Technology Assessment Program – Technical Brief

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Renal Denervation in the Medicare Population

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States.

The Centers for Medicare and Medicaid Services requested this report from the Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following EPC: Johns Hopkins University Evidence-based Practice Center (Contract Number: 290-2015-00006-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Renal Denervation in the Medicare Population

Structured Abstract

Background. Renal denervation refers to catheter-based radiofrequency ablation of renal sympathetic nerves, which may reduce blood pressure in patients with resistant hypertension, but data on its effectiveness are conflicting.

Purpose. The purpose of this technical brief is to evaluate the effectiveness of renal denervation for resistant hypertension, and determine its applicability to the Medicare population.

Methods. We searched for relevant studies using PubMed and input from Key Informants and the experts on our team. Study eligibility criteria were defined in terms of population, intervention, comparison, outcomes, timing, and study design. Two reviewers independently reviewed each article. We reviewed articles if they reported a randomized controlled trial (RCT), a comparative cohort with at least 10 patients in each arm, or a non-comparative cohort with at least 25 patients. We defined between-group differences in 24-hour ambulatory systolic blood pressure as the primary metric for effectiveness of renal denervation.

Findings. We retrieved 1,233 unique citations from our literature search. We selected 83 studies (published in 98 articles) for abstraction; 9 were RCTs, 8 were comparative cohorts, and 66 were non-comparative cohorts. The study populations were only partially comparable to the Medicare-eligible population. In patients with resistant hypertension who continue to receive antihypertensive medications, renal denervation reduced 24-hour ambulatory systolic blood pressure, but the mean absolute change (between-group difference) was small in RCTs (range: -8.0 mm Hg to +2.1 mm Hg). The within-group differences in office systolic blood pressure were higher than the between-group differences for renal denervation in RCTs and comparative cohorts (-42.0 mm Hg to -8 mm Hg) as well as in non-comparative cohorts (range -58.2 mm Hg to 12 mm Hg), likely overestimating the effect of renal denervation due to white coat effect, observation bias, and placebo effect. Data were scant on clinical endpoints, such as stroke, myocardial infarction, kidney events, hospitalization, or death. Adverse effects were uncommon but potentially serious, and included hematomas, pseudoaneurysms, and renal artery interventions.

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Background

Introduction

Hypertension is the leading cause of cardiovascular disease, kidney failure, and death in the general population. In the United States, the prevalence of hypertension in adults was 29 percent in 2012.[1, 2] Hypertension prevalence is even higher in the Medicare population, exceeding 60 percent for adults older than 65 years and over 90 percent for Medicare dialysis patients.[3, 4] Evidence-based practice guidelines affirm that treatment of hypertension reduces the risks of cardiovascular disease and death, and multiple medications and lifestyle interventions can reduce blood pressure.[5-8]

Despite guidelines supporting blood pressure control, less than half of adults with hypertension reach goal blood pressure, as defined by the older guidelines (less than 140/90 mm Hg).[1] Recently, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) reported that targeting a systolic blood pressure of 120 mm Hg instead of 140 mm Hg reduced rates of cardiovascular events by almost a third and the risk of death by almost a quarter.[9] If this lower blood pressure target is adopted by clinicians, an even greater proportion of adults with hypertension will be above the goal blood pressure, highlighting the importance of new methods for controlling blood pressure.

Failure to reach goal blood pressure despite "adequate" treatment is operationally defined as "apparent treatment resistant hypertension."[10, 11] This definition was developed to: a) identify patients with secondary causes of hypertension, such as pheochromocytoma, syndrome of apparent mineralocorticoid excess, or renal artery stenosis, that have specific medical or surgical treatments; b) identify patients with uncontrolled blood pressure that may benefit from specialized hypertension care; and c) provide a framework for testing therapies for resistant hypertension. Patients with apparent treatment resistant hypertension can include those with "pseudo-resistance" from dietary, lifestyle, and medication non-adherence, as well as those with "true resistance." Data from 14,684 participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggest that irrespective of the mechanism, patients with apparent treatment resistant hypertension are at a 30 to 50 percent higher risk for death, stroke, or coronary heart disease, and almost a 2-fold higher risk of end-stage renal disease and new-onset heart failure compared with patients without apparent treatment resistant hypertension.[12]

In this context, innovative methods to reduce blood pressure may offer a way to improve cardiovascular outcomes and reduce the risk of myocardial infarction, stroke, heart failure, kidney failure, disability, and death. Renal denervation is a relatively new technology involving catheter-based radiofrequency (or sonar) ablation of renal sympathetic nerves to reduce blood pressure. Clinical trial data are conflicting about the efficacy of renal denervation in lowering blood pressure, with resulting uncertainty regarding its role in hypertensive patients.

Clarifying the role of renal denervation in routine care of Medicare beneficiaries requires an understanding of: a) the pathogenesis of hypertension in patients over the age of 65 years, disabled individuals, and those on dialysis; b) factors that contribute to apparent treatment resistant hypertension in these subgroups; c) other options for treatment; and d) a synthesis of the available studies.

Guiding Questions

In this section we map the generic Guiding Questions (GQ) used in technical briefs prepared by the Evidence-based Practice Centers (EPCs) to the specific Key Questions (KQ) addressed in this technical brief.

GQ 1: Describe the Technology/Intervention

- KQ 1. What is the theoretical renal denervation mechanism of action?

GQ 2: Describe the Context in which the Technology/Intervention Is Used

- KQ 2. What is the evidence for blood pressure measurement and use as a surrogate outcome?
- KQ 3. What is the clinical definition of resistant hypertension, and what are the treatment alternatives?
- KQ 4. For randomized controlled trials (RCTs) and observational studies of renal denervation, what are the inclusion criteria for patients, and how do clinical characteristics match the clinical definition of resistant hypertension?

GQ 3: Describe the Current Evidence of the Technology/Intervention

- KQ 5. What are the predictors of response in Medicare eligible patients who are appropriate candidates for renal denervation?
- KQ 6. What is the evidence for renal denervation effectiveness in reducing blood pressure, stroke, myocardial infarction, and hospitalization and/or improving survival in Medicare eligible patients with resistant hypertension?
- KQ 7. What is the evidence for renal denervation effectiveness in other conditions such as heart failure and arrhythmias?
- KQ 8. What are the adverse effects or complications associated with renal denervation in the Medicare population?

GQ 4: Identify the Important Issues Raised by the Technology/Intervention

Methods

We sought input from Key Informants in addition to searching for relevant studies.

Discussion with Key Informants

We recruited eight Key Informants to give input on our approach to preparing the technical brief. Key Informants included stakeholders, representing clinical experts, investigators, government agencies, and patient/consumer advocates. As partners, Centers for Medicare and Medicaid Services (CMS) representatives were included among our Key Informants.

Prior to a conference call with the Key Informants, we drafted a narrative review to address KQs 1-3. We presented the draft narrative review on these KQs to the Key Informants, and asked them to comment on our interpretation of the prevailing views of experts and to point out any divergent viewpoints that should receive more attention.

For the systematic review of evidence on KQs 4-8, we asked the Key Informants to provide feedback on our strategy for preparing a summary of the evidence. The goal of this activity was to direct us to better perform the work in a systematic, yet efficient manner. We also prepared a flow diagram and list of included studies, and asked the Key Informants if they were aware of any studies we had missed.

Search Strategy

We conducted searches for relevant studies using PubMed, and we also identified articles from investigators' existing resources, including recommendations by Key Informants and the experts on our team. The search strategy for PubMed is provided in Appendix A. We limited the search to the last 10 years because we did not feel studies published before 2006 were relevant. Indeed, the first reported use of the renal denervation technology in a person was not published until 2010.[13] We updated the search in March 2016.

Eligibility Criteria

Two reviewers independently reviewed titles, abstracts, and full-text articles. We excluded abstracts and full-text articles if both reviewers agreed that the study should be excluded. We resolved any differences regarding inclusion through consensus adjudication.

We developed final eligibility criteria based on Key Informant input and Task Order Officer (TOO) approval. We defined the eligibility criteria in terms of population, intervention, comparison, outcomes, timing, and study design, and these criteria were individualized to the questions (Table 1).

Table 1. Inclusion and exclusion criteria for renal denervation studies

	Inclusion	Exclusion
Population	• Studies of adults with resistant hypertension (on at least three medications and blood pressure > 140/90 mm Hg)	
Intervention	• Studies that evaluate a non-surgical renal denervation device	
Comparison	• Studies that compare renal denervation with either anti-hypertensive drugs or lifestyle changes • Concurrent comparison groups and before/after comparisons	
Outcomes	• Studies addressing at least one of the following outcomes: o Office or ambulatory systolic blood pressure o Number of blood pressure medications o Mortality, CVD mortality, stroke, myocardial infarction, congestive heart failure, hospitalization o Adverse events	
Timing	• Studies of any followup duration	
Study design	• Randomized controlled trials, comparative observational studies with at least 10 participants per arm, or non-comparative observational studies with less than 25 participants receiving renal denervation • Clinical trials published only as meeting or conference abstracts if the meeting or conference was for a major medical society and was held within the last 2 years	• Case reports • Studies with no original data • Studies not published in English

CVD = cardiovascular disease; mm Hg = millimeters of mercury

Data Abstraction and Management

We abstracted data on the items listed in Table 2. One reviewer abstracted the data and a senior reviewer checked it. The data abstraction forms are provided in Appendix B.

Table 2. Items for data abstraction

Population	• Age • Gender • Race/ethnicity • Body mass index • Kidney function • Diabetes status • Left ventricular hypertrophy • Medication use (mean number of medications used and percent using a diuretic
Intervention	• Manufacturer and model of renal denervation device • Individual who performed the procedure • Type of training for procedure • Whether up-titration of antihypertensive medications was allowed • Percent of patients who did not receive their assigned treatment
Comparator	• Type of comparator, if any
Outcomes	• Change in office or ambulatory systolic blood pressure • Change in number of blood pressure medications • Rates of stroke, myocardial infarction, hospitalization, and mortality • Adverse events
Timing	• Duration of run-in period • Followup duration
Study design	• Study design, including whether or not there was a run-in period • Inclusion/exclusion criteria, including the minimum number of antihypertensive medications, minimum blood pressure, and minimum duration of resistant hypertension. • Number of patients screened versus the number enrolled
Setting	• Geographic location

Quality Assessment

Two reviewers independently assessed study quality. We assessed the quality of RCTs using the Cochrane Risk of Bias tool.[14] We assessed the quality of comparative observational studies only if the study was multi-centered, had a run-in period, included over 25 participants per arm, and if it measured ambulatory blood pressure. If a comparative observational study met these criteria, we used selective items from the Downs and Black tool.[15] We did not assess the quality of the non-comparative studies because the lack of a comparison group equates to having a weak study design.

Data Presentation

We used a narrative review to answer KQs 1-3, emphasizing the prevailing view on each question, while noting where different views existed.

We used a systematic approach to answer KQs 4-8. It included:

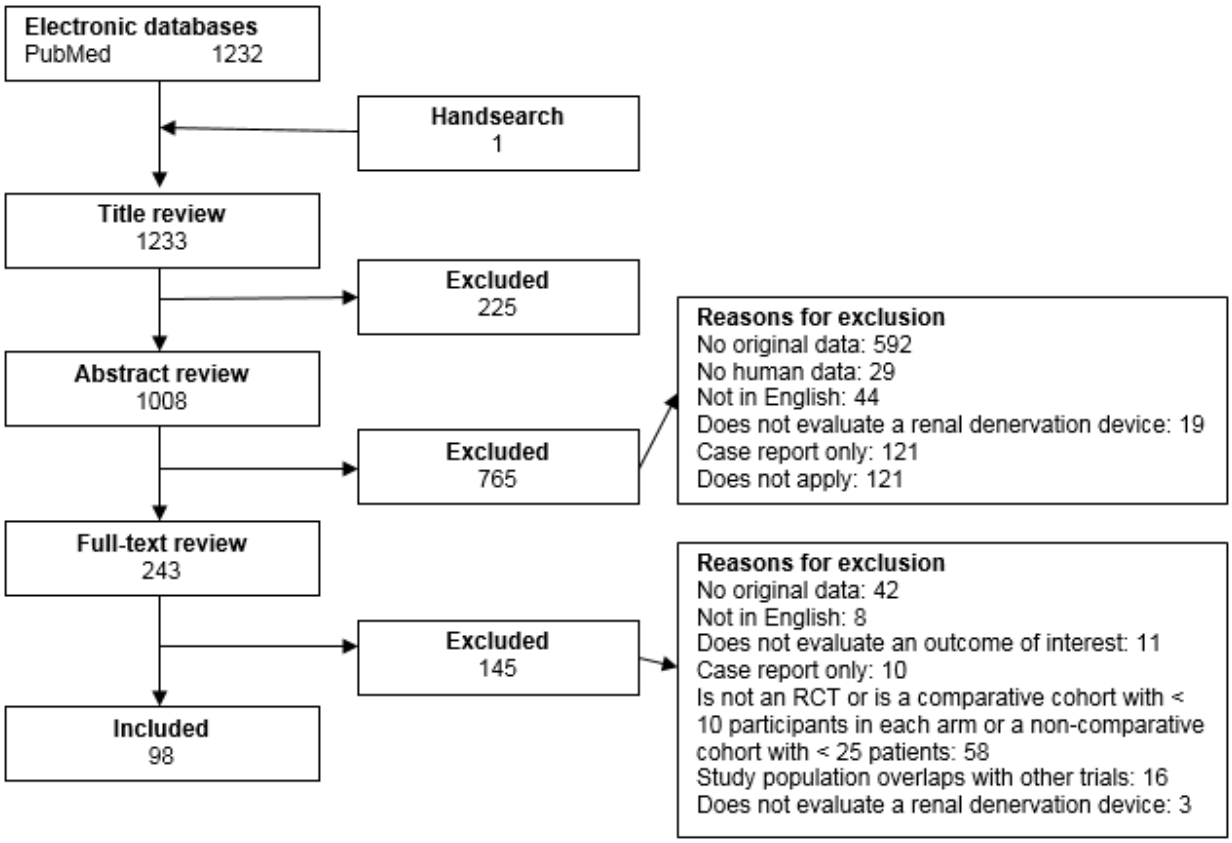
- Comparing the study eligibility criteria with the consensus definition of resistant hypertension, given that the inclusion criteria in observational studies and RCTs were variable;
- Examining and comparing results of the subgroup analyses by age in each of the trials;
- Summarizing any analyses of demographic or clinical characteristics associated with response to renal denervation;
- Addressing the same issues in trials of renal denervation that focused on patients with heart failure or arrhythmias; and
- Summarizing and comparing the data on adverse effects and complications in each of the trials.

