



## Renal nerve denervation for resistant hypertension, systematic review and meta-analysis

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### Abstract

**Background:** Systemic hypertension is a major burden to the individual and society. Its association with major adverse cardiac and cerebral events and beneficial effects of antihypertensive therapy are undisputed. However, despite multidrug therapy, blood pressures are frequently sub-optimally controlled. Controversy regarding the effects of Renal Nerve Denervation (RND) for Resistant Hypertension (RH) has surfaced after a randomized, single-blind, multicenter, prospective, controlled clinical trial Simplicity HTN-3 in 2014 did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal artery denervation as compared with a sham control. Many other previous clinical data show that RND reduces blood pressure in patients with resistant hypertension however in results from Simplicity HTN-3 suggested that the effectiveness of RND is still controversial.

### Objective

- To evaluate the short- and long-term effects of renal nerve denervation in individuals with resistant hypertension on:
- Patient-centered endpoints including blood pressure control; Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)
- 24 hours Ambulatory Blood Pressure Monitoring (AMBP)

**Search method:** We searched research published since January 1, 2009 through computer (since the first report of RND in 2009) to the clinical studies published until 15 December 2023 in PubMed, Cochrane and Library in Clinicaltrial.gov database. The following keywords were employed: "hypertension" or "blood pressure" or "resistant hypertension" or "refractory hypertension" or "uncontrolled hypertension" or "susceptible drug-resistant hypertension" or "and" denervation "or" catheter-based renal denervation "or" renal sympathetic denervation "or" percutaneous renal sympathectomy "or" radiofrequency catheter-based renal sympathetic denervation "or" renal nerve denervation.

**Selection Criteria:** Literature screening mainly according to the inclusion criteria and exclusion criteria, through literature reading of articles and abstract screening; to meet the inclusion criteria and exclusion standard. Clinical study full text study were done to extract relevant data; if reading the text found exactly the same research group, only selected the related literature.

**Data Collection and analysis:** Data were collected by one author (AKM) and checked by other author (RNM). Potential eligible studies were excluded when the results presentation prevented adequate extraction of data.

**Main Results:** In this systematic review and meta-analysis, according to inclusion criteria and exclusion criteria, 38 clinical studies on RND were included. Total of 38 studies, 6 studies were Randomized Control Trials, 10 studies were prospective observational study with control group and remaining 22 studies were prospective observational studies without control group. Out of all 38 studies included 33 studies involving 2135 cases of patients reported the result of SBP at 6 months after RND, 27 studies involving 1377 patients reported the result of DBP 6 months after RND. The statistical result shows that RND can reduce 22.50 mmHg of SBP [95% confidence interval (CI: -24.14, -20.86),  $P < 0.00001$ ,  $Z = 26.90$ ] and 8.99 mmHg of DBP [95% Confidence interval (CI: -10.51, -7.46),  $P < 0.00001$ ,  $Z = 11.56$ ]. For 24 hours ambulatory blood pressure monitoring over all clinical research, RND can reduce the systolic blood pressure of 10.44 mmHg [95% confidence interval (CI: -12.85, -8.02),  $P = 0.0002$ ,  $Z = 8.46$ ]; RND can also reduce the diastolic blood pressure of 5.88 mmHg [95% confidence interval (CI: -6.71, -5.05),  $P < 0.00001$ ,  $Z = 13.88$ ].

**Authors Conclusions:** The meta-analysis observed that RND could effectively reduce the systolic blood pressure in office and 24-hour ambulatory blood pressure monitoring in patients with resistant hypertension.

These results suggest that the RND for patients with resistant hypertension can play a hypotensive effect; RND could exert protective effect on patients with resistant high blood pressure through its antihypertensive effect.

**Keywords:** Renal nerve denervation, resistant hypertension, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP)

### Introduction

Treatment of Resistant Hypertension with Renal Nerve Denervation

Resistant hypertension is a frequent form of arterial hypertension that, with the exception of malignant hypertension, constitutes the most dangerous stage of arterial hypertension<sup>[1]</sup>. When blood pressure is consistently high it can lead to complications such as myocardial

infarction or stroke. Resistant hypertension is defined as the use of at least 3 kinds of antihypertensive drugs (including diuretics); blood pressure is still higher than the target level<sup>[2]</sup>. However, despite multidrug therapy, blood pressures are frequently sub-optimally controlled. Moreover, adverse drug effects often interfere with patients' life-styles and affect compliance. Therefore, alternative treatment strategies have been explored. Most recently, attention has been redirected

to the sympathetic nervous system (SNS) in the pathogenesis of hypertension. Recently, percutaneous catheter renal nerve denervation (RND) has emerged as a new method to treat resistant hypertension.

We identified Total of 38 studies, 6 Randomized Control Trials, 10 prospective observational studies with control group and remaining 22 studies were prospective observational studies without control group involving total of 2834 people. 16 studies compared RND with Pharmacotherapy and 22 studies observe the risk and benefit of RND in patients with resistant hypertension.

## Background

### Description and the condition

Systemic hypertension is a major burden to the individual and society. Its association with major adverse cardiac and cerebral events and beneficial effects of antihypertensive therapy are undisputed [1, 3]. However, despite multidrug therapy, blood pressures are frequently sub-optimally controlled [4]. Moreover, adverse drug effects often interfere with patients' life- styles and affect compliance. Therefore, alternative treatment strategies have been explored. Most recently, attention has been redirected to the sympathetic nervous system (SNS) in the pathogenesis of hypertension [5]. In addition, interruption of the renal SNS in humans with resistant hypertension has been studied with promising results [4, 5].

In recent years, catheter-based renal nerve denervation (RND) has emerged as a new technique to treat resistant hypertension. The new technique can be used not only in patients with resistant hypertension but also in patients with any excessive activation of sympathetic nervous system, and thus has become the focus of attention. Many clinical data show that RND reduces blood pressure in patients with resistant hypertension [1]. However, in 2014, a randomized, single-blind, multicenter, prospective, controlled clinical trial Symplicity HTN-3 did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal nerve denervation as compared with a sham control. These results have suggested that the effectiveness of RND is still controversial.

### Description of intervention

Catheter based renal nerve sympathetic denervation by radiofrequency is a new technique that can disrupt both the efferent and afferent sympathetic nervous fibers that follow the renal artery to the kidney within the adventitia [6]. This, in turn, reduces renal sympathetic tone and subsequently BP.

