% (0/74)	0 *	5% (8/165) *

	SOLO (Azizi 2018)		Radiance II (Azizi 2023)		SPYRAL HTN OFF (Böhm 2020)	
Cerebrovascular event(s)	0.0% (0/74)	0.0% (0/72)	0.0% (0/150)	0.0% (0/74)	1% (1/166) *	0*
Peripheral Artery Disease	2.7% (2/74)	0% (0/72)	0% (0/150)	0% (0/74)	1% (1/166)	0
Office Systolic BP (mmHg)	142.6 ± 14.7^	144.6 ± 15.9^	155.8 ± 11.1	154.3 ± 10.6	162.7 ± 7.8	162.9 ± 7.5
Office Diastolic BP (mmHg)	92.3 ± 10.1^	93.6 ± 8.3^	101.3 ± 6.7	99.1 ± 5.6	101.2 ± 7.0	102.0 ± 7.1
24-hour Systolic BP, mean (mmHg)	142.6 ± 8.1	143.8 ±10.4	150.2 ± 8.6**	151.3 ± 9.0**	151.4 ± 8.1	151.0 ± 7.5
24-hour Diastolic BP, mean (mmHg)	87.3 ± 5.0	88.6 ± 5.7	93.8 ± 5.2**	93.2± 5.6**	98.0 ± 7.7	99.0 ± 7.4
Pulse (bpm)						
Screening	73.2 ± 12.4	73.2 ± 12.4	74.1 ± 12.0	73.6 ± 11.9	NR	NR
Baseline	72.0 ± 12.1^^	72.6 ± 12.3^^	74.3 ± 11.3	72.5 ± 11.5	NR	NR

^Office blood pressure before antihypertensive medication washout.
^^ Office heart rate before antihypertensive medication washout.
*These events occurred more than 3 months before randomization.
**There were 145 patients in the ultrasound renal denervation group and 73 patients in the sham procedure group with data.
BMI: body mass index; BP: blood pressure; bpm: beats per minute; DM: diabetes mellitus; HTN: hypertension; NR: not reported; rfRDN: radiofrequency renal denervation; SD: standard deviation; uRDN: ultrasound renal denervation

Table C2. Comparison of baseline patient characteristics in the trials with the presence of antihypertensive medications RADIANCE TRIO, REQUIRE and SPYRAL HTN-ON trials.

	TRIO (Azizi 2021)		REQUIRE (Kario 2022)		SPYRAL HTN ON (Kandzari 2023)	
Characteristics	**uRDN (n=69)**	**Sham Procedure (n=67)**	**uRDN (n = 69)**	**Sham procedure (n = 67)**	**rfRDN (n = 206)**	**Sham procedure (n = 131)**
Sex, Male, % (n/N)	81.1% (56/69)	79.1% (53/67)	69.6% (48/69)	79.1% (53/67)	81.1% (167/206)	78.6% (103/131)
Age, mean/ median ± SD	52.3 ± 7.5	52.8 ± 9.1	50.7 ± 11.4	55.6 ± 12.1	55.2 ± 9.0	54.6 ± 9.4
Race, % (n/N)						
Caucasian	66.2% (45/68)	77.3% (51/66)	NR	NR	34.5% (71/206)	36.6% (48/131)
Black	20.6% (14/68)	19.7% (13/66)	NR	NR	16.9% (35/206)	19.1% (25/131)
American Indian or Alaska Native	0.0% (0/68)	1.5% (1/66)	NR	NR	NR	NR
Asian	1.5% (1/68)	1.5% (1/66)	NR	NR	1% (2/206)	3.0% (4/131)
Hispanic or Latino	7.4% (5/68)	0.0% (0/66)	NR	NR	NR	NR
Native Hawaiian or Pacific Islander	0.0% (0/68)	0.0% (0/66)	NR	NR	NR	NR