Results

Results of the Literature Searches

We retrieved 1,233 unique citations from our literature search (Figure 1). After reviewing titles and abstracts, we included 243 articles in our full-text review. After reviewing full text, we included 83 studies (published in 98 articles) and excluded 145 articles. The reasons for excluding the 145 articles are presented in Appendix C. There were 16 articles that we would have otherwise included, but the study populations overlap with other trials. Since we were unable to determine unique study participants, we excluded these studies from the analysis. These articles are listed in Appendix D.

Figure 1. Search flow diagram



RCT = randomized controlled trial

GQ 1: Describe the Technology/Intervention

KQ 1. What is the theoretical renal denervation mechanism of action?

The renal sympathetic nervous system is thought to play a key role in hypertension and mediates the complex interactions between the brain and the kidney. Efferent sympathetic nerve fibers travelling from the brain to the kidney begin at the sympathetic ganglion at the lower thoracic and upper lumbar vertebrae, and course through the renal artery adventitia to provide

sympathetic innervation of the renal vasculature, renal tubules, and juxta-glomerular apparatus. Effects mediated by alpha 1 receptors lead to vasoconstriction, decreased renal blood flow, volume retention and sodium resorption, while beta 1 receptor activation contributes to renin release and subsequent renin–angiotensin–aldosterone system activation. Afferent sympathetic nerve fibers travelling from the kidney to the brain act through the hypothalamus to regulate central sympathetic outflow to control systemic hemodynamics and reflexive sympathetic efferent activity as part of an important feedback loop.[16, 17]

Studies of surgical sympathectomy demonstrated its efficacy in uncontrolled hypertension, but orthostatic hypotension often resulted, 10-year mortality was high (approximately 40%), and advancements in pharmacotherapy for hypertension eventually rendered the procedure obsolete.[18, 19] Catheter-based renal denervation involves placement of a catheter into the lumen of the renal arteries through which radiofrequency (or ultrasound) energy is applied to the vessel wall causing thermal (or sonic) injury to the sympathetic nerves coursing through the adventitia. This action reduces efferent renal sympathetic activity as evidenced by a reduction in renal noradrenaline spillover levels[20] and is accompanied by a commensurate increase in renal blood flow and reduction in plasma renin activity. Reductions in whole-body noradrenaline spillover levels and skeletal muscle sympathetic nerve activity have also been measured following renal denervation and are thought to reflect the effects of reduced afferent renal sympathetic activity.[21, 22] Thus, ablation of both the afferent and efferent renal nerves is thought to be the primary mechanism of blood pressure reduction with renal denervation.[23]

Despite the theoretical benefits of renal denervation for resistant hypertension, a number of issues remain. First, most of the published studies that we reviewed for this report used the Medtronic Symplicity® catheter for renal denervation. The Medtronic Symplicity catheter uses about 8 watts of radiofrequency energy for ablation.[24] Other catheter designs include ultrasound energy (The ReCor Medical PARADISE® catheter), peri-vascular chemical injury (Ablative Solutions Peregrine System™ catheter), and a multi-electrode design (St. Jude Medical's EnligHTN™, Boston Scientific Vessix™, Medtronic SPYRAL) to allow simultaneous delivery of radio-frequency energy to multiple ablation points within a renal artery.[24] There are no studies with head-to-head comparison of these devices. Second, while the effectiveness of renal denervation may be assessed after the procedure by whole-body noradrenaline spillover levels and skeletal muscle sympathetic nerve activity, these tests are not available for use at point-of-care. Therefore, the completeness of renal denervation cannot be confirmed at the time of the procedure. Third, most of the studies did not report the training, certification of the interventionalist, or the quality control used when performing renal denervation. As a result, procedural variability may diminish the effectiveness of the procedure. Finally, although renal sympathetic hyperactivity is one of the many mechanisms for resistant hypertension, it remains difficult to determine the contribution of sympathetic hyperactivity to resistant hypertension at an individual level and thereby identify patients most likely to benefit from reducing sympathetic overactivity by renal denervation. We further discuss the predictors of response to renal denervation in the KQ 5 section of this report.

The renal denervation procedure is invasive and inherently involves risks. These include those associated with arterial access (e.g., hematoma or pseudoaneurysm), renal cannulation (e.g., renal artery stenosis and dissection) and systemic effects (e.g., embolization). Most studies selectively included individuals with favorable renal anatomy which reduces the risk of complications. We discuss the complications in detail in the KQ 8 section of this report.

GQ 2: Describe the Context in which the Technology/Intervention Is Used

KQ 2. What is the evidence for blood pressure measurement and use as a surrogate outcome?

Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated etiologies. Blood pressure is a biomarker of this syndrome.[25] Data from observational studies involving over 1 million individuals indicate a linear association between increasing blood pressure and the risk of ischemic heart disease or death.[26]

Overwhelming evidence supports the use of antihypertensive therapy to lower blood pressure.[27] Numerous clinical trials demonstrate the benefits of lowering blood pressure on reducing the risk of stroke, coronary heart disease, heart failure, and death.[12, 28-32] In patients with both blood pressure of 140-159/90-99 mm Hg and cardiovascular disease, a sustained reduction in systolic blood pressure of 12 mm Hg over 10 years will prevent one death for every 11 patients treated.[33]

A systematic review of 62,605 hypertensive patients demonstrated a linear association between reduction of systolic blood pressure with drug treatment and the risk of death.[34] Most recently, the Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 hypertensive non-diabetic patients with a systolic blood pressure of greater than 130 mm Hg and an increased cardiovascular risk to a systolic blood pressure target of less than 120 mm Hg (intensive treatment) or less than 140 mm Hg (standard treatment).[32] The trial was terminated early due to a significantly lower risk of death in the intensive treatment group (hazard ratio, 0.73; 95% confidence interval [CI], 0.60 to 0.90). If this lower blood pressure becomes a new target for clinicians, novel methods for controlling blood pressure may need to be developed to achieve this target.

The Food and Drug Administration considers blood pressure to be a surrogate endpoint for cardiovascular risk. The rationale for using blood pressure as a surrogate endpoint is based on the numerous studies of blood pressure reduction and improved cardiovascular outcomes, and the concern that a requirement for clinical endpoints may restrict the availability of newer drugs to control blood pressure.[35]

Use of blood pressure as a surrogate endpoint and the choice of antihypertensive medications to reach blood pressure goals was assessed in a large meta-analysis by Law, et al.[36] The meta-analysis included 147 RCTs conducted from 1996 to 2007 including 464,000 people. Blood pressure reduction with drug treatments was associated with significantly lower risk of coronary heart disease events or strokes, regardless of age or baseline blood pressure (as low as 110/70 mm Hg). All antihypertensive drugs (e.g., thiazide-type diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) had similar effects on prevention of coronary heart disease events, driven by blood pressure reduction rather than by drug-specific effects. While blood pressure was, overall, a surrogate endpoint for strokes, there were antihypertensive class-specific differences in the risk of stroke, with calcium channel blockers demonstrating the lowest risk of stroke.

Blood pressure control has also been associated with decreased risk of kidney disease progression;[37] however, differences between drugs have been noted in clinical trials. For example, despite similar blood pressure control, losartan was superior to atenolol in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study,[38] ramipril was superior to

amlodipine or metoprolol in slowing progression of kidney function decline in blacks with proteinuria in the African American Study of Kidney Disease and Hypertension (AASK),[39] and chlorthalidone was superior to lisinopril or amlodipine in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[12, 40, 41]

It is debatable whether or not these differences in antihypertensive medications are the exception versus the rule, and if they are due to differences in central aortic blood pressures (versus peripheral cuff blood pressure). Similar concerns about surrogate endpoints have been raised after the failure of a dual renin-angiotensin system blockade to reduce progression of kidney disease in patients with albuminuria,[42, 43] despite albuminuria being one of the strongest risk factors for progression of kidney disease and adverse outcomes in patients with chronic kidney disease.

In summary, strong evidence supports the use of blood pressure as a surrogate cardiovascular and mortality endpoint when treating patients using antihypertensive agents. Whether or not these findings apply to device-based approaches is not known at this time.[44] It is also not known if blood pressure reduction achieved through renal denervation has effects on clinical endpoints that are similar to blood pressure reduction achieved through antihypertensive agents.

KQ 3. What is the clinical definition of resistant hypertension, and what are the treatment alternatives?

Definition and Prevalence

A consensus statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research defines resistant hypertension as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive medications of different classes.[6] Ideally, one of the three medications should be a diuretic, and all medications should be prescribed in ways that take advantage of synergistic effects of different classes of agents and promote adherence to therapy. This definition includes all patients with blood pressure above their goal who are on three medications and also patients with blood pressure at goal but who require four or more medications.

The prevalence of treatment resistant hypertension is high. Based on the sequential National Health and Nutrition Examination Survey (NHANES) data, prevalence of treatment resistant hypertension, defined as blood pressure of 140/90 mm Hg or more while taking three or more antihypertensive medications, increased from 5.5 percent in the 1988 to 1994 survey to 11.8 percent in the 2005 to 2008 survey.[10] Older age, African American race, obesity, and chronic kidney disease were associated with treatment resistant hypertension.[10] Prevalence of treatment resistant hypertension is even higher (17%) in community-based cohorts of patients with a history of stroke or transient ischemic attacks.[45] It is important to note that the prevalence of treatment resistant hypertension is based on a target blood pressure of less than 140/90 mm Hg.

Causes and Treatment

The causes of treatment resistant hypertension are numerous and can include lifestyle factors, secondary causes, and antihypertensive medication effects. Common causes of treatment resistant hypertension include pseudoresistance (i.e., white coat effect), non-adherence to diet (particularly dietary sodium intake) or medications, lifestyle factors (e.g., obesity, lack of exercise), use of non-steroidal anti-inflammatory drugs, secondary causes of hypertension (e.g., primary hyperaldosteronism, renal artery stenosis, chronic kidney disease), and physician inertia

in up-titrating antihypertensive medications.[6] Guidelines for overall blood pressure management have been published,[46, 47] but choice of antihypertensive agent and titration is still individualized by the treating physician. For this reason, non-adherence to medications can also be a major contributing factor to treatment resistant hypertension. In one study, 48 percent of patients undergoing renal denervation were non-adherent for antihypertensive medications in plasma and urine as assessed by liquid chromatography high resolution tandem mass spectrometry.[48]

Management strategies for treatment resistant hypertension have not been well studied. Overall, the goal is to establish the true resistance by correct measurement of blood pressure and out of office blood pressure readings. After addressing lifestyle factors, dietary salt intake, and medication adherence, and excluding/treating secondary causes of hypertension, the management is drug escalation, and in particular, maximizing diuretic therapy[49] with addition of mineralocorticoid receptor antagonists.[6] In a recent, double-blind, placebo-controlled, cross-over, RCT of resistant hypertension in the United Kingdom (The Prevention and Treatment of Hypertension with Algorithm based Therapy [PATHWAY-2]), aldosterone antagonist spironolactone reduced home systolic blood pressure by 8.70 mm Hg (95% CI, 9.72 to 7.69) and allowed blood pressure control in 65 percent of the patients.[50] In comparative studies, aldosterone antagonists reduced systolic blood pressure by 24.3 mm Hg (95% CI, 8.7 to 39.9).[51] For patients with resistant hypertension referred for specialty care, 10 percent continue to experience uncontrolled hypertension despite being on a six drug regimen.[52] Given the continued difficulty in controlling treatment resistant hypertension with medications, other options are needed for clinicians, patients, and other key stakeholders. Renal denervation is one such option.

KQ 4. For randomized controlled trials and observational studies of renal denervation, what are the inclusion criteria for patients, and how do clinical characteristics match the clinical definition of resistant hypertension?

Key Point

- Most studies included patients with uncontrolled hypertension, defined as systolic blood pressure over 140 mm Hg or 160 mm Hg while taking a minimum of three anti-hypertensive medications. Most studies excluded patients with secondary causes of hypertension. Most did not assess medication adherence.

We considered the definition of resistant hypertension according to clinical consensus (see KQ1) as "blood pressure that remains above goal in spite of the concurrent use of three antihypertensive medications of different classes."[6] Ideally, one of the three medications should be a diuretic and all medications should be prescribed at optimal amounts. We also evaluated reporting of antihypertensive medication adherence, exclusion of patients with secondary causes of hypertension, and whether or not a run-in observation period was considered prior to renal denervation. Studies were evaluated for both inclusion and exclusion criteria, and the degree to which these studies excluded other treatable causes of resistant hypertension (i.e., potentially treated by change in lifestyle or medications) and reduced biases in measurement are reported below.

Number of Antihypertensive Medications

The majority of studies specified three as the minimum number of anti-hypertensive medications (Table 3). Many but not all studies [44/83 (53%)] also required use of a diuretic as an inclusion criterion. However, in most studies, an optimal antihypertensive dose was not specified.

Systolic Blood Pressure Inclusion Criterion

Considering systolic blood pressure greater than 140 mm Hg to be uncontrolled hypertension, almost all studies included patients with uncontrolled hypertension; however, the systolic blood pressure criterion varied in this definition, with some studies defining resistant hypertension as 140 mm Hg systolic or greater, and others as 160 mm Hg or greater.

Exclusion of Secondary Causes of Hypertension

Fourteen (82%) of the RCTs and comparative studies and 44 (67%) of the non-comparative studies reported considering secondary causes of hypertension as an exclusion criterion.

Medication Adherence Prior to Enrollment or Study Entry

Of the RCTs and comparative studies, only five (29%) reported any evaluation of adherence prior to enrollment (Table 4). In two studies, this evaluation was in the form of a medication diary.