Because of the problems associated with surgical sympathectomy, a minimally invasive catheter-based approach was developed to directly target the sympathetic nerves adjacent to the renal artery [7]. In this procedure, an endovascular catheter, using a 6F or 8F guide, is inserted via the femoral artery and is advanced until it has entered the distal renal artery. The procedure is performed with a radiofrequency ablation device applied via an electrode on the tip of the catheter. Symplicity Catheter was developed by Ardian, Inc. (Mountain View, CA). The procedure is performed via multiple radiofrequency treatments. First, the ablations are performed distally in the renal artery; the catheter is retracted 5 mm, rotated circumferentially, and then another radiofrequency ablation treatment is applied [7]. This process is repeated 4-6 times until the entire

circumference of the artery has received an ablation treatment. Each ablation lasts  $\leq 2$  minutes, and the entire bilateral procedure has an average duration of one hour. There are few periprocedural complications. Loin pain, related to the period of ablation, confirmed the presence of afferent C fibers and their ablation. The pain is managed with conscious intravenous sedation. No evidence of renal artery thrombosis or embolization has been seen, and renal artery dissection has proven to be a rare complication.

### How the intervention might work

The kidneys are under the control of the autonomic nervous system by way of an intricate network of postganglionic sympathetic neuronal innervations. This sympathetic innervation, along with other neurohormonal and hemodynamic etiologies, has been suggested to play a major role in the pathogenesis of hypertension [7]. The radical sympathectomy procedure (splanchnicectomy), practiced in 1940's for the treatment of hypertension, supports this mechanism, because the procedure often reduced elevated BP in patients with hypertension [8].

Experimental studies have shown that the kidneys can contribute to high blood pressure through several pathways linked to their afferent and efferent sympathetic nerve output [9]. The kidneys contribute to high blood pressure via their sympathetic nerves by enhancing norepinephrine production, inducing renin secretion and sodium (Na<sup>+</sup>) retention (mediated by beta 1-adrenergic receptors), reducing renal blood flow (RBF) (mediated by alpha-adrenergic receptors), altering the renal vasculature, and stimulating the central nervous system to increase sympathetic tone [10].

There is a strong correlation between the activation of the kidneys' sympathetic innervation and an increase in norepinephrine production or spillover, especially in obese patients [7]. In hypertensive patients, the renal sympathetic tone is doubled compared with that in normotensive individuals. This increase in production of norepinephrine leads to increased stimulation of the cardiac sympathetic nerves and increases the risk of a patient developing left ventricular hypertrophy and ventricular arrhythmias with subsequent sudden cardiac death.

### Why it is important to do this review

Catheter based renal nerve denervation for treatment of resistant hypertension is still a technique in its very early development. Despite promising preliminary results, several uncertainties remain regarding its benefit/risk ratio.

When a treated hypertensive patient has not reached the BP objective despite the prescription of triple therapy including medicinal products prescribed at the maximum tolerated dosage and including a diuretic, he or she is described as having 'resistant Hypertension', according to the definition used in the recommendations [11].

Resistant Hypertension, when confirmed, requires specialized treatment as per the recommendations [2]. Treatment should include: reinforcement of treatment (increase of the dose of anti-hypertensive agents up to the maximum tolerated dose, choice of another diuretic); the addition of an aldosterone antagonist (spironolactone); the addition of other pharmacological groups (alpha blockers, central antihypertensive agents, direct vasodilator agents);

RND is a new promising technique that facilitates BP control in resistant hypertension not responding to 3 or more drugs. Several observational studies, observational control study and randomized control trials have shown positive results but some other randomized control trials mainly Symplicity HTN-3 did not show a benefit of renal artery denervation with respect to either of the efficacy end points for which the study was powered (reduction in office or ambulatory systolic blood pressure at 6 months). These findings contradict the published clinical data regarding renal nerve denervation, which showed larger reductions in blood pressure 6 months after denervation it is evident that more data are required.

### Objectives

- To evaluate the short- and long-term effects of renal sympathetic denervation in individuals with resistant hypertension on:
- Patient-centered endpoints including blood pressure control; Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)
- 24 hours Ambulatory Blood Pressure Monitoring (AMBP)

### Methods

#### Criteria for considering studies for this review

##### Types of studies

Randomized controlled trials (RCTs), Observational control study and observational studies assessing and comparing the effectiveness of RND treatment for resistant hypertension. According to inclusion and exclusion criteria, clinical studies on resistant hypertension were searched by medical literature database, and the primary end point is the change in SBP and DBP at 6 months after RND. Studies were excluded when the trial design was adequate but the published data were inadequate for the purposes of the review.

##### Type of participants

Resistant hypertension patients with inadequate control of BP while taking 3 or more drugs at adequate doses and with apparent drug adherence.

**Inclusion criteria:** (I) research group for patients with resistant hypertension; (II) type of research for clinical studies, including randomized controlled trials, observational control study and observational study without control; (III) intervention for the catheter based renal nerve sympathetic denervation (IV) follow-up period of at least six months; (V) sample size in patients 5 or more than 5 patients.

**Exclusion criteria:** (I) non-clinical research; (II) sample size less than 5 patients; (III) incomplete data; (IV) reviews, commentaries, letters, case reports and conference abstracts and other were excluded.

##### Type of intervention

To be eligible for inclusion, trials had to include intervention of RND against three or more anti-hypertensive medications against each other and include patient with resistant hypertension. The intervention in each group had to last for at least six months.

### Type of outcomes measures

#### Primary outcomes

The Primary efficacy outcome measure was a comparison of SBP and DBP changes from Baseline to 6 months in the RND group and required a superiority margin of 5 mmHg for success.

#### Secondary outcomes

The secondary efficacy outcome measure was the change in mean 24-hour ambulatory SBP and DBP at 6 months.

### Search methods for identification of studies

#### Electronic Search

We searched research published since January 1, 2009 through computer (since the first report of RDN in 2009) to the clinical study published until 15 December 2015 in PubMed, Cochrane and Library in Clinicaltrial.gov database. The following keywords were employed: "hypertension" or "blood pressure" or "resistant hypertension" or "refractory hypertension" or "uncontrolled hypertension" or "susceptible drug-resistant hypertension" or "and" denervation "or" catheter-based renal denervation "or" renal sympathetic denervation "or" percutaneous renal sympathectomy "or" radiofrequency catheter-based renal sympathetic denervation "or" renal nerve denervation

#### Searching other resources

Reference lists of relevant articles were screened

#### Data Collection and analysis

For this review and meta-analysis we used the following methods when assessing the reports identified by the search.

#### Selection of Studies

Two authors (AKM, RNM) assessed for selection of trials for inclusion of all potential studies in the review identified as a result of search strategy.

