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Effectiveness of Renal Denervation Therapy for Resistant Hypertension

A Systematic Review and Meta-Analysis

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Objectives This study sought to determine the current effectiveness and safety of sympathetic renal denervation (RDN) for resistant hypertension.

Background RDN is a novel approach that has been evaluated in multiple small studies.

Methods We performed a systematic review and meta-analysis of published studies evaluating the effect of RDN in patients with resistant hypertension. Studies were stratified according to controlled versus uncontrolled design and analyzed using random-effects meta-analysis models.

Results We identified 2 randomized controlled trials, 1 observational study with a control group, and 9 observational studies without a control group. In controlled studies, there was a reduction in mean systolic and diastolic blood pressure (BP) at 6 months of −28.9 mm Hg (95% confidence interval [CI]: −37.2 to −20.6 mm Hg) and −11.0 mm Hg (95% CI: −16.4 to −5.7 mm Hg), respectively, compared with medically treated patients (for both, $p < 0.0001$). In uncontrolled studies, there was a reduction in mean systolic and diastolic BP at 6 months of −25.0 mm Hg (95% CI: −29.9 to −20.1 mm Hg) and −10.0 mm Hg (95% CI: −12.5 to −7.5 mm Hg), respectively, compared with pre-RDN values (for both, $p < 0.00001$). There was no difference in the effect of RDN according to the 5 catheters employed. Reported procedural complications included 1 renal artery dissection and 4 femoral pseudoaneurysms.

Conclusions RDN resulted in a substantial reduction in mean BP at 6 months in patients with resistant hypertension. The decrease in BP was similar irrespective of study design and type of catheter employed. Large randomized controlled trials with long-term follow-up are needed to confirm the sustained efficacy and safety of RDN. (J Am Coll Cardiol 2013;62:231–41) © 2013 by the American College of Cardiology Foundation

Resistant hypertension (RH) is defined as uncontrolled systolic blood pressures (BP) despite therapy with ≥3 antihypertensive agents from at least 3 different classes including a diuretic. In most studies, 10% to 15% of hypertensive subjects (1,2), but up to 20% of the hypertensive population in some publications (3), have RH, particularly those with advanced age, obesity, diabetes mellitus, sleep apnea, and chronic kidney disease (4–6). In patients with RH, pharmacological options are limited. Historically, a surgical option, namely sympathectomy, led to a significant reduction in BP but was associated with high surgical morbidity (7–9). Although surgical sympathectomy was largely abandoned in clinical practice, there has been a renewed interest in the concept as animal models (10,11) have shown that renal sympathectomy leads to significant reduction in BP and improvement in end organ function (12–15).

Percutaneous renal sympathectomy has emerged as a safer, although invasive approach using radiofrequency probes to ablate the sympathetic fibers along the renal artery. The proof of concept study (16) demonstrated surprisingly good results and was subsequently followed by a series of studies using different catheters. These studies have generated great enthusiasm such that percutaneous renal denervation therapy (RDN) has been adopted at a rate rarely seen in the hypertension field. RDN for RH is currently approved in Europe and Canada and is pending approval in the United States. One RDN catheter system (Medtronic Ardian Inc., Palo Alto, California) has been used to treat over 4,000 patients worldwide thus far (17). Despite the enthusiasm and rapid uptake, there has yet to be a comprehensive review of the available evidence to support the practice of RDN.

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Abbreviations and Acronyms

BP = blood pressure
CI = confidence interval
DBP = diastolic blood pressure
RDN = renal sympathetic denervation
RH = resistant hypertension
SBP = systolic blood pressure

We have systematically reviewed the current body of evidence for RDN and quantified its BP-lowering effect in patients with RH using a random effects meta-analysis model.

Methods

Data sources and search strategy. We performed a systematic review and meta-analysis in accordance with the standards set forth by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (18,19). We searched PubMed, EMBASE, and the Cochrane Collaboration database using the key words "renal denervation," "blood pressure," and "hypertension." The search was limited to English language articles published in the last 5 years (this technology was only developed in that time frame). In addition, we hand-searched references of retrieved articles and used PubMed's related articles feature to identify studies not captured by our primary search strategy. The final search was run on December 1, 2012.