Other Inclusion Criteria and Clinical Characteristics of the Patients

The total number of subjects in the included studies ranged from 18 to 998 (Table 5). In all but thirteen studies, the majority of included subjects were male; in four studies, the gender distribution of the subjects was not reported. Twenty-five trials reported a maximum age exclusion (the most common age exclusion was for people 85 years old or older). Forty-six reported a minimum age exclusion, with most excluding subjects younger than 18 years old. In 77 studies, the race or ethnicity distribution of the subjects was not reported. In studies which reported the mean body mass index of subjects (all but 20 studies), the mean body mass index ranged from 27 to 34. Compared with non-randomized trials, the RCTs were characterized by a larger sample size, a lower prevalence of diabetes, and a mean estimated glomerular filtration rate that was higher than that found in the non-randomized trials.

Table 3. Number (percent) of studies using the following inclusion criteria

	Randomized controlled trials (n=9)	Comparative observational studies (n=8)	Non-comparative studies (n=66)
Office SBP > 140 mm Hg while taking ≥ 3 antihypertensive medications and a minimum ambulatory SBP	3 (33%)	0	5 (7%)
Office SBP > 140 mm Hg while taking ≥ 3 antihypertensive medications but did not specify criteria for ambulatory SBP	1 (11%)	1 (13%)	8 (12%)
Office SBP > 160 mm Hg while taking ≥ 3 antihypertensive medications and a minimum ambulatory SBP	2 (22%)	0	4 (6%)
Office SBP > 160 mm Hg while taking ≥ 3 antihypertensive medications but did not specify criteria for ambulatory SBP	2 (22%)	4 (50%)	30 (44%)
Elevated ambulatory SBP while taking ≥ 3 antihypertensive medications but did not specify criteria for office SBP	1 (11%)	0	2 (3%)
Taking ≥ 3 antihypertensive medications but did not specify criteria for office nor ambulatory SBP	0	1 (13%)	1 (1%)
Elevated office and/or ambulatory SPB while taking ≥ 4 antihypertensive medications	0	0	1 (1%)
Taking ≥ 4 antihypertensive medications but did not specify criteria for office and ambulatory SBP	0	0	1 (1%)
Office SBP between 140 and 160 mm Hg and ambulatory SBP > 130 mm Hg, but did not specify criteria for the number of medications	0	0	1 (1%)
Elevated office SBP, but did not specify criteria for the number of medications or ambulatory SBP	0	0	2 (3%)
Ambulatory SBP > 130 mm Hg, but did not specify criteria for the number of medications or office SBP	0	0	1 (1%)
Did not specify criteria for the number of medications or office or ambulatory SBP	0	2 (25%)	10 (15%)
Required a diuretic	6 (67%)	4 (50%)	28 (42%)

mm Hg = millimeters of mercury; SBP = systolic blood pressure

Table 4. Summary of included studies evaluating renal denervation devices among patients with resistant hypertension (83 studies reported in 98 articles)

	Number of studies (Number of participants)
Study type	
Randomized controlled trial	9 (1030)
Prospective cohort	5 (284)
Retrospective cohort	2 (206)
Before/after study	66 (6059)
Case-control	1 (81)
Run-in period	
Yes	10 (976)
No/not reported/not applicable	73 (6684)
Adherence assessed in randomized controlled trials and comparative studies (n=17)	
Assessed adherence during run-in period	5 (339)
Assessed adherence during study	6 (937)
Location*	
United States	3 (838)
Europe	57 (4038)
Worldwide	2 (1104)
Other	23 (1936)
Not reported	9 (649)
Funding source*	
Manufacturer	28 (3809)
Government/non-profit	23 (2552)
None	3 (302)
Not reported	33 (2285)
Renal denervation devices*	
Symplicity™ Renal Denervation System	53 (5547)
Other	27 (1720)
Unspecified	7 (492)
Specialty*	
Interventional cardiologist	2 (140)
Interventional radiologist	3 (75)
Other	4 (379)
Not reported	81 (8075)
Comparators	
Medications	7 (410)
Sham procedure	3 (636)
Other	7 (375)
Outcomes	
Blood pressure	82 (7607)
Stroke	6 (2329)
Myocardial infarction	7 (2349)
Hospitalization	6 (2373)
Mortality	9 (2703)
Adverse events	32 (3982)

* Responses add up to more than 83 studies because there could be more than one response for each study.

Table 5. Summary of the descriptive characteristics of the enrolled patient population stratified by study design

Characteristic	RCTs (N=9)	Comparative studies (N=8)	Non-comparative studies (N=66)
Sample size, median (range)	71 (18 to 535)	60 (28 to 198)	54 (27 to 998)
Mean age of participants, median (range)	58 years (55 to 65)	62 years (54 to 68)	62 years (45 to 69)*
% male subjects, median (range)	70% (50 to 100)	63% (29 to 80)	60% (13 to 81)*
% Caucasian, median (range)	84% (70 to 98)†	NR	89% (30 to 100)‡
BMI, median (range)	31 kg/m^2 (27 to 34)	31 kg/m^2 (27 to 34)	31 kg/m^2 (27 to 33)§
eGFR, median (range)	80 mL/min/m^2 (41 to 90)¶	75 mL/min/m^2 (67 to 83)‖	75 mL/min/m^2 (49 to 98)**
CKD stages	CKD 3: 13% (5 to 21)††	NR	CKD 2: 64% (63 to 67)‖ CKD 3: 20% (1 to 27) CKD 4: 17% (3 to 19)
% with diabetes, median (range)	32% (8 to 89)	30% (14 to 50)‡	37% (10 to 100)‡‡
% with LVH, median (range)	56 to 60§§	10 to 18§§	22% (12 to 87) ¶
Mean number of antihypertensive medications, median (range)	5.1 (3.6 to 5.4)¶¶	4.6 (0 to 5.3)	5 (1.2 to 6.2)‖‖
% of patients on a diuretic, median (range)	100% (89 to 100)***	50 to 84§§	89% (63 to 100)†††

BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; kg/m^2 = kilograms per meters squared; LVH = left ventricular hypertrophy; mL/min/1.73 m^2 = milliliters per min per 1.72 meters squared; NR =not reported; RCT = randomized controlled trial

* N = 60
† N = 9
‡ N = 6
§ N = 48
¶ N = 5
‖ N = 3
** N = 41
†† N = 2
‡‡ N = 58
§§ N = 1
¶¶ N = 8
‖‖ N = 56
*** N = 7
††† N = 25

GQ 3: Describe the Current Evidence of the Technology/Intervention

KQ 5. What are the predictors of response in Medicare eligible patients who are appropriate candidates for renal denervation?

Key Points

- The most common predictors of response to renal denervation were baseline office systolic blood pressure (13 studies) or other measures of baseline systolic blood pressure (11 studies).

- The patients included in the studies were comparable only in part to the Medicare-eligible population.

Applicability of the Studies to the Medicare Population

With regard to the applicability of these studies to the Medicare population, the reported subject characteristics are relevant. The mean age of the patients was less than 65 years (the general age of Medicare eligibility) in all types of studies (Table 5), indicating that the majority of patients studied would not meet the age criterion for Medicare. However, the range of ages in the studies did include Medicare-eligible ages.

In addition, chronic kidney disease, which is highly prevalent among the Medicare population, was only partially represented among these studies. Two of the RCTs included some patients with stage 3 chronic kidney disease; comparative studies did not report chronic kidney disease stage; and non-comparative studies included a wider range of kidney disease, including stages 3 and 4. None of the studies included patients on dialysis. Thus, the patients in these studies are comparable only in part to the Medicare-eligible population.

Predictors of Response

Twenty-eight studies examined predictors of response to renal denervation (Table 6). Thirteen studies conducted a multivariate analysis (as noted with an asterisk in the last column of Table 6) and 15 conducted a univariate analysis. The most common predictors of response to renal denervation were baseline office systolic blood pressure (13 studies) or other measure of baseline systolic blood pressure (11 studies). Other predictors of response that were found in more than one study included change in heart rate after the renal denervation procedure (2 studies), central pulse pressure (2 studies), and body mass index (2 studies). These studies were heterogeneous in time to followup and definition of renal denervation response. Only two studies assessed these predictors of response comparing renal denervation patients to those undergoing a sham procedure.[53, 54] Both of these studies found that baseline office systolic blood pressure was a predictor of blood pressure response in those undergoing a sham procedure. None of the studies found that gender or age were predictors of response. Only one study reported race (African American) as a predictor of response, but most of the studies in our review were not performed in the United States and did not report race.

Table 6. Predictors of response to renal denervation

Author, year Study design	Response definition	Predictors evaluated	Significant predictors
Flack, 2015[53] RCT N = 535	6-month change in office SBP	Baseline office SBP, SBP ≥ 180 mm Hg, African American race, age ≥ 65 years, history of diabetes, eGFR ≥ 60 mL/min/1.73 m2, gender, 4-quadrant ablation pattern, ≥ 8 full 120-s ablations, ≥ 4 notches, total number of ablation attempts, baseline dipper status, salt sensitivity, baseline number of medication classes, prescription of a calcium antagonist or angiotensin receptor blocker or diuretic, complex antihypertensive medication regimen, and geography	Baseline office SBP ≥ 180 mm Hg, vasodilator use, interaction between African American and baseline office SBP ≥ 180 mm Hg*
Tsioufis, 2015[55] Prospective cohort N = 46	(1) ≥ 10 mm Hg decrease in office BP (2) office SBP reduction of ≥ 10% from baseline	Gender, sleep apnea, history of type 2 diabetes, age, baseline office SBP, baseline office DBP, baseline office HR, BMI, baseline number of medication classes, number of ablations, average diameter of renal arteries, baseline office PP, office HR at 24 months	(1) None* (2) BMI*
Kim, 2015[56] Before-after study N = 1000	(1) 6- month change in office SBP (2) 12-month change in office SBP	Korean vs. Caucasian, baseline office SPB, baseline office DBP, age, gender, diabetes mellitus, baseline HR, BMI, renal insufficiency, history of cardiac disease, heart failure, LVH, current smoker, total number of ablation attempts, number of 120-s ablation attempts, total number of antihypertensive medication classes, and types of antihypertensive medications	(1) baseline office SBP, LVH, calcium channel blockers* (2) Korean vs. Caucasian, baseline office SBP, alpha-adrenergic blocker*
Id, 2015[57] Before-after study N = 101	6-month change in office SBP	Gender, age, BMI, office and ambulatory BP, renal function, diabetes mellitus, number of ablations, and antihypertensive medications	Baseline office SBP, BMI*
Ott, 2015[58] Before-after study N = 63	6-month office SBP reduction	Age, gender, coronary heart disease; diabetes mellitus, HR, central PP, baseline office SBP	Baseline SBP; central PP*
Ott, 2015[59] Before-after study N = 27	6-month change in 24-h SBP	NR	Baseline 24-h SBP†
Dorr, 2015[60] Before-after study N = 100	6-month change in SBP	NR	Baseline SBP, change in brain-derived neurotrophic factor‡
Dorr, 2015[61] Before-after study N = 100	6-month change in SBP	NR	Carboxyl-terminal pro-peptide of type 1 collagen (PICP)‡
Azizi, 2015[62] RCT N = 106	6-month change in daytime ambulatory SBP	NR	Gender, baseline ambulatory daytime SBP; change in HR; number of antihypertensive drugs at 6 months; MMAS-8*

Table 6. Predictors of response to renal denervation (continued)

Author, year Study design	Response definition	Predictors evaluated	Significant predictors
Sievert, 2015[63] Before-after study N = 146	(1) > 10 mm Hg decrease in office SBP at 6 months (2) > 5 mm Hg reduction in ambulatory SBP at 6 months	Baseline DBP, eGFR, number of electrode activations, baseline ambulatory SBP, number of antihypertensive medications, gender, regimen includes a centrally-acting sympatholytic, HR, age, baseline ambulatory DBP, regimen includes a fixed combination, regimen includes an alpha-1 blocker, baseline SBP, accessory renal artery treated	(1) None† (2) Baseline ambulatory SBP; baseline SBP; baseline ambulatory DBP†
Rosa, 2015[64] RCT N = 106	≥ 10 mm Hg decrease in 24-h SBP	NR	Baseline daytime SBP*
Kandzari, 2015[54] RCT N = 535	(1) 6-month change in office SBP (2) 6-month change in 24-h ambulatory SBP	Baseline office SBP ≥180 mmHg, African-American race, age < 65 years, history of diabetes, renal insufficiency, gender, 4-quadrant ablation pattern, ≥ 8 full 120-s ablations, ≥ 4 notches, total number of ablation attempts, as well as baseline prescription of aldosterone antagonist, a-1-blocker, a-2 agonist, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, beta-blocker, calcium-channel blocker, direct renin inhibitor, and vasodilator	(1) Baseline office SBP; total number of ablation attempts; aldosterone antagonist; vasodilator* (2) baseline eGFR >= 60; aldosterone antagonist*
Ewen, 2015[65] Before-after study N = 126	≥ 10 mm Hg decrease in office SBP at 6 months	Gender, age, diabetes mellitus, ≥ 5 antihypertensive drugs, aldosterone antagonist, central sympatholytic, baseline office SBP ≥ 175 mm Hg, baseline ambulatory SBP ≥ 153 mm Hg, baseline PP ≥ 85 mm Hg	Baseline office SBP*
Verloop, 2015[66] Before-after study N = 54	12-month change in BP	Changes in eGFR, BMI, or total daily use of antihypertensive drugs	None*
Dorr, 2015[67] Before-after study N = 60	6-month change in office SBP	Baseline office SBP	Baseline office SBP†
Vink, 2014[68] Before-after study N = 67	6-month change in office SBP	Age, gender, number of antihypertensive drugs, total daily use of antihypertensive drugs, hypercholesterolemia, diabetes mellitus, cardiovascular diseases, BMI, office SBP, office DBP, mean daytime SBP, mean nighttime SBP, mean daytime PP, mean HR during daytime, presence of a non-dipping profile, eGFR, laboratory parameters	Cardiovascular disease; office SBP; office DBP; PP; presence of a non-dipping profile; noradrenaline
Papademetriou, 2014[69] Before-after study N = 46	(1) 6-month change in BP (2) 12-month change in BP	NR	(1) Baseline office SBP, baseline HR (2) Baseline office SBP
Verloop, 2014[70] Before-after study N = 126	6-month change in office SBP	Renal artery anatomy, age, gender, baseline eGFR, baseline SBP, baseline daytime SBP, change in antihypertensive drugs	None†
Poss, 2014[71] Before-after study N = 101	6-month change in SBP	NR	Vitamin D concentration‡