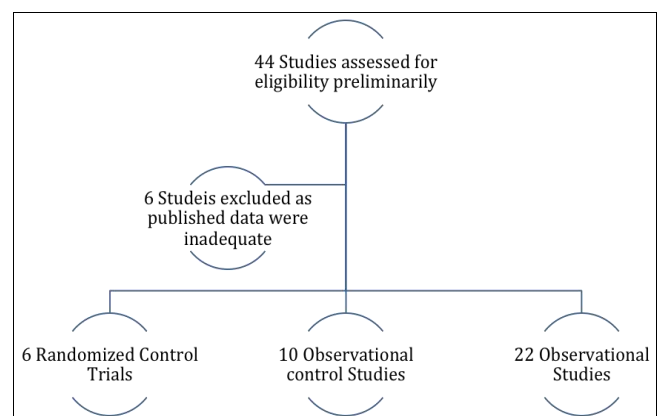


Fig 1: Selection of Studies

#### Data extraction and managements

AKM extracted the data, which were checked by RNM. The data extracted included information relating to the complexities of the topic area, such as patient's characteristics and concomitant treatments, as well as data relating to study eligibility, quality and out-comes. Disagreements between review authors on data extraction were resolved by discussion.

**Assessment of risk of bias in included studies**

First review author (AKM) assessed the risk of bias for each study using the criteria outlined in the Cochrane handbook for systematic Reviews of Interventions. There were three possible judgments: low risk of bias, high risk of bias, and if an insufficient detail was reported the judgment on risk of bias was judged to be unclear. Results were checked and agreed by a second author (RNM). Disagreements were resolved by discussion.

**Blinding**

Low risk of bias, if there was no blinding but the review authors judged that the outcome and the outcome measurements were not likely to be influenced by lack of blinding of participants and key study personnel was ensured and it was unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded but outcome assessment was blinded and non-blinding of other was unlikely to introduce bias.

High risk of bias, if there was no blinding or incomplete blinding and the outcome or the outcome measurement was likely to be influenced by lack of blinding; blinding of key study participants and personnel was attempted but it was likely that the binding could have been broken; either participants or some key study personnel were not blinded and the non-blinding of others was likely to introduce bias.

Unclear risk of bias, if there was insufficient information to permit judgment of low or high risk of bias or the study did not address this outcome (for example where the blinding was described only as double-blind without any other details).

**Measures of treatment effect**

Statistical analyses were undertaken as follows. For continuous variables (for example the change in IC distance between baseline and follow-up) where the data were presented as mean ± standard deviation (SD) the weighted mean difference with 95% confidence interval (CI) was used.

**Assessment of heterogeneity**

Statistical heterogeneity in each meta-analysis was assessed using the Tau2, I2 and Chi2 statistics. We regarded heterogeneity as substantial if I2 was greater than 30% and either the Tau2 was greater than zero, or there was a low P value (less than 0.10) in the Chi2 test for heterogeneity.

**Assessment of reporting biases**

We investigated reporting bias (such as publication bias) using funnel plots. We assessed funnel plots asymmetry visually and used formal test for funnel plot asymmetry.

**Data synthesis**

We carried our statistical analysis using the review manager software (RevMan 5.3). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effects: i.e. where trials were examining the same intervention, and the trials populations and methods were judged sufficiently similar.

**Sensitivity analysis**

Sensitivity analysis was not performed.

**Results**

**Description of studies**

Details for each trials and studies can be found in the characteristics of included studies and the characteristics of excluded studies table.

**Result of the search**

For this review and meta-analysis, following screening of titles and abstracts full texts of 44 studies were obtained and considered. 38 studies were included in this review and meta-analysis and 6 studies were excluded.

Details of each trials and studies can be found in the characteristics of included studies table and the characteristics of excluded studies table.

**Table 1:** Characteristics of included studies preliminarily

Study	Journal / Year	Research	Group	Sample	Study endpoint
<b>Randomized Control Trials (6)</b>					
HTN-2 [3]	Lancet 2010	Resistant Hypertension	RND Group Control Group	52 54	Effectiveness & Safety
Pokushalov [12]	JACC 2012	RH + Af	RND Group Control Group	13 14	BP & Af
HTN-3 [13]	NEJM 2014	Resistant Hypertension	RND Group Control Group	364 171	BP & Safety
HTN-Jp [14]	Circulation 2015	Resistant Hypertension	RND Group Control Group	22 19	Effectiveness & Safety
DENERHTN-15 [15]	Lancet 2015	Resistant Hypertension	RND Group Control Group	48 53	Effectiveness & Safety
Parague-15 [16]	Hypertension 2015	Resistant Hypertension	RND Group Control Group	52 54	Effectiveness & Safety
<b>Observational Control Study (10)</b>					
Henry Krum [17]	Lancet 2009	Resistant Hypertension	RND Group Control Group	45 5	Effectiveness & Safety
Christian Ukena [18]	JACC 2011	Resistant Hypertension	RND Group Control Group	37 9	Cardiac & Pulmonary response
Felix Mahfoud [19]	Hypertension 2012	Resistant Hypertension	RND Group Control Group	88 12	Renal Blood Flow & Function
Murry D [20]	Circulation 2012	Resistant Hypertension	RND Group Control Group	52 54	Effectiveness & Safety