	TRIO (Azizi 2021)		**REQUIRE (Kario 2022)**		**SPYRAL HTN ON (Kandzari 2023)**	
Other/Mixed Race	4.4% (3/68)	0.0% (0/66)	NR	NR	NR	NR
Not reported	-	-	-	-	38.8% (80/206)	35.1% (46/131)
BMI, mean ± SD	32.8 ± 5.7	32.6 ± 5.4	29.5 ± 5.5	28.4 ± 4.5	NR	NR
eGFR, mL/min per 1.73 m^2	NR	NR	74.2 ± 16.2	69.6 ± 17.1	NR	NR
Comorbidities, % (n/N)						
Type 2 DM	30.4% (21/69)	25.3% (17/67)	26.1% (18/69)	29.9% (20/67)	10/7% (22/206)	17.5% (23/131)
Current smoker	NR	NR	NR	NR	15.5% (32/206)	16.0% (21/131)
Cardiovascular disease	NR	NR	13.0% (9/69)	13.4% (9/67)	NR	NR
Coronary Artery Disease	NR	NR	NR	NR	5.3% (11/206)	6.9% (9/131)
Obstructive sleep apnea	27.5% (19/69)	16.4% (11/67)	15.9% (11/69)	11.9% (8/67)	11% (23/206)	17.5% (23/131)
Dyslipidemia	NR	NR	56.5% (39/69)	59.7% (40/67)	NR	NR
Cerebrovascular event(s)	8.7% (6/69)	5.9% (4/67)	0.0% (0/69)	7.5% (5/67)	0.4% (1/206)	1.5% (2/131)
Peripheral Artery Disease	1.4 % (1/69)	4.48% (3/67)	1.4% (1/69)	3.0% (2/67)	0% (0/206)	0% (0/131)
Currently Using CPAP/BiPAP	NR	NR	NR	NR	7.8% (16/206)	16.0% (21/131)
Office Systolic BP, mean ± SD **(mmHg)**	161.9 ± 15.5	163.6 ± 16.8	157.6±19.5	160.4 ± 14.9	163.0 ± 7.7	163.1 ± 7.9
Office Diastolic BP, mean ± SD **(mmHg)**	105.1 ± 11.6	103.3 ± 12.7	97.7 ± 16.6	95.3 ± 14.2	101.2 ± 7.0	101.5 ± 7.3
24-hour Systolic BP, mean ± SD **(mmHg)**	143.9 ± 13.4	145.4±14.0	161.9±13.4	161.5 ± 13.1	149.6 ± 7.0	149.3 ± 7.0
24-hour Diastolic BP, mean ± SD **(mmHg)**	88.9 ± 8.2	89.5 ± 9.5	94.9 ± 9.3	92.7 ± 9.4	96.6 ± 7.6	95.7 ± 7.7
Pulse, mean ± SD **(bpm)**	76.9 ± 12.2	82.0 ± 12.1	75.3 ± 10.8	71.5 ± 12.8	73.2 ± 10.9	74.8 ± 11.4
Anti-hypertensive drug classes, % (n/N)						

	TRIO (Azizi 2021)		REQUIRE (Kario 2022)		SPYRAL HTN ON (Kandzari 2023)	
RAS blocker	97% (67/69)	94% (63/67)	98.6% (68/69)	98.5% (66/67)	77% (158/206)	76% (99/131)
Calcium channel blocker	88% (61/69)	84% (56/67)	91.3% (63/69)	88.1% (59/67)	53% (110/206)	56% (73/131)
Diuretic	91% (63/69)	96% (64/67)	92.8% (64/69)	63 (94.0% (63/67)	41% (84/206)	44% (57/131)
MR blocker	NR	NR	24.6% (17/69)	14.9% (10/67)	NR	NR
alpha-blocker	9% (6/69)	15% (10/67)	20.3% (14/69)	17.9% (12/67)	NR	NR
beta-blocker	54% (37/69)	43% (29/67)	34.8% (24/69)	37.3% (25/67)	18% (37/206)	18% (24/131)
alpha-/beta-blocker	NR	NR	21.7% (15/69)	17 (25.4% (17/67)	NR	NR
Medication burden, mean ± SD	4.0 ± 1.0	3.9 ± 1.1	4.1 ± 1.6	3.9 ± 1.1	2.9 ± 3.7	2.7 ± 3.1
Patients on 1 AH medication, % (n/N)	NR	NR	NR	NR	39% (80/206)	35.9% (47/131)
Patients on 2 AH medications, % (n/N)	NR	NR	NR	NR	33% (67/206)	35.9% (47/131)
Patients on 3 AH medications, % (n/N)	39% (27/69)	42% (28/67)	46.4% (32/69)	43.3% (29/67)	29% (59/206)	28.2% (37/131)
Patients on 4 AH medications, % (n/N)	32% (22/69)	36% (24/67)	29.0% (20/69)	34.3% (23/67)	NR	NR
Patients on ≥5 AH medications, % (n/N)	29% (20/69)	22% (15/67)	24.6% (17/69)	22.4% (15/67)	NR	NR

AH: antihypertensive; BiPAP: bilevel positive airway pressure; BMI: body mass index; bpm: beats per minute; CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HTN: hypertension; MR: mineralocorticoid receptor; NR: Not reported; RAS: renin-angiotensin system; rfRDN: radiofrequency renal denervation; SBP: systolic blood pressure; SD: standard deviation; uRDN: ultrasound renal denervation

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