Table 6. Predictors of response to renal denervation (continued)

Author, year Study design	Response definition	Predictors evaluated	Significant predictors
Lenski, 2013[72] Before-after study N = 119	≥ 10 mm Hg decrease in SBP at 6 months	Psychological factors	None‡
Vogel, 2014[73] Before-after study N = 63	Change in office SBP	Baseline office SBP, number of ablation points	Baseline office SBP†
Zuern, 2013[74] Before-after study N = 50	≥ 10 mm Hg decrease in ambulatory SBP at 6 months	NR	Cardiac baroreflex sensitivity*
Ott, 2013[75] Before-after study N = 54	3-month and 6-month change in office SBP	Change in HR	None†
Worthley, 2013[76] Before-after study N = 46	6-month change in office SBP	NR	Baseline SBP; baseline HR; reduction in HR‡
Schmid, 2013[77] Before-after study N = 53	6-month change in office SBP	Baseline office SBP, renal artery supply, total number of ablations, eGFR	Baseline office SBP*
Prochnau, 2013[78] Before-after study N = 43	≥ 10 mm Hg decrease in ambulatory SBP at 6 months	Age, BMI, creatinine, baseline 24-h ambulatory SBP	Baseline ambulatory SBP*
Symplicity, 2011[79] Before-after study N = 153	12-month change in SBP	Age, gender, race, BMI, SBP, DBP, PP, HR, drug class, number of antihypertensive drugs, eGFR, hypercholesterolemia, coronary artery disease	Baseline SBP; use of central sympatholytic agents*
De Sousa Almeida, 2016[80] Before-after study N = 65	12-month change in ambulatory SBP	LV mass	None†
Burchell, 2016[81] Before-after study N = 29	6-month change in office SBP	NR	Number of ablations per artery, total number of ablations†
Sharp, 2016[82] Before-after study N = 253	(1) Change in office SBP (2) Change in ambulatory SBP	Use of aldosterone antagonist, age, gender, diabetes, eGFR, number of drugs taken, baseline BP	(1) Baseline office SBP* (2) Baseline ambulatory SBP*
Tiroch, 2015[83] Before-after study N = 46	6-month change in office SBP	Baseline office BP, veno-arterial norepinephrine gradient reduction, BMI, medication status	Baseline office BP, veno-arterial norepinephrine gradient reduction*
Rohla, 2016[84] Before-after study N = 103	(1) 6-month change in ambulatory SBP (2) 12-month change in ambulatory SBP	Baseline ambulatory SBP, number of ablation points, age, BMI, gender, diabetes, hyperlipidemia, coronary artery disease, peripheral artery disease, prior stroke or transient ischemic attack, number of antihypertensives, use of renin-inhibitors, aldosterone antagonists, and alpha-blockers	(1) Baseline ambulatory SBP, BMI, number of antihypertensive drugs* (2) Baseline ambulatory SBP, number of antihypertensive drugs*

BP = blood pressure; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; h = hours; HR = heart rate; LVH = left ventricular hypertrophy; mm Hg = millimeters of mercury; MMAS-8 = Morisky Medication Adherence Scale; NR = not reported; PP = pulse pressure; RCT = randomized controlled trial; s = seconds; SBP = systolic blood pressure

* Significant in a multivariate analysis

† Significant in a univariate analysis.

‡ Unclear if a univariate or multivariate analysis.

KQ 6. What is the evidence for renal denervation effectiveness in reducing blood pressure, stroke, myocardial infarction, and hospitalization and/or improving survival in Medicare eligible patients with resistant hypertension?

Key Points

- The between-group difference in change in 24-hour ambulatory systolic blood pressure from baseline to 6 months was highly variable in six RCTs and two comparative cohorts, ranging from -20 mm Hg to -1.96 mm Hg.
- The between-group differences in change in office systolic blood pressure from baseline to 6 months ranged from -42 mm Hg to 1.9 mm Hg in ten RCTs and comparative cohorts.
- We did not identify any studies designed to assess the efficacy or effectiveness of renal denervation in reducing stroke, myocardial infarction, hospitalizations, or survival in patients with resistant hypertension.

In KQ3, we described the relative lack of applicability of the studies to the Medicare eligible population. We *a priori* considered an optimal study design to assess the efficacy of renal denervation on blood pressure reduction in patients with resistant hypertension. This study design would exclude other treatable causes of hypertension (e.g., lifestyle, adherence, and secondary causes), be conducted on a background of a stable and optimized antihypertensive regimen, and minimize investigator bias in blood pressure and treatment measurement. Thus, the study would effectively evaluate the impact of interventional procedures on blood pressure and would have the following explicit characteristics: 1) the study will exclude patients with secondary causes of hypertension; 2) the study will exclude patients with uncontrolled hypertension due to non-adherence to diet (in particular salt intake) and medications; 3) the study will include a sufficiently long run-in period to reduce regression to the mean and ensure compliance; 4) the study will exclude white coat effect by home or ambulatory blood pressure monitoring prior to randomization; 5) the study will include a placebo (sham) group; 6) the study will continue to evaluate dietary and medication adherence during followup; and 7) the study will use ambulatory blood pressure as the primary outcome measure. We abstracted the published studies of renal denervation and assessed whether or not the studies met these characteristics.

Systolic Blood Pressure

A number of different measures are used in clinical practice to assess systolic blood pressure. These include office-based blood pressure and readings from ambulatory blood pressure measurement (e.g., overall, daytime, and nighttime).

Studies have supported ambulatory measurements as being more predictive than office measurements for morbidity and mortality in the general population[85] and in patients with resistant hypertension.[86] Below, we report all blood pressure outcomes identified in studies of renal denervation that are both least biased (ambulatory) and commonly used by clinicians (office) but are inherently more biased.

Change in Ambulatory Blood Pressure

Twenty-Four-Hour Ambulatory Systolic Blood Pressure

We identified nine RCTs and controlled studies that reported 24-hour ambulatory blood pressure measurements (Table 7).[23, 62, 64, 87-92]

In studies using a sham control group, the mean between-group difference in change in 24-hour ambulatory systolic blood pressure from baseline to 6 months was small and not statistically significant in two RCTs (-1.96 and -3.5 mm Hg).[87, 88, 92] In comparative studies without a sham control group, the largest mean between-group difference in change in 24-hour ambulatory systolic blood pressure from baseline to 6 months was seen in two prospective cohort studies which reported a statistically significant difference (-20 and -9.6 mm Hg), with smaller differences in the seven RCTs that lacked a sham control (-6.2 to +2.1 mm Hg), of which only one trial reported a statistically significant difference.[23, 64, 89-92]

Only two RCTs reported a change in ambulatory systolic blood pressure over 12 months. The between-group differences were not statistical significant at -1.5 and 1.9 mm Hg.[64, 87]

Figure 2 shows the mean between-group difference in the change of ambulatory and office systolic blood pressure between renal denervation and the control arms. The mean between-group differences were smaller for ambulatory systolic blood pressure than for office systolic blood pressure.

Table 8 describes the changes in ambulatory systolic blood pressure in non-controlled observational studies.[48, 55, 57-60, 63, 65-70, 75, 76, 78, 91-121] The median change in 24-hour ambulatory systolic blood pressure (48 studies with 3,486 patients) was –9 mm Hg, the median change in daytime ambulatory systolic blood pressure (18 studies with 1,413 patients) was –8.7 mm Hg, and the median change in nighttime ambulatory systolic blood pressure (14 studies with 1,053 patients) was –5.2 mm Hg.

Figure 3 plots the change in ambulatory systolic blood pressure 6 months after renal denervation. The change in systolic blood pressure after denervation varied among the studies.

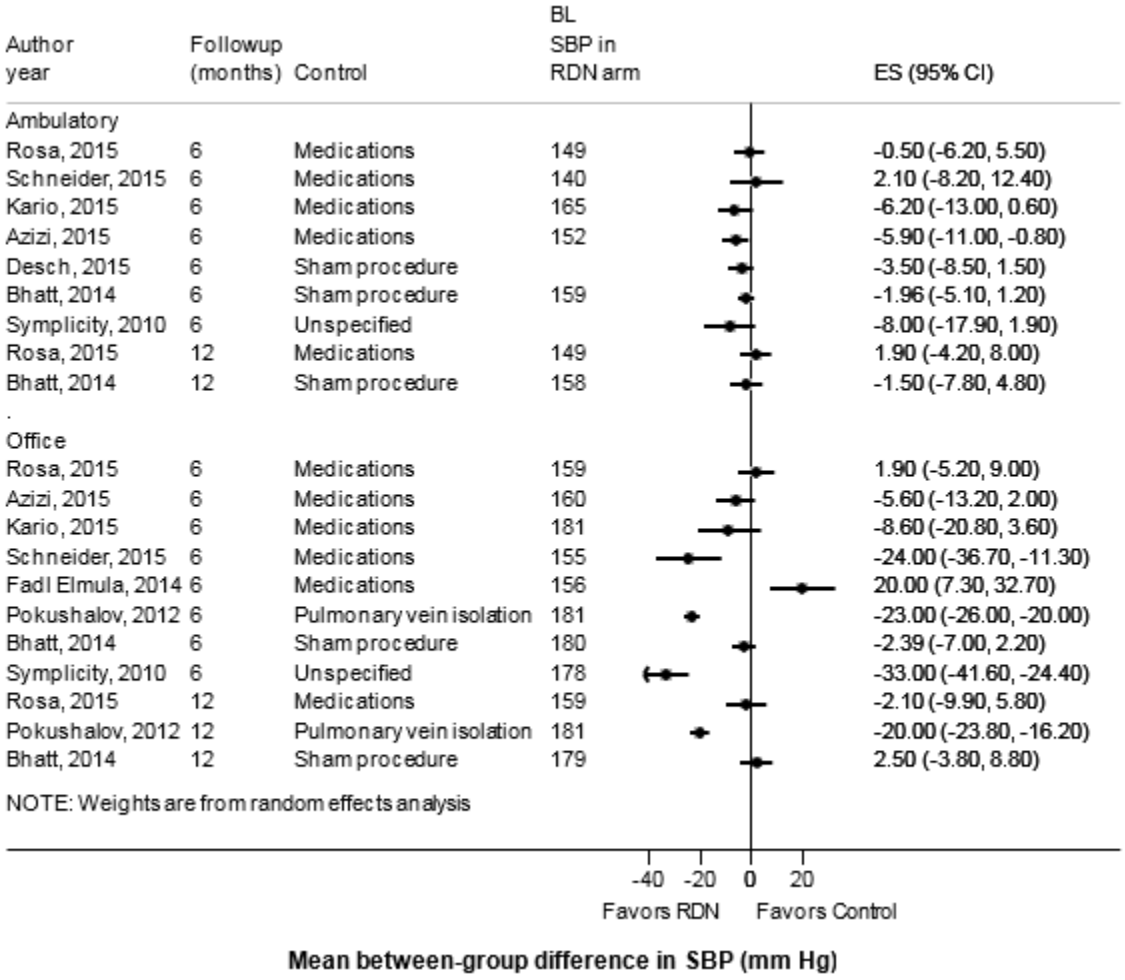
Table 7. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on 24-hour ambulatory systolic blood pressure

Author, year Study design	Mean followup (months)	RDN, N	Control group, N	Mean baseline 24-hour ABPM (SD) in RDN group, mm Hg	Mean baseline 24-hour ABPM (SD) in control group, mm Hg	Mean change (95% CI) from baseline in 24-hour ABPM in RDN group, mm Hg	Mean change (95% CI) from baseline in 24-hour ABPM in control group, mm Hg	Mean between-group difference* (95% CI), mm Hg*
Azizi, 2015[62] RCT	6	RDN (Medtronic Simplicity), 48	Continuation of anti-hypertensive drugs, 53	151.6 (16.3)	146.8 (15.2)	-15.4 (-19.1 to -11.7)	-9.5 (-13.0 to -6.0)	-5.9 (-11.0 to -0.8)
Bhatt, 2014[87] RCT	6	RDN (Medtronic Symplicity), 360	Sham procedure, 167	159.1 (13.2)	159.5 (15.3)	-6.75 (-8.4 to -5.1)	-4.79 (-7.4 to -2.1)	-1.96 (-5.1 to 1.2)
Desch, 2015[88] RCT	6	RDN (Medtronic Symplicity), 32	Sham procedure, 35	140.2 (4.6)	140.4 (5.6)	-7 (-10.8 to -3.2)	-3.5 (-6.7 to -0.2)	-3.5 (-8.5 to 1.5)
Kario, 2015[89] RCT	6	RDN (Medtronic Symplicity), 22	Continuation of anti-hypertensive drugs, 19	164.7 (18.3)	163.3 (17.2)	-7.5 (-12.5 to -2.5)	-1.4 (-6 to 3.2)	-6.2 (-13 to 0.6)
Rosa, 2015[64] RCT	6	RDN (Medtronic Symplicity), 52	Intensification of anti-hypertensive drugs, 54	149 (12)	147 (13)	-9 (-11.8 to -5.3)	-8.1 (-12.7 to -3.4) P=0.001	-0.5 (-6.2 to 5.2)
Schneider, 2015[90] RCT	6	RDN (Medtronic Flex), 9	Continuation of anti-hypertensive drugs, 9	140 (13)	143 (12)	-2.88 (-10.1 to 4.4)	-5 (-12.3 to 2.3)	2.1 (-8.2 to 12.4)
Symplicity, 2010[23] RCT	6	RDN (Medtronic Symplicity), 20	Unspecified, but allowed to crossover to RDN after 6 months, 25	NR	NR	-11 (-17.6 to -4.4)	-3 (-10.4 to 4.4)	-8 (-17.9 to 1.9)
Tsioufis, 2015[91] Prospective cohort	6	RDN (St. Jude Medical EnligHTN), 18	No renal denervation, 10	153 (16)	149 (11)	-20 (-22.7 to -17.3)	0 (-2.8 to 2.8)	-20 (-34.6 to -5.4)
Tsioufis, 2015[92] Prospective cohort	6	RDN (St. Jude Medical EnligHTN), 31	No renal denervation, 12	147.5 (12)	145.3 (9.2)	-10.2 (-11.5 to -8.9)	-0.6 (-2.2 to 1)	-9.6 (-18.9 to -0.3)
Bhatt, 2014[87] RCT	12	RDN (Medtronic Symplicity), 247	Sham procedure, 20	158 (NR)	151 (NR)	-7.6 (-7.9 to -7.3)	-6.1 (-12.4 to 0.2)	-1.5 (-7.8 to 4.8)
Rosa, 2015[64] RCT	12	RDN (Medtronic Simplicity), 52	Continuation of anti-hypertensive drugs, 54	149 (12)	147 (13)	-6.4 (-10.1 to -2.7)	-8.2 (-13.3 to -3.3)	1.9 (-4.2 to 8.0)

ABPM = ambulatory blood pressure monitoring; CI = confidence interval; mm Hg = millimeters mercury; NR = not reported; RCT = randomized controlled trial; RDN = renal denervation; SD = standard deviation

* The mean between-group difference is calculated as the mean change from baseline in the renal denervation group minus the mean change from baseline in the control group.