Mathias C <sup>[21]</sup>	JACC 2013	Resistant Hypertension	RND Group Control Group	110 10	Atrial Stiffness & Blood Flow
Dagmara Hering <sup>[22]</sup>	JH 2013	Resistant Hypertension	RND Group Control Group	40 10	Augmentation Index
Dagmara Hering <sup>[23]</sup>	Hypertension 2013	Resistant Hypertension	RND Group Control Group	25 10	BP
Costas Tsioufis <sup>[24]</sup>	IJC 2014	Resistant Hypertension	RND Group Control Group	31 12	Effectiveness & Safety
Felix Mahfoud <sup>[25]</sup>	EHI 2014	Resistant Hypertension	RND Group Control Group	55 17	Effectiveness & Safety
Sabastin Ewen <sup>[26]</sup>	Hypertension 2014	Resistant Hypertension	RND Group Control Group	50 10	Effectiveness & Safety
<b>Observational Study (28)</b>					
HTN-1 <sup>[27]</sup>	Hypertension 2011	Resistant Hypertension	RND	153	BP & Safety
Adam Witkowski <sup>[28]</sup>	Hypertension 2011	RH + Sleep Apnea	RND	10	BP & Sleep Apnea
Dagmara Hering <sup>[29]</sup>	JASN 2012	RH + Mod & Severe CKD	RND	15	GFR
Kai Mortensen <sup>[30]</sup>	JCH 2012	Resistant Hypertension	RND	21	Stiffness & Blood Flow
Christine Zuern <sup>[31]</sup>	Frontiers in Physiology 2012	Resistant Hypertension	RND	11	BP Variation
Humera Ahmed <sup>[32]</sup>	JACC 2012	Resistant Hypertension	RND	10	BP & Safety
Drik Prochnau <sup>[33]</sup>	Euro-intervention 2012	Resistant Hypertension	RND	30	Safety & Effectiveness
Gavin W <sup>[34]</sup>	Hypertension 2012	Resistant Hypertension	RND	62	Quality of Life
Justin E <sup>[35]</sup>	Int J Cardio 2013	Chronic Stable HF	RND	7	Safety
Marc Doren -kamp <sup>[36]</sup>	EHI 2013	Resistant Hypertension	RND	N/A	Cost Vs. CVS event
Christian Ukena <sup>[37]</sup>	IJC 2013	Resistant Hypertension	RND	136	HR & Node Function
M. G. Kiuchi <sup>[38]</sup>	EHI 2013	RH+Chronic Stable HF	RND	24	BP & Renal Function
Dani MD <sup>[39]</sup>	JACCI 2013	Resistant Hypertension	RND	54	Renal Artery
Stephen G <sup>[40]</sup>	EHI 2013	Resistant Hypertension	RND	46	BP & Adverse Effect
Oliver Dorr <sup>[41]</sup>	JIC 2013	Resistant Hypertension	RND	30	Quality of Life
Christine S <sup>[42]</sup>	JACC 2013	Resistant Hypertension	RND	50	Cardiopulmonary Reflex
Felix Mahfoud <sup>[43]</sup>	Circulation 2013	Resistant Hypertension	RND	346	ABP
Christian Ott <sup>[44]</sup>	CJASN 2013	Resistant Hypertension	RND	19	Change in Blood Flow
Gajendra Manakshe <sup>[45]</sup>	Indian Heart Journal 2013	Resistant Hypertension	RND	18	BP
Benjamin Kaltenbach <sup>[46]</sup>	CCI 2013	Resistant Hypertension	RND	20	BP & Safety
Christian Ott <sup>[47]</sup>	JACC 2013	Resistant Hypertension	RND	54	Sexual Function
Matthias Lenski <sup>[48]</sup>	IJC 2013	Resistant Hypertension	RND	36	Effectiveness & Safety
Fadi Elmula <sup>[49]</sup>	Hypertension 2013	Resistant Hypertension	RND	6	BP
Markus P <sup>[50]</sup>	IJC 2013	End Stage Renal Function	RND	12	BP & Nerve
Henry Krum <sup>[51]</sup>	Lancet 2014	Resistant Hypertension	RND	153	Effectiveness & Safety
Mustafa Ezzahiti <sup>[52]</sup>	JH 2014	Resistant Hypertension	RND	17	BP & Hormone
Janine Poss <sup>[53]</sup>	CRS 2014	Resistant Hypertension	RND	101	Vit D
Stephan H <sup>[54]</sup>	JACC 2014	Resistant Hypertension	RND	66	LVH & Comfort

**Included studies**

6 Randomized controlled trials (n=921), 10 Observational control studies (n=682) and 22 Observational studies

without control (n= 1231) were included in this review and meta-analysis. All included trials are small. The largest study recruited 535 people with resistant hypertension.

**Table 2:** Characteristics of studies finally included in meta-analysis

Study	Journal / Year	Research	Group	Sample	Study endpoint
<b>Randomized Control Trials (6)</b>					
HTN-2	Lancet 2010	Resistant Hypertension	RND Group Control Group	52 54	Effectiveness & Safety
Pokushalov	JACC 2012	RH + Af	RND Group Control Group	13 14	BP & Af
HTN-3	NEJM 2014	Resistant Hypertension	RND Group Control Group	364 171	BP & Safety
HTN-Jp	Circulation 2015	Resistant Hypertension	RND Group Control Group	22 19	Effectiveness & Safety
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<b>Observational Study (22)</b>					
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Christine Zuern	Frontiers in Physiology 201	Resistant Hypertension	RND	11	BP Variation
Humera Ahmed	JACC CI 2012	Resistant Hypertension	RND	10	BP & Safety
Drik Prochnau	Euro-intervention 2012	Resistant Hypertension	RND	30	Safety & Effectiveness
Justin E	IJC 2012	Chronic Stable HF	RND	7	Safety
M. G. Kiuchi	EJH 2013	RH+Chronic Stable HF	RND	24	BP & Renal Function
Dani LD	JACC 2013	Resistant Hypertension	RND	54	Renal Artery
Stephen G	EJH 2013	Resistant Hypertension	RND	46	BP & Adverse Effect
Christine S	JACC 2013	Resistant Hypertension	RND	50	Cardiopulmonary Reflex
Felix Mahfoud	Circulation 2013	Resistant Hypertension	RND	346	ABP
Christian Ott	CJASN 2013	Resistant Hypertension	RND	19	Change in Blood Flow
Gajendra Manakshe	IJH 2013	Resistant Hypertension	RND	18	BP
Benjamin Kaltenbach	CCI 2013	Resistant Hypertension	RND	20	BP & Safety
Christian Ott	JACC 2013	Resistant Hypertension	RND	54	Sexual Function
Fadi Elmula	Hypertension 2013	Resistant Hypertension	RND	6	BP
Henry Krum	Lancet 2014	Resistant Hypertension	RND	153	Effectiveness & Safety
Mustafa Ezzahti	JH 2014	Resistant Hypertension	RND	17	BP & Hormone
Janine Poss	CRS 2014	Resistant Hypertension	RND	101	Vit D
Stephan H	JACC 2014	Resistant Hypertension	RND	66	LVH & Comfort

**Risk of bias in included studies**

Overall, the quality of the studies included in this review is moderate to poor.

**Interventions**

Eligible patients were randomized to immediate renal denervation with catheter based renal sympathetic denervation system or to the control group. Patient in the treatment group underwent renal nerve denervation with the radiofrequency energy delivery; both groups were maintained on their baseline antihypertensive medication regimen during the first 6 months of the trial. Changes in antihypertensive medication were not allowed during the 6-month follow up period unless they were considered to be clinically necessary. These studies compared renal nerve denervation and anti-hypertensive drugs alone against each other.

**Description of Resistant hypertension**

The description of how resistant hypertension was diagnosed differed between the included studies. In the SYMPLICITY HTN-3 patient on stable antihypertensive drug regime including maximally tolerated doses of ≥3 antihypertensive medication of complementary classes,

including an appropriately dosed diuretic, were required to have seated office SBP ≥160 mmHg using the average of 3 measurements [13]. In the DENERHTN study resistant hypertension was defined by supine office systolic blood pressure of more than or equal to 140 mmHg or diastolic blood pressure of more than or equal to 90 mmHg despite a stable medication regime of maximum tolerated doses of three or more antihypertensive drugs of different classes (including a diuretic drug) with a suitable renal artery anatomy or CT angiogram, Magnetic resonance angiogram, or renal angiogram done within the previous year [15].