Study selection. We included randomized and observational studies comparing BP response in patients treated with RDN versus patients treated with standard medical therapy (controlled studies) and observational studies comparing BP in a single group of patients before and after RDN (uncontrolled studies). Inclusion criteria were: 1) RDN performed using contemporary percutaneous catheters and radiofrequency probes; 2) patient population with RH (not meeting BP target despite therapy with 3 or more antihypertensive agents from at least 3 different classes); 3) at least 10 study participants; and 4) at least 3 months of follow-up for BP response. BP measurements could include manual, automated, or invasive BP recordings, as long as the same method was used before and after RDN. Reviews, editorials, letters, animal studies, case reports, and conference abstracts were excluded. Once full articles were retrieved, studies were further excluded if there was an overlap in patients with another study within the same analysis (in which case, the larger sample size of the 2 studies was selected). Thus, whereas some patients could possibly have been included in both the controlled and uncontrolled study analyses, they were only included once in any given analysis. Consequently, there was no overlap in patients included in our meta-analyses.

Data extraction. Data was extracted in duplicate by 2 independent reviewers (M.D., D.Z.). Disagreements were resolved by consensus. We extracted data pertaining to baseline characteristics of study subjects (number of subjects, age, sex, comorbidities, antihypertensive agents), trial inclusion and exclusion criteria, method of BP measurement, type of catheter used, BP response to RDN (including BP before and after RDN), nonresponder rate, procedural complications, maximal length of follow-up, and mortality.

Outcomes. The primary outcome measure was mean systolic and diastolic BP reduction following RDN between 3 and 6 months of follow-up. Secondary outcome measures included: 1) nonresponder rate, defined as an achieved decrease in systolic BP of <10 mm Hg; 2) mean BP reduction stratified by catheter type; and 3) reported procedural complications and averse outcomes including death from any cause.

Methodological quality. To determine the quality of the included studies, we used the Cochrane Collaboration Risk of Bias Tool (Online Appendix 1) for the 2 randomized control trials and the Newcastle-Ottawa scale for the observational studies. We set a follow-up rate of >70% at 6 months as a limit to determine high risks of bias at follow-up for studies evaluated with the Newcastle-Ottawa scale in the outcome section of this scale (Online Appendix 2).

Data synthesis and statistical analysis. For controlled studies, the difference in BP change with RDN versus medical therapy was pooled across studies and analyzed using random-effects meta-analysis models with inverse variance weighting. Separate models were constructed for 3 and 6 months of follow-up. For uncontrolled studies, the BP change before versus after RDN was pooled and analyzed using the same meta-analysis models. The magnitude of heterogeneity present was estimated using the I^2 statistic, an estimate of the proportion of the total observed variance that is attributed to between-study variance. To compare the magnitude of BP reduction based on the type of RDN catheter used, we constructed a separate meta-analysis stratified by catheter type using a random-effects generic inverse variance-weighting model to compare heterogeneity using the I^2 statistic.

Certain studies reported measures of variability other than SD. In these cases, 95% confidence intervals or standard error of the mean were converted to SD to maintain consistency of the reported results. In a study by Witkowski et al. (20), the only measure of variability reported was interquartile range. By including this study in the meta-analysis models, we are assuming a normal distribution of change in BP. In the study by Prochnau et al. (21), no estimate of variance was reported, thus we assumed a SD equal to the mean of other reported SD. Sensitivity analyses were performed excluding these 2 studies. We considered $p < 0.05$ significant. Throughout, values are presented as mean ± SD unless otherwise stated. Analyses were performed using the Cochrane Collaboration Review Manager (version 5.1.7, Cochrane Collaboration, Copenhagen, Denmark) and the GraphPad Prism (version 6.0, GraphPad Software, La Jolla, California) software packages.

Results

Study selection and characteristics. Our literature search identified 294 potentially relevant studies as shown in the flow diagram (Fig. 1). Of these, 18 studies met the inclusion criteria. Six additional studies were excluded due to overlap