Figure 2. Mean between-group difference in the change in ambulatory and office systolic blood pressure* between renal denervation and control in randomized controlled trials of patients with resistant hypertension



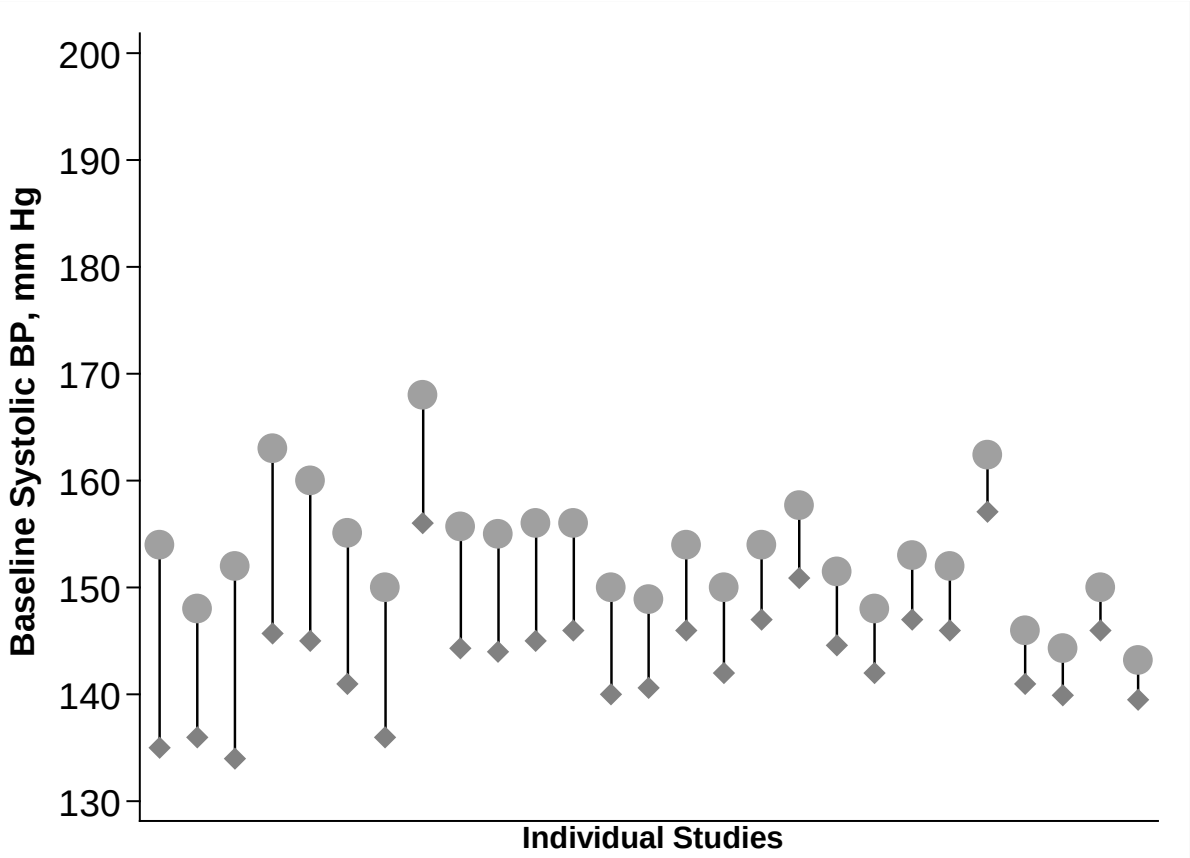
BL = baseline; CI = confidence interval; ES = effect size (mean between-group difference); mm Hg = millimeters mercury; NR = not reported; RDN = renal denervation; SBP = systolic blood pressure
Circles indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence interval for each study.
* We present further details of the studies reporting ambulatory systolic blood pressure in Table 7 and office systolic blood pressure in Table 11.

Table 8. Range in effects on blood pressure reported in non-controlled studies of renal denervation devices

Blood pressure measure	N studies (N participants)	Mean followup (months)	Median (range) in change from baseline, mm Hg
Office SBP	66 (5811)	9.9	-19.7 (-58.2 to 12)
Daytime ambulatory SBP	18 (1413)	8.7	-7.8 (-15 to 5)
Nighttime ambulatory SBP	14 (1035)	8.6	-5.2 (-14 to 0)
24-hour ambulatory SBP	48 (3486)	9.1	-9 (-31 to 20)
Number of BP medications	23 (2740)	13.0	-0.1 (-1.4 to 0.2)

BP = blood pressure; mm Hg = millimeters mercury

Figure 3. Change from baseline ambulatory systolic blood pressure 6 months after renal denervation reported in non-controlled studies, sorted by the magnitude of change



BP = blood pressure; mm Hg = millimeters of mercury
Circles represent baseline systolic ambulatory blood pressure. Diamonds represent systolic ambulatory blood pressure 6 months after renal denervation.

Daytime and Nighttime Ambulatory Systolic Blood Pressures

Five of the eight studies that reported 24-hour ambulatory systolic blood pressures also reported daytime ambulatory blood pressure measurements (Table 9)[64, 87, 88, 90, 92] and/or nighttime (Table 10) ambulatory blood pressure measurements.[64, 87, 90, 92] We also identified two studies that reported only daytime ambulatory systolic blood pressure, but not 24-hour ambulatory blood pressures.[62, 122] Of these two studies, one also reported nighttime ambulatory blood pressures.[62]

The mean between-group difference in change in daytime ambulatory systolic blood pressure from baseline to 6 months, comparing renal denervation group with the control group (six RCTs and one controlled study; total N=879) ranged from –10.6 mm Hg to 6.68 mm Hg.[62, 64, 87, 88, 90, 92, 122] The largest difference was in the prospective cohort study, which was statistically significant. Only two of the RCTs reported a statistically significant difference.

The mean between-group difference in mean change in nighttime ambulatory systolic blood pressure from baseline to 6 months, comparing renal denervation group with the control group (four RCTs and one controlled study; total N=798) ranged from –12.35 mm Hg to –0.5 mm Hg.[62, 64, 87, 90, 92] A very small prospective cohort study reported the largest between-group difference. Only two of the RCTs reported a statistically significant difference.

Table 9. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on daytime ambulatory systolic blood pressure

Author, year Study design	Mean followup (months)	RDN, N	Control group, N	Mean baseline daytime ABPM (SD) in RDN group, mmHg	Mean baseline daytime ABPM (SD) in control group, mmHg	Mean change (95% CI) from baseline in daytime ABPM in RDN group, mm Hg	Mean change (95% CI) from baseline in daytime ABPM in control group, mm Hg	Mean between-group difference* (95% CI), mm Hg
Azizi, 2015[62] RCT	6	RDN (Medtronic Symplicity) plus intensification of anti-hypertensive drugs, 48	Intensification of anti-hypertensive drugs, 53	155.5 (16.1)	151 (16)	-15.8 (-19.7 to -11.9)	-9.9 (-13.6 to -6.2)	-5.9 (-11.3 to -0.5)
Bhatt, 2014[87] RCT	6	RDN (Medtronic Symplicity), 361	Sham procedure, 168	163 (13.4)	164.2 (15)	-7.2 (-8.9 to -5.5)	-6.1 (-8.9 to -3.3)	-1.1 (-4.4 to 2.2)
Desch, 2015[88] RCT	6	RDN (Medtronic Symplicity), 29	Sham procedure, 34	144.4 (4.8)	143.0 (4.7)	-9.9 (-13.4 to -6.5)	-3.7 (-7.1 to -0.2)	-6.2 (-11.1 to -1.3)
Fadl Elmula, 2014[122] RCT	6	RDN (Medtronic Symplicity), 9	Continuation of anti-hypertensive drugs, 10	152 (10)	152 (12)	-10 (-17.8 to -2.2)	-19 (-26.4 to -11.6)	9 (-1.8 to 19.8)
Rosa, 2015[64] RCT	6	RDN (Medtronic Symplicity), 52	Intensification of anti-hypertensive drugs, 54	152 (12)	150 (13)	-9 (-13.2 to -4.7)	-8.2 (-12.4 to -4)	-0.8 (-6.8 to 5.2)
Schneider, 2015[90] RCT	6	RDN (Medtronic Flex), 9	Continuation of anti-hypertensive drugs, 9	NR	NR	1.5 (-7.3 to 10.3)	-5.18 (-13.4 to 3.1)	6.68 (-5.3 to 18.7)
Tsioufis, 2015[92] Prospective cohort	6	RDN (St. Jude Medical EnligHTN), 31	No renal denervation, 12	151.1 (13.5)	148 (9.1)	-9.9 (-11.4 to -8.4)	0.7 (-1 to 2.4)	-10.6 (-20.7 to -0.5)

ABPM = ambulatory blood pressure monitoring; CI = confidence interval; mm Hg = millimeters mercury; RCT = randomized controlled trial; RDN = renal denervation

* The mean between-group difference is calculated as the mean change from baseline in the renal denervation group minus the mean change from baseline in the control group.

Table 10. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on nighttime ambulatory systolic blood pressure

Author, year Study design	Mean followup (months)	RDN, N	Control group, N	Mean baseline nighttime ABPM (SD) in RDN group, mmHg	Mean baseline nighttime ABPM (SD) in control group, mmHg	Mean change (95% CI) from baseline in nighttime AMBP in RDN group, mm Hg	Mean change (95% CI) from baseline in nighttime AMBP in control group, mm Hg	Mean between-group* difference (95% CI), mm Hg
Azizi, 2015[62] RCT	6	RDN (Medtronic Symplicity) plus intensification of anti-hypertensive drugs, 48	Intensification of anti-hypertensive drugs, 53	141.4 (17.3)	135.5 (14.3)	-13.9 (-18 to -9.8)	-7.6 (-11.4 to -3.7)	-6.3 (-12.0 to -0.6)
Bhatt, 2014[87] RCT	6	RDN (Medtronic Symplicity), 362	Sham procedure, 168	152.5 (16.3)	151.4 (18.7)	-5.6 (-7.6 to -3.7)	-2.4 (-5.2 to 0.5)	-3.3 (-6.8 to 0.2)
Desch, 2015[88] RCT	6	RDN (Medtronic Symplicity), 29	Sham procedure, 34	130.5 (9.7)	132.3 (11.7)	-1.9 (-6.9 to 3.0)	-3.8 (-8.1 to 0.5)	1.9 (-4.7 to 8.5)
Rosa, 2015[64] RCT	6	RDN (Medtronic Symplicity), 52	Intensification of anti-hypertensive drugs, 54	141 (16)	141 (17)	-8 (-12.7 to -3.6)	-7.6 (-12.1 to -3.1)	-0.5 (-6.9 to 5.9)
Schneider, 2015[90] RCT	6	RDN (Medtronic Flex), 9	Continuation of anti-hypertensive drugs, 9	NR	NR	-10.38 (-18.7 to -2)	-1.97 (-9.9 to 6)	-12.35 (-23.9 to -0.8)
Tsioufis, 2015[92] Prospective cohort	6	RDN (St. Jude Medical EnligHTN), 31	No renal denervation, 12	140.6 (13)	137.9 (12.8)	-10.5 (-12.1 to -8.9)	-2.2 (-4.3 to -0.1)	-8.3 (-19.6 to 3)

ABPM = ambulatory blood pressure monitoring; CI = confidence interval; mm Hg = millimeters mercury; RCT = randomized controlled trial; RDN = renal denervation

* The mean between-group difference is calculated as the mean change from baseline in the renal denervation group minus the mean change from baseline in the control group.

Change in Office Blood Pressure

We identified 11 RCTs and controlled studies that reported changes in office systolic blood pressures (Table 11).[23, 62, 64, 87, 89-91, 122-125] Of these 11 studies, the longest followup was 3 months for 1 study,[123] 12 months for 2 studies, [87, 124] and 36 months for 1 study.[23] The remaining seven studies reported 6-month followup.

Three-Month Change in Office Blood Pressure

The mean between-group difference in change in office systolic blood pressure from baseline to 3 months, comparing renal denervation group with the control group (1 controlled study; total N=125) was –16 mm Hg, which was statistically significant.[123]

Six-Month Change in Office Blood Pressure

The range of the between-group difference in mean change in office systolic blood pressure from baseline to 6 months, comparing renal denervation group with the control group (eight RCTs and two controlled studies; total N=1035) was –42 mm Hg to 1.9 mm Hg.[23, 62, 64, 87, 89-91, 122, 124, 125] The between-group differences were statistically significant in four of the RCTs and in the one prospective cohort study.