**Definition of resistant hypertension**

The studies used a variety of different criteria to define resistant hypertension. Resistant hypertension is defined as blood pressure above a goal despite adherence to at least three optimally dosed antihypertensive medications of different classes, one of which is a diuretic.

**Excluded studies**

Six studies were excluded from the systematic review and meta-analysis, the reason for the exclusion was published data were inadequate for the purpose of the review and meta-analysis.

**Table 3:** Characteristics of studies excluded from meta-analysis

Study	Journal / Year	Research	Group	Sample	Study endpoint
Gavin W	Hypertension 2012	Resistant Hypertension	RND	62	Quality of Life
Marc Dorenkamp	EJH 2013	Resistant Hypertension	RND	N/A	Cost Vs CVS event
Christian Ukena	IJC 2013	Resistant Hypertension	RND	136	HR & Node Function
Oliver Dorr	JIC 2013	Resistant Hypertension	RND	30	Quality of Life
Matthias Lenski	IJC 2013	Resistant Hypertension	RND	36	Effectiveness & Safety
Markus P	IJC 2013	End Stage Renal Function	RND	12	BP & Nerve

**Effects of intervention**

The search strategy and the inclusion criteria and exclusion criteria, through retrieval of the three databases of PubMed, Cochrane Library, and Clinicaltrial.gov, preliminarily acquiring 44 RND for treatment of Resistant Hypertension English literature (Table 1). In 44 articles at the beginning of the screening of the literature, after careful verification, 6 studies were excluded because there was no blood pressure data or the sample size was less than 5 were excluded. Finally, 38 articles of clinical research were selected for the review and meta-analysis. Out of 38 clinical researches, 6 studies are randomized controlled clinical trial, 10 clinical researches are observational control study and the remaining 22 studies are observation studies without control (Table 2).

**Data and Analysis**

**Change in BP over all at 6-month follow-up post-RND**

**Systolic Blood Pressure:** 38 studies included in this review and meta-analysis, a total of 33 studies reported the results of the systolic blood pressure of 6-month follow-up post-RND, Heterogeneity existed between studies ( $I^2=92%$ ,  $P<0.05$ ), The random effects model was used to analyze the results of follow-up systolic blood pressure 6 months post-RND, Results show, RND involved 2313 patients and post-RND follow-up after 6-month with 2135 patients, 6-month systolic blood pressure follow-up rate was 92.30%. 6-month post-RND systolic blood pressure overall meta-analysis effect estimate Difference =-22.50 mmHg Mean, [95% confidence interval (CI: -24.14, -20.86),  $p<0.00001$ ,  $Z=26.90$ ]. RND treatment of resistant hypertension group,

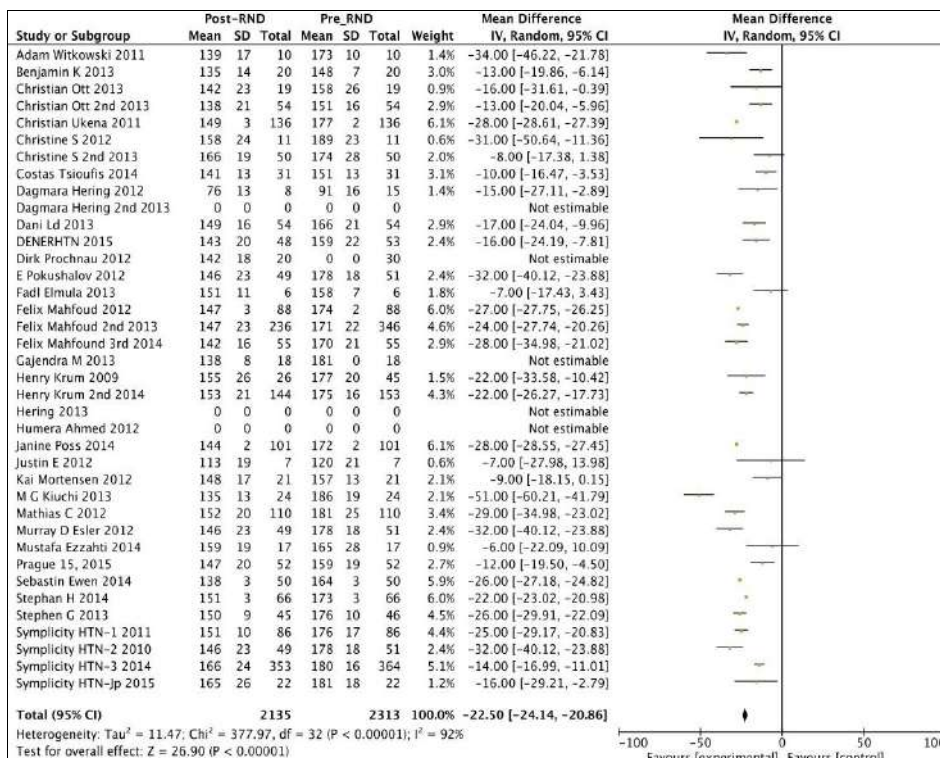
SBP 6-month post-RND when compared with SBP Pre-RND, results indicates that RND was able to reduce the systolic blood pressure by 22.50 mmHg at 6-month follow-up and reached statistical significance.

A meta-analysis of the effect of RND on the reduction of SBP in all studies after 6-month (Analysis 1).