Twelve-Month Change in Office Blood Pressure

The mean between-group difference in change in office blood pressure at 12 months in two RCTs (total N=394) were 2.5 mm Hg and -20 mm Hg, and statistically significant in the latter study.[87, 124] One RCT did not report between-group differences at 12 months.[23]

Three-Year Change in Office Blood Pressure

Between-group differences in systolic blood pressure were not reported in the RCT with 3-year followup.[23]

Non-Controlled Studies

In 66 non-controlled studies that included 5,811 participants with a mean follow-up of 9.9 months, the median change in office systolic blood pressure from baseline was –19.7 mm Hg, with a range of change from –58.2 mm Hg to 12 mm Hg (Table 8).[48, 55-60, 63, 65, 67-77, 79-83, 91, 93-101, 103-108, 110-112, 114-116, 118-120, 123, 125-138]

Table 11. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on office systolic blood pressure

Author, year Study design	Mean followup (months)	RDN, N	Control group, N	Mean baseline OSBP (SD) in RDN group, mmHg	Mean baseline OSBP (SD) in RDN group, mmHg	Mean (95% CI) change from baseline in RDN group, mm Hg	Mean (95% CI) change from baseline in control group, mm Hg	Mean between-group difference* (95% CI), mm Hg
Lambert, 2012[123] Prospective cohort	3	RDN (Medtronic Symplicity), 62	Unmedicated normotensive subjects, 63	166 (3)	122 (1)	NR	NR	-16 (-16.7 to -15.3)
Azizi, 2015[62] RCT	6	RDN (Medtronic Symplicity) plus intensification of anti-hypertensive drugs, 48	Intensification of anti-hypertensive drugs, 53	159.3 (22.7)	155.9 (21.9)	-15.1 (-20.6 to -9.5)	-9.5 (-14.7 to -4.2)	-5.6 (-13.2 to 2)
Bhatt, 2014[87] RCT	6	RDN (Medtronic Symplicity), 364	Sham procedure, 171	179.7 (16.1)	180.2 (16.8)	-14.13 (-16.6 to -11.6)	-11.74 (-15.6 to -7.9)	-2.39 (-7 to 2.2)
Fadl Elmula, 2014[122] RCT	6	RDN (Medtronic Symplicity), 9	Continuation of anti-hypertensive drugs, 10	156 (13)	160 (14)	-8 (-17.8 to 1.8)	-28 (-36.1 to -19.9)	20 (7.3 to 32.7)
Kario, 2015[89] RCT	6	RDN (Medtronic Symplicity), 22	Continuation of anti-hypertensive drugs, 19	181 (18)	178.7 (17.8)	-15.3 (-24.3 to -8.9)	-7.9 (-17.3 to 1.5)	-8.6 (-20.8 to 3.6)
Pokushalov, 2012[124] RCT	6	RDN (Unspecified), 13	Pulmonary vein isolation, 14	181 (7)	178 (8)	-28 (-30.7 to -25.3)	-5 (-6.3 to -3.7)	-23 (-26 to -20)
Rosa, 2015[64] RCT	6	RDN (Medtronic Symplicity), 52	Intensification of anti-hypertensive drugs, 54	159 (19)	155 (17)	-12 (-17 to -7.8)	-14.3 (-19.7 to -8.9)	1.9 (-5.2 to 9)
Schneider, 2015[90] RCT	6	RDN (Medtronic Flex), 9	Continuation of anti-hypertensive drugs, 9	155 (14)	146 (6)	-23 (-32.5 to -13.5)	1 (-7.5 to 9.5)	-24 (-36.7 to -11.3)
Symplicity, 2010[23] RCT	6	RDN (Medtronic Symplicity), 49	Unspecified, but allowed to crossover to RDN after 6 months, 51	178 (18)	178 (17)	-32 (-38.4 to -25.6)	1 (-4.8 to 6.8)	-33 (-41.6 to -24.4)
Ewen, 2014[125] Prospective cohort	6	RDN (Medtronic Symplicity), 50	Unspecified, 10	164 (3)	155 (4)	-26 (-27.4 to -24.6)	-2 (-6.8 to 2.8)	-24 (-42.2 to -5.8)
Tsioufis, 2015[91] Prospective cohort	6	RDN (St. Jude Medical EnligHTN), 18	Sham procedure, 10	182 (19)	182 (12)	-42 (-45.1 to -38.9)	0 (-3 to 3)	-42 (-58.4 to -25.6)

Table 11. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on office systolic blood pressure (continued)

Author, year Study design	Mean followup (months)	RDN, N	Control group, N	Mean baseline OSBP (SD) in RDN group, mmHg	Mean baseline OSBP (SD) in RDN group, mmHg	Mean (95% CI) change from baseline in RDN group, mm Hg	Mean (95% CI) change from baseline in control group, mm Hg	Mean between-group difference* (95% CI), mm Hg
Bhatt, 2014[87] RCT	12	RDN (Medtronic Symplicity), 319	Sham procedure, 48	179 (NR)	176 (NR)	-18.9 (-21.7 to -16.1)	-21.4 (-27 to -15.8)	2.5 (-3.8 to 8.8)
Rosa, 2015[64] RCT	12	RDN (Medtronic Simplicity), 51	Continuation of anti-hypertensive drugs, 50	159 (19)	155 (17)	NR (-18.9 to -7.9)	-11.3 (-17.1 to -5.5)	-2.1 (-10.1 to 5.9)
Pokushalov, 2012[124] RCT	12	RDN (Unspecified), 13	Pulmonary vein isolation, 14	181 (7)	178 (8)	-25 (-27.7 to -22.3)	-5 (-7.6 to -2.4)	-20 (-23.8 to -16.2)
Symplicity, 2010[23] RCT	12	RDN (Medtronic Symplicity), 49	Unspecified, but allowed to crossover to RDN after 6 months	178.3 (18.2)	NR	-28.1 (-35.4 to -20.7)	NR	NR
Symplicity, 2010[23] RCT	36	RDN (Medtronic Symplicity), 52	Unspecified, but allowed to crossover to RDN after 6 months	178 (18)	NR	-33 (-40 to -25)	NR	NR

CI = confidence interval; mm Hg = millimeters mercury; RCT = randomized controlled trial; RDN = renal denervation; SBP = systolic blood pressure

* The mean between-group difference is calculated as the mean change from baseline in the renal denervation group minus the mean change from baseline in the control group.

Change in Number of Antihypertensive Medications after Renal Denervation

Changes in the number of antihypertensive medications after renal denervation were neither consistently nor systematically reported. Only 27 of the 83 studies reported some metric of this change.

RCTs and Comparative Studies

The mean between-group difference in the change in the number of antihypertensive medications from baseline to maximum followup, comparing the renal denervation group with the control group (three RCTs; total N=747) ranged from -0.7 to -0.1 (Table 12).[64, 87, 124] The difference was statistically significant in two of the studies. Two other RCTs did not report on the mean between-group difference.

Non-comparative Studies

The range of mean change in the number of antihypertensive medications from baseline to maximum followup, in the renal denervation group (within-group difference; 18 studies; total N=3003) was -1 to 0.2.[48, 55-57, 65, 66, 68, 74, 79, 98, 104, 107-109, 118, 130, 132, 134]

Table 12. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on change in number of blood pressure medication classes

Author, year Study design	Mean followup (months)	RDN, N	Control group, N	Mean baseline medications in RDN group, (SD)	Mean baseline medications in control group, (SD)	Mean change (95% CI) from baseline in number of medications in RDN group	Mean change (95% CI) from baseline in number of medications in control group	Mean between-group difference* (95% CI)
Azizi, 2015[62] RCT	6	RDN (Medtronic Symplicity), 53	Continuation of anti-hypertensive drugs, 53	3 (NR)	3 (NR)	Baseline median: 3 Final median: 5	Baseline median: 3 Final median: 5	NR
Rosa, 2015[64] RCT	6	RDN (Medtronic Symplicity), 52	Intensification of anti-hypertensive drugs, 54	5.1 (1.2)	5.4 (1.2)	-0.02 (-0.2 to 0.1) P=0.81	0.3 (0.2 to 0.5) P=<0.001	-0.3 (-0.5 to -0.1) P=<0.01
Bhatt, 2014[87] RCT	6	RDN (Medtronic Symplicity), 364	Sham procedure, 171	5.1 (1.4)	5.2 (1.4)	-0.1 (-0.1 to -0.1)	0 (0 to 0)	-0.1 (-0.5 to 0.3)
Pokushalov, 2012[124] RCT	12	RDN (Unspecified), 13	Pulmonary vein isolation, 14	3.8 (0.4)	3.6 (0.6)	-0.5 (-0.6 to -0.4)	0.2 (0.1 to 0.3)	-0.7 (-1.4 to 0)
Rosa, 2015[64] RCT	12	RDN (Medtronic Simplicity), 51	Continuation of anti-hypertensive drugs, 50	5.1 (1.2)	5.4 (1.2)	0.1 (-0.06 to 0.3) P = 0.2	0.2 (-0.2 to 0.6) P = 0.33	-0.1 (-0.5 to 2) P = 0.69
Symplicity, 2010[23] RCT	36	RDN (Medtronic Symplicity), 40	Unspecified, but allowed to crossover to RDN after 6 months	5.1 (1.5)	NR	-0.5 (-0.6 to -0.4) P=0.02	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation; SD=standard deviation

* The mean between-group difference is calculated as the mean change from baseline in the renal denervation group minus the mean change from baseline in the control group.

Stroke, Myocardial Infarction, Hospitalization, and Mortality

We did not identify any studies designed to assess the efficacy or effectiveness of renal denervation in reducing stroke, myocardial infarction, hospitalizations, or survival in patients with resistant hypertension. Most of the studies reported a short duration of followup with emphasis on adverse outcomes related to renal denervation rather than long-term outcomes.

Stroke

Three RCTs reported the incidence of stroke during followup (Table 13).[62, 64, 87] There were eight strokes with an absolute risk difference of 2.2% (95% CI, -2 to 6.4%)[62] and -0.1% (95% CI, -2.1 to 1.9)[87] in the two studies that reported on stroke incidence in both study groups. Three non-controlled studies (1,302 patients) reported stroke events during a mean followup of 10 months (Table 14).[56, 104, 107] The range of risk estimates was 0% to 2.2%. The studies did not show any statistically significant differences in risk of stroke.

Table 13. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on stroke

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Rosa, 2015[64] RCT	6	Stroke (ischemic stroke)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (1.9)	NR	NR
Azizi, 2015[62] RCT	6	Stroke (Not specified)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 46 (2.2)	0 / 53 (0)	2.2 (-2 to 6.4)
Bhatt, 2014[87] RCT	6	Stroke (Not specified)	Medtronic Symplicity	Sham procedure	4 / 352 (1.1)	2 / 171 (1.2)	-0.1 (-2.1 to 1.9)
Rosa, 2015[64] RCT	12	Stroke (Ischemic stroke)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (1.9)	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm. The 95% confidence interval was calculated the absolute risk difference ± 1.96 * square root of the standard error. The standard error was calculated as ((the proportion in the renal denervation group * (1 – the proportion in the renal denervation group)) divided by the sample size in the renal denervation group) plus ((the proportion in the control group * (1 – the proportion in the control group)) divided by the sample size in the control group).

Table 14. Range in rates of stroke, myocardial infarction, hospitalization, and mortality reported in non-controlled studies of renal denervation devices

Blood pressure measure	N studies (N participants)	Mean followup (months)	Median (range) in risk estimate
Stroke	3 (1302)	10	0% to 2.2%
Myocardial infarction	3 (1302)	10	0% to 2%
Hospitalization	4 (1455)	16.5	0% to 8.5%
Mortality	4 (1455)	16.5	0% to 2%
Cardiovascular mortality	2 (1153)	9	0.7% to 2%

Myocardial Infarction

Four RCTs reported 13 myocardial infarctions during followup (Table 15).[62, 64, 87, 122] Data were available in two studies to calculate absolute risk difference; the results were not statistically significant. Three non-controlled studies (1,302 patients) reported myocardial infarction events during a mean followup of 10 months (Table 14).[56, 104, 107] The range of risk estimates was 0% to 2%. No statistically significant differences were seen in risk of myocardial infarction in these studies.

Table 15. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on myocardial infarction

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Azizi, 2015[62] RCT	6	Myocardial infarction (Not specified)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 46 (2.2)	1 / 53 (1.9)	0.3 (-5.3 to 5.9)
Bhatt, 2014[87] RCT	6	Myocardial infarction (Not specified)	Medtronic Symplicity	Sham procedure	6 / 352 (1.7)	3 / 171 (1.8)	-0.1 (-2.5 to 2.3)
Fadl Elmula, 2014[122] RCT	6	Myocardial infarction (Not specified)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 9 (11.1)	NR	NR
Rosa, 2015[64] RCT	12	Myocardial infarction (Not specified)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (1.9)	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

Hospitalizations

Hospitalizations during followup were reported in two RCTs.[23, 87] The causes included hypertensive crisis, hypotension, atrial fibrillation, angina, and transient ischemic attack (Table 16). Hospitalizations were reported in four non-controlled studies (1,455 patients) with risk estimates ranging from 0% to 8.5% (Table 14).[56, 104, 107, 134] No statistically significant differences were seen in risk of hospitalizations in these studies.

Table 16. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on hospitalization

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Symplicity, 2010[23] RCT	6	Hospitalization (for nausea and edema)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR
Symplicity, 2010[23] RCT	6	Hospitalization (for hypertensive event)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	NR	2 / 35 (5.7)	NR
Symplicity, 2010[23] RCT	6	Hospitalization (for hypotensive episode)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	NR	1 / 35 (2.9)	NR
Symplicity, 2010[23] RCT	from 12 to 36	Hospitalization (for hypertensive events)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	5 / 69 (7.2)	NR	NR
Symplicity, 2010[23] RCT	6	Hospitalization (for transient ischemic attack)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	2 / 54 (3.7)	-1.8 (-8.1 to 4.5)
Bhatt, 2014[87] RCT	6	Hospitalization (for atrial fibrillation)	Medtronic Symplicity	Sham procedure	5 / 352 (1.4)	1 / 171 (0.6)	0.8 (-0.9 to 2.5)
Symplicity, 2010[23] RCT	6	Hospitalization (for coronary stent for angina)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	1 / 54 (1.9)	0 (-5.2 to 5.2)
Symplicity, 2010[23] RCT	6	Hospitalization (for hypertensive emergency)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	3 / 52 (5.8)	2 / 54 (3.7)	2.1 (-6 to 10.2)
Symplicity, 2010[23] RCT	6	Hospitalization (for hypotensive episode)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR
Bhatt, 2014[87] RCT	6	Hospitalization (for new-onset heart failure)	Medtronic Symplicity	Sham procedure	9 / 352 (2.6)	3 / 171 (1.8)	0.8 (-1.8 to 3.4)
Symplicity, 2010[23] RCT	between 12 and 36	Hospitalization (for atrial fibrillation)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	2 / 69 (2.9)	NR	NR
Symplicity, 2010[23] RCT	6	Hospitalization (for hypertension crisis after abrupt stopping of clonidine)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

Mortality

Mortality was reported in three RCTs (Table 17)[23, 64, 87, 88] and four non-controlled studies (Table 14).[56, 104, 107, 134] The studies reported very few deaths, with no statistically significant differences.