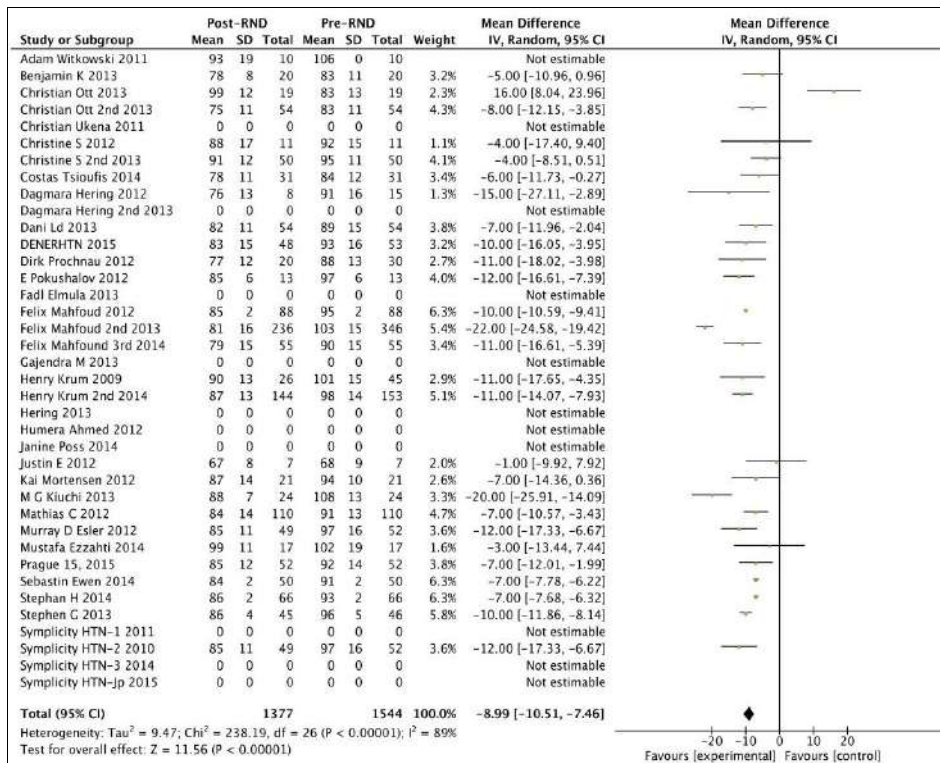
**Diastolic Blood Pressure:** This analysis included 38 studies, a total of 28 studies reported the results of the systolic blood pressure of 6-month post-RND, Heterogeneity existed between studies ( $I^2=89%$ ,  $P<0.00001$ ), Using the random effects model, the results of diastolic blood pressure after 6-months post-RND were analyzed, Results show, RND involved 1544 patients and post-RND follow-up after 6-month with 1377 patients, 6-month diastolic blood pressure follow-up rate was 89.18%. 6-month post-RND diastolic blood pressure overall meta-analysis effect estimate Difference =-8.99 mmHg Mean, [95% confidence interval (CI: -10.51, -7.46),  $p<0.00001$ ,  $Z=11.56$ ]. RND treatment of resistant hypertension group, DBP 6-month post-RND when compared with DBP Pre-RND, results indicates that RND was able to reduce the diastolic blood pressure by 8.99 mmHg at 6-month follow-up and reached statistical significance.

A meta-analysis of the effect of RND on the reduction of DBP in all studies after 6-month (Analysis 2).

**Publication bias evaluation:** The inverted funnel plot shows asymmetry, which suggests that there is a certain degree of bias in the study (Fig. 2 & 3).



**Analysis 1:** Changes in SBP at 6-months post-RND (overall effects)



Analysis 2: Changes in DBP at 6-months post-RND (overall effects)

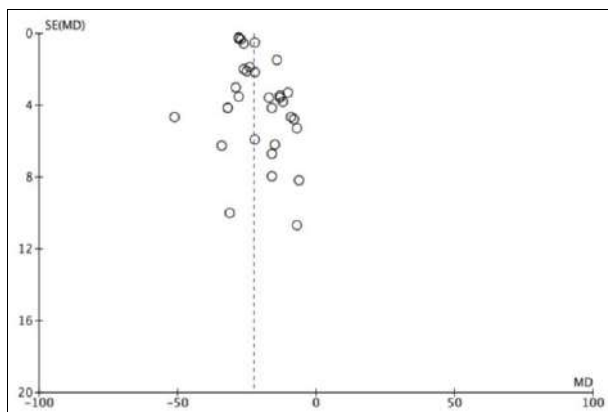


Fig 2: Assessment for publication bias of SBP at 6-Month post-RND

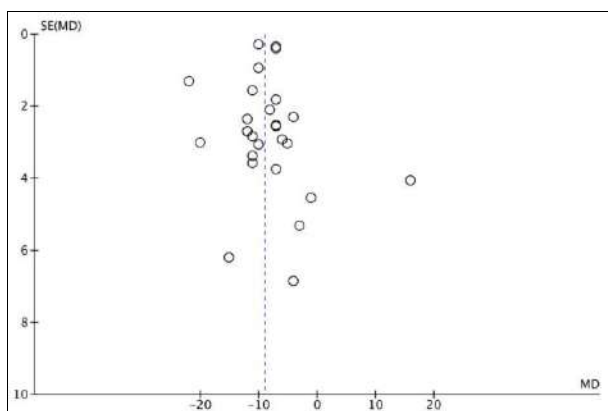


Fig 3: Assessment for publication bias of DBP at 6-Month post-RND

**Subgroup analysis**

**Effects of studies types on blood pressure**

This sub group analyze the effects of different types of studies on systolic blood pressure on 6-month follow-up

post-RND, all 38 articles were included in the research, according to the study category studies were divided into 3 types: (I) randomized controlled trial; (II) observational studies with control group; (III) observational studies without control group. Out of 38 studies only 33 studies reported Systolic BP observation on 6-month follow-up post-RND results. Detailed data can be seen in table 4. There existed different degrees of heterogeneity between the various types of studies, randomized controlled trials (I<sup>2</sup>=93%, P<0.05), observational studies with control group (I<sup>2</sup>=98%, P<0.05), observational studies without control group (I<sup>2</sup>=92%, P<0.05) Therefore, the random effects model analysis were used.

In a randomized controlled trials 550 cases of RND involving the object of study, involving 537 cases post-RND at 6-months follow up; the follow-up rate was 97.63%. Mean Difference =-15.07 mmHg meta-analysis effect estimates and [95% confidence interval (CI: -17.16, -12.89), p<0.00001, Z=13.52]; RND results suggested for treatment of resistant hypertension groups, compared with pre-RND intervention can reduce the systolic blood pressure of 15.7mmHg 6-month post-RND and reached statistical significance;

For the observational studies with control group, RND study involved 566 cases of RND involving 545 patients post-RND at 6-months follow-up; the follow-up rate was 96.28%, the effect estimate for meta-analysis Mean Difference =-26.36mmHg, [95% confidence interval (CI: -26.81, -25.91), p<0.00001, Z=115.13]. The results suggest that RND for the treatment of resistant hypertension group, compared with the pre-RND can reduce the systolic blood pressure of 26.36mmHg and reached statistical significance For the observational studies without control group, RND involved 1124 cases, involving 997 patients post-RND at 6-months follow-up, the follow-up rate was 88.7%, meta-analysis effect estimates for the mean difference =-26.27mmHg, [95% confidence interval (CI: -26.74, -25.81),