Table 17. Randomized controlled trials and controlled studies comparing the effects of renal denervation devices on mortality

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Bhatt, 2014[87] RCT	6	Mortality (Not specified)	Medtronic Symplicity	Sham procedure	2 / 352 (0.6)	1 / 171 (0.6)	0 (-1.4 to 1.4)
Bhatt, 2014[87] RCT	12	Mortality (Not specified)	Medtronic Symplicity	Sham procedure	6 / 355 (1.8)	2 / 69 (3.6)	-1.8 (-6.4 to 2.8)
Rosa, 2015[64] RCT	12	Mortality (Not specified)	Medtronic Symplicity	Continuation of anti-hypertensive drugs	0 / 52 (0)	0 / 54 (0)	0 (0 to 0)
Symplicity, 2010[23] RCT	between 12 and 36	Mortality (Not specified)	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6	3 / 69 (4.3)	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

KQ 7. What is the evidence for renal denervation effectiveness in other conditions such as heart failure and arrhythmias?

Key Point

- Data were very limited on the efficacy of renal denervation for conditions other than resistant hypertension. We provide a narrative review of literature in this area and note that scant data preclude further analyses or conclusions.

Sympathetic nervous system over-activity is thought to play a maladaptive role in multiple conditions including cardiac arrhythmias, congestive heart failure, metabolic syndrome, and sleep apnea. The evidence for the effectiveness of renal denervation in these sympathetically driven conditions is lacking in humans, and is limited primarily to case reports, case series, and first-in-man studies.

Cardiac Arrhythmias

The cardiac arrhythmia most widely studied with regards to the application of renal denervation is atrial fibrillation. Hypertension is a major risk factor for atrial fibrillation and the sympathetic nervous system is thought to play a pathological role in atrial electrical and structural remodeling and the development of atrial fibrillation.[139] In a very small randomized trial (N = 27) of patients with symptomatic drug-refractory atrial fibrillation and drug-resistant hypertension (i.e., office-based systolic blood pressure greater than or equal to 160 mm Hg on three or more anti-hypertensive medications) undergoing pulmonary vein isolation with and without renal denervation, there was a lower recurrence of atrial fibrillation with renal denervation plus pulmonary vein isolation compared with pulmonary vein isolation alone at one

year (69 percent versus 29 percent, P = 0.03).[124] These results do not include atrial fibrillation that occurred within the first 3 months. As reported by the authors, the primary endpoint of the study was atrial fibrillation occurring after 3 months because early recurrence after pulmonary vein isolation is common, and does not necessarily portend an unsuccessful long-term outcome.[140]

Numerous clinical trials involving atrial fibrillation are ongoing, including the SYMPLICITY AF trial (NCT02064764), which is an industry-sponsored study of renal denervation in patients with hypertension and paroxysmal and persistent atrial fibrillation. The evidence for the efficacy of renal denervation in suppressing ventricular arrhythmias is limited to case reports of acute control of recurrent monomorphic ventricular tachycardia[141] and ventricular electrical storm.[142]

Congestive Heart Failure

The sympathetic nervous system and neuro-hormonal dysregulation play a fundamental role in cardiomyopathy and heart failure with an extreme example of this being stress cardiomyopathy which is a syndrome of profound myocardial stunning from catecholamine toxicity often triggered by acute emotional stress.[143] At the level of the kidney, renal sympathetic efferent activation stimulates renin release, sodium and water retention, and reduced renal blood flow that leads to further sympathetic activation as part of a maladaptive feedback loop.[144]

Large RCTs of renal denervation in heart failure are lacking. The Renal Artery Denervation in Chronic Heart Failure (REACH) study was a first-in-man pilot study of renal denervation in seven non-hypertensive patients with New York Heart Association (NYHA) class III to IV heart failure and a left ventricular ejection fraction of 28 percent to 58 percent with improvement in the 6-minute walk distance (mean ± standard deviation, 221 ± 33 meters to 249 ± 34 meters, P = 0.03) and reduced diuretic requirements in four patients (P = 0.046) at 6 months following renal denervation.[145] A study of 46 patients with resistant hypertension who underwent renal denervation demonstrated that along with significant reductions in blood pressure, there were significant reductions in mean inter-ventricular septum thickness, left ventricular mass index, surrogate echocardiographic markers of left ventricular diastolic filling pressure, and isovolumic relaxation time accompanied by an increase in ejection fraction at 6 months. This highlights the improvement in overall cardiac performance and the potential cardiac remodeling benefits of renal denervation in this population.[146] The SYMPLICITY HF trial (NCT01392196) is an ongoing industry-sponsored study designed to evaluate the safety and efficacy of renal denervation in the treatment of patients with NYHA class II to III congestive heart failure, impaired left ventricular function (i.e., ejection fraction less than 40 percent), and impaired renal function (i.e., glomerular filtration rate 30 to 75 mL/min/1.73 m2).

Metabolic Syndrome and Diabetes

An imbalance between the sympathetic and parasympathetic nervous system may play a role in the development of metabolic syndrome and diabetes mellitus.[147] The sympathetic nervous system facilitates rapid accessibility of energy stores through glycogenolysis, gluconeogenesis, and lipolysis as part of the fight-or-flight response to stress. Poor parasympathetic tone, manifesting as slower heart rate recovery after exercise, has also been correlated with the development of diabetes mellitus.[148-150] As a result, renal denervation has been investigated as a novel treatment for metabolic syndrome and diabetes mellitus. A small, non-randomized cohort study of patients with resistant hypertension showed that renal denervation (N = 37) had a mean

within-group reduction in fasting glucose levels (-9.4 mg/dL; P = 0.039), fasting insulin levels (-11.6 μIU/mL; P = 0.006), and fasting C-peptide levels (-2.3 ng/mL (P = 0.002) at 3 months, compared with no significant changes in the control group (N = 13).[151] A small Dutch trial investigated the effects of renal denervation in 29 patients with metabolic syndrome and found that renal denervation failed to improve insulin sensitivity at 12 months and had no effect on sympathetic nerve activity.[108] Another trial of renal denervation and glucose metabolism in 51 patients with resistant hypertension also found no favorable effect of renal denervation on fasting glucose, C-peptide, or glycated hemoglobin at 12 months.[152]

Sleep Apnea

Sleep apnea is an important cardiovascular risk factor for hypertension, stroke, atrial fibrillation, and congestive heart failure; sympathetic nervous system activation has been attributed to it as both a cause and an effect.[153] One "proof of concept" study of ten patients with refractory hypertension and sleep apnea showed that at 6 months following renal denervation, there was a significant reduction in office-based blood pressure, indices of glucose control (e.g., hemoglobin A_{1c} and plasma glucose concentration 2 hours after glucose administration), and the apnea-hypopnea index (median: 16.3 versus 4.5 events per hour; P = 0.059).[154] An analysis of the Global SYMPLICITY Registry demonstrated significant blood pressure reductions at 6 months in patients with and without sleep apnea. The investigators observed that continuous positive airway pressure treatment did not seem to have an impact on blood pressure reduction in this population,[155] highlighting the fact that like the other sympathetically driven conditions discussed, further study is necessary.

KQ 8. What are the adverse effects or complications associated with renal denervation in the Medicare population?

Key Point

- Reporting of complications was neither comprehensive nor standardized across studies. Overall, relatively few complications were reported in the published studies.

RCTs and Comparative Cohort Studies

Of the 17 RCTs and comparative cohort studies that we reviewed, only 8 (47%) reported any complication in the renal denervation group. Complications related to femoral artery puncture (e.g., pseudoaneurysm or hematoma) were reported in 11 patients, and renal artery interventions (e.g., dissection, stenosis) were reported in six patients (Tables 18 and 19). Embolic events were reported in two patients, and renal events (increase in serum creatinine, acute kidney injury or end-stage renal disease) were reported in ten patients (Tables 20 and 21). Most studies had a short duration of followup (6 months) with only three studies having followup of 1 year or more.[23, 87, 124]

The studies reported a number of other adverse events that are described in Tables 22 and 23. Of these events, 104 were due to changes in blood pressure (e.g., hypotension or hypertension). The remainders were highly variable; some were related to the procedure (e.g., renal artery spasms after application of radiofrequency energy) while others were related to the effect of conscious sedation/analgesia (e.g., laryngospasm).

Non-comparative Cohort Studies

Of the 59 non-comparative studies, we found reports of complications in 23 (39%) (Appendix E, Table 9). Complications related to femoral artery puncture (e.g., pseudoaneurysm or hematoma) were reported in 12 patients, and renal artery interventions (e.g., dissection, stenosis) were reported in 15 patients. No embolic events were reported. Renal events (e.g., increase in serum creatinine, acute kidney injury or end-stage renal disease) were reported in 30 patients.

Table 18. Adverse events related to femoral artery puncture reported in randomized controlled trials or controlled studies evaluating renal denervation devices

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*	Number needed to harm†
Schneider, 2015[90] RCT	6	Pseudoaneurysm at the femoral vascular access site	Medtronic Flex	Continuation of anti-hypertensive drugs	2 / 9 (22.2)	NR	NR	NR
Rosa, 2015[64] RCT	6	Postpunctual pseudoaneurysm	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (2)	NR	NR	NR
Symplicity, 2010[23] RCT	6	Femoral artery pseudoaneurysm	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR	NR
Azizi, 2015[62] RCT	6	Groin hematoma	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 46 (2.2)	0 / 53 (0)	2.2 (-2 to 6.4)	45
Fadl Elmula, 2014[122] RCT	6	Mild-to-moderate hematomas at the femoral access site	Medtronic Symplicity	Continuation of anti-hypertensive drugs	4 / 9 (44.4)	NR	NR	NR
Rosa, 2015[64] RCT	6	Arterio-venous fistula	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (2)	NR	NR	NR
Bhatt, 2014[87] RCT	6	Vascular complication requiring treatment	Medtronic Symplicity	Sham procedure	1 / 352 (0.3)	0 / 171 (0)	0.3 (-0.3 to 0.9)	333
Bhatt, 2014[87] RCT	12	Vascular complication	Medtronic Symplicity	Sham procedure	1 / 355 (0.3)	0 / 69 (0)	0.3 (-0.3 to 0.9)	333

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

† Number needed to harm = the inverse of the absolute risk difference.

Table 19. Adverse events related to renal artery interventions reported in randomized controlled trials or controlled studies evaluating renal denervation devices

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*	Number needed to harm†
Bhatt, 2014[87] RCT	6	New renal-artery stenosis of >70%	Medtronic Symplicity	Sham procedure	1 / 332 (0.3)	0 / 165 (0)	0.3 (-0.3 to 0.9)	333.3
Bhatt, 2014[87] RCT	6	Renal-artery intervention	Medtronic Symplicity	Sham procedure	0 / 352 (0)	0 / 171 (0)	0 (0 to 0)	NR
Pokushalov, 2012[124] RCT	6	Renal artery stenosis	Unspecified	Pulmonary vein isolation	0 / 13 (0)	0 / 14 (0)	0 (0 to 0)	NR
Rosa, 2015[64] RCT	6	Dissection of renal artery	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (2)	NR	NR	NR
Symplicity, 2010[23] RCT	6	Renal artery dissection	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	NR	1 / 35 (2.9)	NR	NR
Symplicity, 2010[23] RCT	6	Progression of atherosclerotic lesion	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 43 (2.3)	NR	NR	NR
Bhatt, 2014[87] RCT	12	New renal artery stenosis > 70%	Medtronic Symplicity	Sham procedure	NR	0 / 69 (0)	NR	NR
Bhatt, 2014[87] RCT	12	Renal artery reintervention	Medtronic Symplicity	Sham procedure	2 / 355 (0.6)	0 / 69 (0)	0.6 (-0.2 to 1.4)	166.7

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

† Number needed to harm = the inverse of the absolute risk difference.

Table 20. Adverse events related to embolic events reported in randomized controlled trials or controlled studies evaluating renal denervation devices

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*	Number needed to harm†
Bhatt, 2014[87] RCT	6	Embolic event resulting in end-organ damage	Medtronic Symplicity	Sham procedure	1 / 352 (0.3)	0 / 171 (0)	0.3 (-0.3 to 0.9)	333.3
Bhatt, 2014[87] RCT	12	Significant embolic event resulting in end-organ damage	Medtronic Symplicity	Sham procedure	1 / 355 (0.3)	0 / 69 (0)	0.3 (-0.3 to 0.9)	333.3

RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

† Number needed to harm = the inverse of the absolute risk difference.