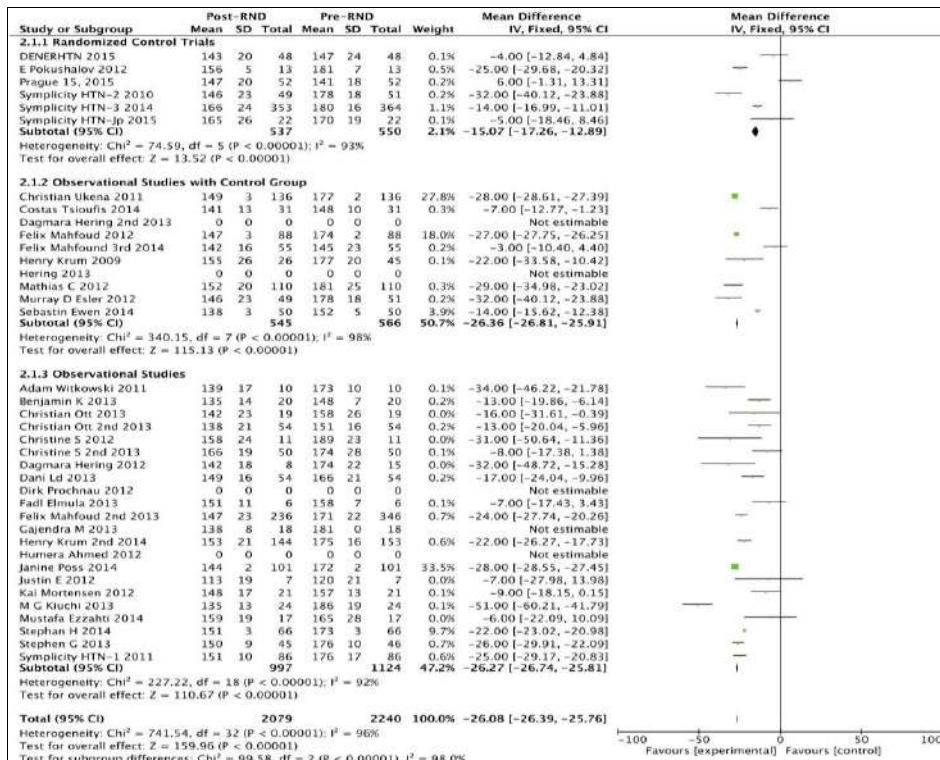
$P < 0.00001$ ,  $Z=110.67$ ]. The results suggested that RND for treatment of resistant hypertension groups, compared with pre-RND can reduce the systolic blood pressure of

26.27mmHg and reached statistical significance. The details of baseline and 6-month post-RND blood pressure in the meta-analysis (Table 4)

**Table 4:** SBP levels of different study types baseline and 6-months post-RND

Research	Journal Year	Arm	Sample	BP Measure	Baseline	6 Month
<b>Randomized Control Trials (6)</b>						
HTN-2	Lancet 2010	RND Control	52 54	OfficeBP 24h ABPM	178/97±18/16 178/98±16/17	-32/-12±23/11 (n=49) -1/0±21/10 (n=51)
Pokushalov	JACC 2012	RND Control	13 14	Office BP	181/97±7/6 178/96±8/4	-25/-10±5/4 -5/-3±8/6
HTN-3	NEJM 2014	RND Sham	364 171	Office BP 24h ABPM	180±16 180±17	-14±24 (n=353) -11±26 (n=171)
HTN-Jp	Circulation 2015	RND Control	22 19	Office BP 24h ABPM	181±18 178±17	165±26 170±19
DENERHTN-15	Lancet 2015	RND Control	48 53	Office BP 24h ABPM	159/93±22/16 155/91±21/13	143/83±20/15 147/85±24/12
Parague-15	Hypertension 2015	RND Control	52 54	Office BP 24h ABPM	159/92±19/14 155/89±17/14	147/85±20/12 141/82±18/13
<b>Observational Control Study (10)</b>						
Henry Krum	Lancet 2009	RND Control	45 5	Office BP	177/101±20/15 173/98±8/9	-22/-11±26/13 (n=26) +14/+9±16/13 (n=5)
Christian Ukena	JACC 2011	RND Control	37 9	Office BP	172±24/94±19 166±23/90±7	N/A
Felix Mahfoud	Hypertension 2012	RND Control	88 12	Office BP	174/95±2/2 184/97±7/5	-27/-10±3/2 -4/-3±6/4
Murry D	Circulation 2012	RND Control	52 54	Office BP 24h ABPM	178/97±18/16 178/98±16/17	-32/-12±23/11 (n=49) -1/0±21/10 (n=51)
Mathias C	JACC 2013	RND Control	110 10	Office BP	181/91±25/13 184/97±19/19	-29/-7±20/14 +13/+6±15/18
Dagmara Hering	JH 2013	RND Control	40 10	Office BP	170/92±19/15 171/93±14/8	N/A
Dagmara Hering	Hypertension 2013	RND Control	25 10	Office BP	164/93±3/3 164/87±8/4	N/A
Costas Tsioufifis	IJC 2014	RND Control	31 12	Office BP 24h ABPM	151/84±13/12 148/86±9/7	141/78±13/11 148/89±10/7
Felix Mahfoud	EHJ 2014	RND Control	55 17	Office BP	170/90±21/15 157/83±15/10	142/79±16/15 145/77±23/15
Sabastin Ewen	Hypertension 2014	RND Control	50 10	Office BP	164/91±3/2 155/87±4/2	138/84±3/2 152/87±5/1
<b>Observational Study (22)</b>						
HTN-1	Hypertension 2011	RND	153	Office BP	176/98±17/15	151/87±10/8 (n=86)
Adam Witkowski	Hypertension 2011	RND	10	Office BP 24h ABPM	173/106±10 140/82	139/93±17/19 No difference
Dagmara Hering	JASN 2012	RND	15	Office BP	174/91±22/16	142/76±18/13 (n=8)
Kai Mortensen	JCH 2012	RND	21	Office BP	159/94±13/10	148/87±17/14
Christine Zuern	Frontiers in Physiology 201	RND	11	Office BP 24h ABPM	189/92±23/15 149/82±19/17	158/88±24/17 142/79±18/15
Humera Ahmed	JACC CI 2012	RND	10	24h ABPM	158/88±16/15	135/76±8/8
Drik Prochnau	Euro-intervention 2012	RND	30	24h ABPM	166/88±22/13	-22/-11 (n=20)
Justin E	IJC 2012	RND	7	Office BP	120/68±21/9	113/67±19/8
M. G. Kiuchi	EHJ 2013	RND	24	Office BP 24h ABPM	186/108±19/13 151/92±18/11	135/88±13/7 132/85±15/11
Dani LD	JACC 2013	Group I GroupII	54 20	Office BP 24h ABPM	166/89±21/15 164/89±20/15	149/82±16/11 158/89±20/11
Stephen G	EHJ 2013	RND	46	Office BP 24h ABPM	176/96±10/5 150/83±5/3	150/86±9/4 140/77±4/2
Christine S	JACC 2013	RND	50	Office BP 24h ABPM	174/95±28/11 157/89±22/16	166/91±19/12
Felix Mahfoud	Circulation 2013	RND	346	Office BP 24h ABPM	171/91±22/15 150/85±20/13	147/81±23/16 142/81±17/13
Christian Ott	CJASN 2013	RND	19	Office BP 24h ABPM	158/83±26/13 159/84±17/13	142/99±23/12 152/80±17/8