Table 21. Adverse events related to renal events reported in randomized controlled trials or controlled studies evaluating renal denervation devices

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Kario, 2015[89] RCT	6	50% increase in serum creatinine	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 22 (4.5)	0 / 19 (0)	4.5 (-4.2 to 13.2)
Bhatt, 2014[87] RCT	6	Increase in serum creatinine >50% from baseline	Medtronic Symplicity	Sham procedure	5 / 352 (1.4)	1 / 171 (0.6)	0.8 (-0.9 to 2.5)
Bhatt, 2014[87] RCT	6	New-onset end-stage renal disease	Medtronic Symplicity	Sham procedure	0 / 352 (0)	0 / 171 (0)	0 (0 to 0)
Fadl Elmula, 2014[122] RCT	6	Detectable change in renal function	Medtronic Symplicity	Continuation of anti-hypertensive drugs	0 / 9 (0)	0 / 10 (0)	0 (0 to 0)
Rosa, 2015[64] RCT	6	Worsening of renal function	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	1 / 54 (2)	NR
Bhatt, 2014[87] RCT	12	New-onset end-stage renal disease	Medtronic Symplicity	Sham procedure	1 / 355 (0.3)	0 / 70 (0)	0.3 (-0.3 to 0.9)
Symplicity, 2010[23] RCT	Between 12 and 36	Acute renal failure	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 69 (1.4)	NR	NR
Symplicity, 2010[23] RCT	Between 12 and 36	Renal vascular events	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	0 / 69 (0)	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

Table 22. Adverse events related to blood pressure reported in randomized controlled trials or controlled studies evaluating renal denervation devices

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Azizi, 2015[62] RCT	6	Hypertension crisis	Medtronic Symplicity	Continuation of anti-hypertensive drugs	3 / 46 (6.5)	3 / 53 (5.7)	0.8 (-8.7 to 10.3)
Azizi, 2015[62] RCT	6	Syncope	Medtronic Symplicity	Continuation of anti-hypertensive drugs	0 / 46 (0)	1 / 53 (1.9)	-1.9 (-5.6 to 1.8)
Bhatt, 2014[87] RCT	6	Hypertensive crisis or emergency	Medtronic Symplicity	Sham procedure	9 / 352 (2.6)	9 / 171 (5.3)	-2.7 (-6.4 to 1)
Fadl Elmula, 2014[122] RCT	6	Symptomatic hypotension	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 9 (11.1)	4 / 10 (40)	-28.9 (-65.5 to 7.7)
Rosa, 2015[64] RCT	6	Refusal to continue treatment with spironolactone because of symptomatic blood pressure reduction	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	5 / 54 (9)	NR
Rosa, 2015[64] RCT	6	Refusal to start spironolactone treatment	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	2 / 54 (4)	NR
Symplicity, 2010[23] RCT	6	Post-procedural drop in blood pressure resulting in reduction in anti-hypertensive drugs	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR
Bhatt, 2014[87] RCT	12	Hypertensive crisis/emergency	Medtronic Symplicity	Sham procedure	17 / 355 (4.8)	4 / 69 (5.5)	-0.7 (-6.5 to 5.1)

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

Table 23. Other adverse events reported in randomized controlled trials or controlled studies evaluating renal denervation devices

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Kario, 2015[89] RCT	6	Major adverse event	Medtronic Symplicity	Continuation of anti-hypertensive drugs	0 / 22 (0)	0 / 19 (0)	0 (0 to 0)
Azizi, 2015[62] RCT	6	Lumbar pain	Medtronic Symplicity	Continuation of anti-hypertensive drugs	2 / 46 (4.3)	0 / 53 (0)	4.3 (-1.6 to 10.2)
Azizi, 2015[62] RCT	6	Hypokalemia	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 46 (2.2)	0 / 53 (0)	2.2 (-2 to 6.4)
Azizi, 2015[62] RCT	6	Hyperkalemia	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 46 (2.2)	0 / 53 (0)	2.2 (-2 to 6.4)
Azizi, 2015[62] RCT	6	Pancreatitis	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 46 (2.2)	0 / 53 (0)	2.2 (-2 to 6.4)
Rosa, 2015[64] RCT	6	Unstable angina	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	1 / 54 (1.9)	NR
Rosa, 2015[64] RCT	6	Spasms after application of radiofrequency energy	Medtronic Symplicity	Continuation of anti-hypertensive drugs	4 / 52 (8)	NR	NR
Rosa, 2015[64] RCT	6	Laryngospasm after analgosedation	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (2)	NR	NR
Rosa, 2015[64] RCT	6	Asymptomatic bradycardia after procedure	Medtronic Symplicity	Continuation of anti-hypertensive drugs	2 / 52 (4)	NR	NR
Rosa, 2015[64] RCT	6	Phlebitis associated with peripheral line	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 52 (2)	NR	NR
Rosa, 2015[64] RCT	6	Hyperkalemia	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	6 / 54 (11)	NR
Rosa, 2015[64] RCT	6	Antiandrogen effect of spironolactone	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	7 / 54 (13)	NR
Fadl Elmula, 2014[122] RCT	6	Bradycardia	Medtronic Symplicity	Continuation of anti-hypertensive drugs	1 / 9 (11.1)	NR	NR
Fadl Elmula, 2014[122] RCT	6	Sexual dysfunction	Medtronic Symplicity	Continuation of anti-hypertensive drugs	NR	2 / 10 (20)	NR
Symplicity, 2010[23] RCT	6	Urinary tract infection	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR
Symplicity, 2010[23] RCT	6	Extended hospital admission for assessment of paresthesia	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR

Table 23. Other adverse events reported in randomized controlled trials or controlled studies evaluating renal denervation devices (continued)

Author, year Study design	Mean followup (months)	Outcome definition	RDN	Control group	n/N (%) in RDN group	n/N (%) in control group	Absolute risk difference, %*
Symplicity, 2010[23] RCT	6	Back pain	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	1 / 52 (1.9)	NR	NR
Symplicity, 2010[23] RCT	6	Bradycardia	Medtronic Symplicity	Unspecified, but allowed to crossover to RDN after 6 months	7 / 52 (13)	NR	NR

NR = not reported; RCT = randomized controlled trial; RDN = renal denervation

* Absolute risk difference = event rate in the renal denervation arm minus the event rate in the control arm.

Discussion

Summary of Study Findings

We conducted a systematic review of literature to assess the effectiveness of renal denervation for treatment of resistant hypertension in Medicare-eligible patients. We have abstracted data from available studies, and extrapolated from these studies to the Medicare-eligible population when possible.

We abstracted 83 studies (published in 98 articles) that included 7,660 patients. This is the most comprehensive review of this topic (Table 24). Of the 83 studies, 9 were RCTs, 8 were comparative cohorts, and 66 were non-comparative cohorts. The study populations studied are only partly comparable to the Medicare-eligible population. Since the causes of treatment resistant hypertension are multifactorial, excluding all other causes of resistance (and biases in measurement) before potential need for renal denervation is difficult. None of the abstracted studies match this optimal design as described in KQ 6.

In particular, adherence to diet and medications was not routinely assessed, and only 10 (12%) of all studies described a run-in period prior to randomization. We considered the key blood pressure metric that minimizes white coat effect, observer bias, and placebo effect to be the between-group difference in 24-hour ambulatory systolic blood pressure. This metric represents the difference in blood pressure change over time between the renal denervation group and the control group. The between-group difference in 24-hour ambulatory systolic blood pressure at 6 months was highly variable in six RCTs and two comparative cohorts, ranging from -20 mm Hg to -1.96 mm Hg. After excluding two comparative cohorts,[91, 92] the between-group difference in 24-hour ambulatory systolic blood pressure change at 6 months in the RCTs, all of which used Medtronic's Symplicity device, ranged from -8 mm Hg to -0.5 mm Hg; the results were not statistically significant in all but one RCT. The within-group changes in office systolic blood pressure at 6 months with renal denervation, usually the primary outcome in reported studies, ranged from -42 mm Hg to 1.9 mm Hg in RCTs and comparative cohorts, and from -58.2 mm Hg to 12 mm Hg in non-comparative cohorts.

Unlike treatment with oral antihypertensive medications, the renal denervation procedure is invasive, and despite the carefully selected study populations, complications occurred, such as femoral artery pseudoaneurysm or hematoma, and renal artery stenosis or dissection requiring further interventions.

Table 24. Summary of other systematic reviews of renal denervation devices

Author, Year	Objective	Population	Date of most recent search	Number of studies included	Findings	Risk of bias
Sun, 2015[156]	To compare the effectiveness of RDN with pharmacotherapy to treat resistant hypertension	Patients with uncontrolled BP	NR	9 studies (6 RCTs and 3 CTs)	RDN significantly reduced office systolic and diastolic BP compared with pharmacotherapy.* Pooled results from the RCTS showed no significant decrease in systolic BP with RDN compared with pharmacotherapy.	High
Fadl Elmula, 2015[157]	To evaluate the efficacy and safety of RDN in treatment-resistant hypertensive patients	Patients with treatment-resistant hypertension taking ≥3 drug classes	NR	8 RCTs	RDN "modestly" decreased office systolic and diastolic BP compared with control. Rates of major adverse events were similar in the control and RDN groups. RDN did not change glomerular filtration rate.	High
Kwok, 2014[158]	To evaluate the efficacy and safety of RDN in patients with resistant hypertension	Patients who underwent catheter-based RDN	April 2014	3 RCTs, 8 prospective observational studies, 1 study with matched control	The highest quality evidence suggests that RDN does not significantly reduce systolic and diastolic BP. However, lower quality evidence from non-blinded RCTs and observational studies suggests that there are significant reductions in BP with RDN.	Low
Pancholy, 2014[159]	To compare the effect of RDN with pharmacotherapy on BP and PP after 6 months in patients with resistant hypertension	Patients with resistant, uncontrolled hypertension	April 28, 2014	3 RCTs, 3 CTs	Compared to pharmacotherapy, RDN significantly reduces BP. However, there is high heterogeneity and further research is needed.	Low
Shantha, 2015[153]	To evaluate the effect of RDN on OSA severity in patients with OSA	Patients with OSA and hypertension and reported an apnea-hypopnea index 6 months post-RDN	January 5, 2014	5 prospective cohorts	Six months post RDN, patients reported significant improvement in the apnea-hypopnea index. There is also a significant reduction is office systolic BP and a non-significant reduction in office diastolic BP.	Low
Davis, 2013[160]	To determine the current effectiveness and safety of sympathetic renal denervation for resistant hypertension.	Patients with resistant hypertension who underwent RDN.	December 1, 2012	2 RCTs, 1 observational study, 9 non-controlled observational studies	RDN significantly reduced BP 6 months after the procedure.	Low

BP = blood pressure; CT = controlled trial; NR = not reported; OSA = obstructive sleep apnea; PP = pulse pressure; RCT = randomized controlled trial; RDN = renal denervation
* Results are based on a flawed analysis, which included randomized controlled trials and non-randomized studies and did not have independent study samples.

Limitations of Evidence

Blood pressure change alone may be an imperfect surrogate for clinical outcomes; therefore, studies of clinical endpoints are needed. The renal denervation studies were not designed or powered to detect a long-term difference between groups in clinical endpoints such as stroke, myocardial infarction, hospitalization, or mortality, and few studies report these outcomes. The reports of benefits of renal denervation in other conditions, such as heart failure and arrhythmia, were limited to case reports and case series. Benefits of renal denervation by specific subgroups (age, gender, race/ethnicity), were seldom reported and inconsistent, and often did not specifically address the Medicare-eligible population.

We specifically evaluated the published studies for procedure characteristics, but details on the technique of the procedure and the training or experience of the interventionalist were not uniformly reported. Most studies reported short-term complications of the procedure, generally during 6 months of follow-up. Long-term sequelae of renal denervation or procedure-related complications are not known. The large variability in within-group changes in office systolic blood pressure with renal denervation is likely from white coat effect, observation bias, and placebo effect; the RCTs with a sham procedure and blinding minimized these biases and reported smaller changes in blood pressure. Other potential explanations of the disparity between observational studies and RCTs include heterogeneity of the "resistant hypertension" patient population and variable eligibility criteria.

Differences in denervation technique and completeness of the renal denervation procedure in ablating renal sympathetic nerves may also contribute to the differences between RCTs and observational studies. The learning curve and limited operator experience with first generation renal denervation technology could play a role in the variability in blood pressure response to treatment. However, the robust blood pressure drop in the early clinical trials was seen with use of first generation renal denervation devices with limited operator experience, suggesting that flaws in trial design, bias, or other factors (patient selection, medication adherence, etc.) may be more important than technique. Next generation renal denervation technology uses multi-polar catheters or alternative modalities of nerve ablation such as ultrasound or chemical-based denervation, and are in development or in the early trial phase. Coupled with technical factors, such as more targeted nerve ablation (distal renal arteries, branch vessel origins, circumferential, four quadrant), these issues may help to mitigate operator error and improve the completeness and efficacy of denervation, though this remains to be seen.

Limitations of the Review Process

We limited our search to English language articles indexed by PubMed and may have missed relevant, non-English published literature. As our review was limited to published literature, it was therefore subject to publication or selective outcome reporting bias (i.e., where the authors do not publish negative results). We excluded studies with sample size less than 10, attempting to balance the risk of bias associated with including only large studies of this topic, with selective reporting of small studies. However, throughout the report, we try to focus on the studies that have the lowest risk of bias, such as RCTs, regardless of sample size. We also excluded studies where the study population overlapped a study population in other published trials. Finally, we limited our data abstraction to systolic blood pressure as systolic hypertension is the predominant form of hypertension in the Medicare-eligible population, aged 65 years or older.

Future Research Needs

In this report, we focused on the use of renal denervation in patients with treatment resistant hypertension, which is a complicated multifactorial process and a highly heterogeneous clinical syndrome. Renal sympathetic system overactivity is likely one of the many contributors to uncontrolled blood pressure in such patients. At present, there are no techniques or biomarkers to identify individual patients with hypertension where renal sympathetic system activation is a key contributor to elevated blood pressure. Future research is needed in this area to allow selection of appropriate candidates for renal denervation. Such studies should carefully screen and exclude patients with secondary causes of hypertension.

Research is also needed to standardize renal denervation techniques and develop tests to assess adequacy of renal denervation while the procedure is being performed. As was noted by the Joint UK Societies in 2014 when it issued a consensus statement calling for a continued moratorium on routine use of renal denervation for resistant hypertension, there is much room for improvement in the design and conduct of research on the effectiveness of renal denervation for resistant hypertension.[161] The well-known biases in blood pressure assessment (e.g., white coat effect, observer bias, and placebo effect) require that future studies of renal denervation efficacy should consider between-group differences in ambulatory blood pressure change as the primary metric of interest, rather than the convenient, but often inaccurate, office blood pressure measurements. Future trials should carefully monitor medication adherence using objective methods such as pill counts.[162]

The long-term consequences of the renal denervation procedures and of disrupting the renal sympathetic nervous system are unknown. Future research should ensure long-term followup of the patients undergoing renal denervation to assess for long-term procedure-related outcomes, unintended consequences of blood pressure lowering, as well as clinically valid endpoints such as stroke, myocardial infarction, and cardiovascular death. Furthermore, an RCT is needed that directly compares renal denervation with an antihypertensive medication strategy to reduce blood pressure and prevent long-term cardiovascular complications.

Conclusions and Implications

Limited evidence suggests that renal denervation in patients with treatment resistant hypertension lowers systolic blood pressure, but the results were highly variable and the studies reviewed were not designed to determine improvement in clinical endpoints. The most rigorously conducted RCTs showed much smaller blood pressure reduction as compared with observational non-comparative studies. Further research is needed to identify optimal candidates for renal denervation, refine next generation renal denervation technology, develop methods for assessing completeness of renal denervation procedure, and demonstrate efficacy of renal denervation in reducing blood pressure and improving clinical endpoints including the risk of stroke, myocardial infarction, heart failure, and death in patients with hypertension.

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