Gajendra Manakshe	IHJ 2013	RND	18	Office BP	181/103	138/81 ± 8/4
Benjamin Kaltenbach	CCI 2013	RND	20	Office BP 24h ABPM	148/83 ± 7/11 147/80 ± 10/10	-13/-5 ± 14/8 -11/-4 ± 9/7
Christian Ott	JACC 2013	RND	54	Office BP 24h ABPM	151/83 ± 16/11 150/83 ± 16/10	138/75 ± 21/11 136/76 ± 16/10
Fadi Elmula	Hypertension 2013	RND	6	Office BP 24h ABPM	158 ± 7 152 ± 8	151 ± 11 148 ± 9
Henry Krum	Lancet 2014	RND	153	Office BP	175/98 ± 16/14	153/87 ± 21/13 (n=144)
Mustafa Ezzahti	JH 2014	RND	17	Office BP 24h ABPM	165/102 ± 28/19 152/94 ± 13/10	159/99 ± 19/11 No Change
Janine Poss	CRS 2014	RND	101	Office BP	172 ± 2	144 ± 2
Stephan H	JACC 2014	RND	66	Office BP	173/93 ± 3/2	151/86 ± 3/2



Analysis 3: Influence of the studies type on SBP at 6-month post-RND

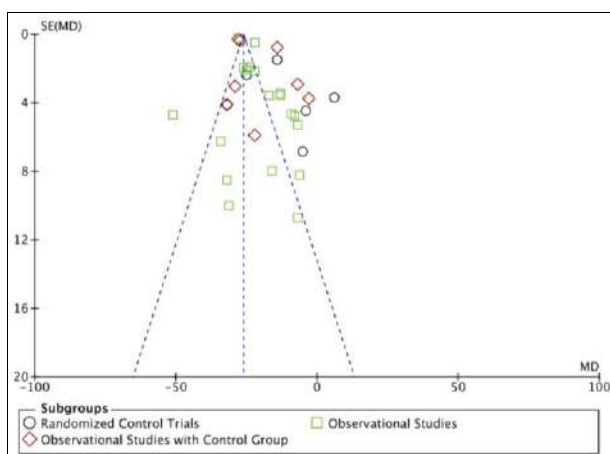


Fig 4: Assessment of publication bias of studies type on SBP at 6-months post-RND

**The effect of RND on 24 hours ambulatory blood pressure**

Effect of RND intervention on 24-hours ambulatory systolic blood pressure monitoring (ABPM) 6-month post-RND intervention analyzed in this sub group. Out of all 38 studies, total of 14 studies reported 24-hour ambulatory

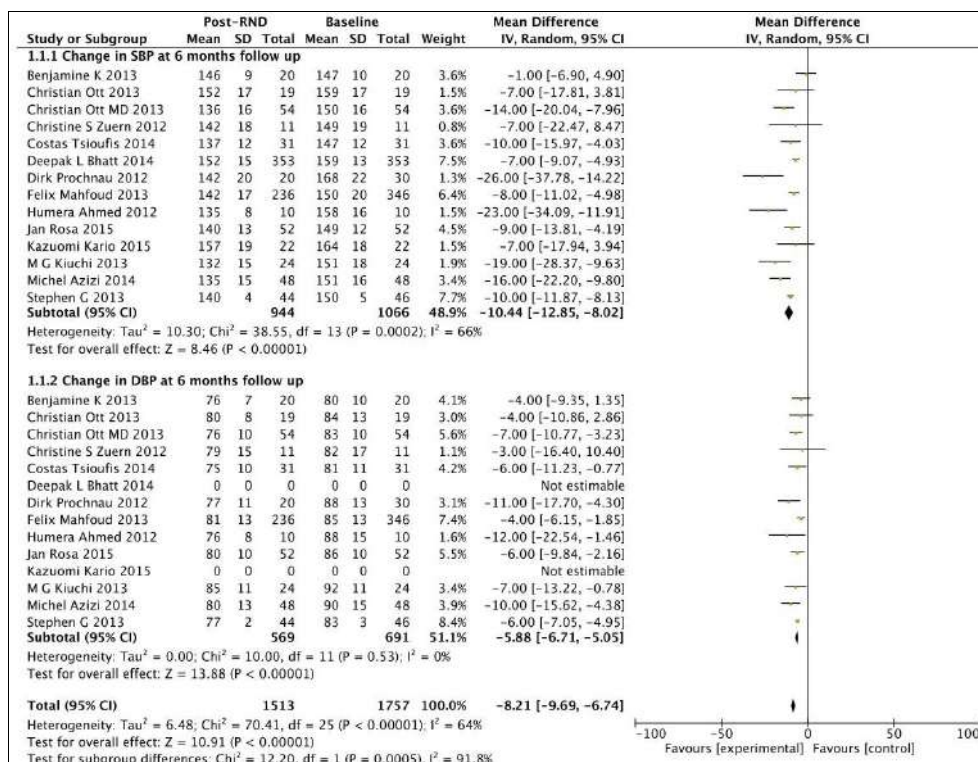
systolic blood pressure result 6-month post-RND. Pre-RND involving 1066 cases and 6 month post-RND follow up of 944 cases. The follow-up rate was 88.55%, using a random effects model, meta-analysis effect estimates for the mean difference = -10.44mmHg, [95% confidence interval (CI: -12.85, -8.02), P=0.0002, Z=8.46]. Among the studies exists heterogeneity (I<sup>2</sup>=66%, P < 0.05). The results indicate that compared with Baseline post-RND intervention after 6 months can lower systolic blood pressure by 10.44 mmHg.

In addition, a total of 12 studies reported 6-month post-RND 24-hour ambulatory diastolic blood pressure results, involving 691 RND cases, post-RND 6-month follow-up of 569 patients. The follow-up rate was 82.34%, meta-analysis effect estimates for the mean difference = -5.88 mmHg, [95% confidence interval (CI: -6.71, -5.05), P < 0.00001, Z=13.88]. Among the studies no heterogeneity existed (I<sup>2</sup>=0%, P = 0.53). Results indicate that compared with Baseline 6-month post-RND intervention decreases 24-hour ambulatory diastolic blood pressure of 5.88mmHg.

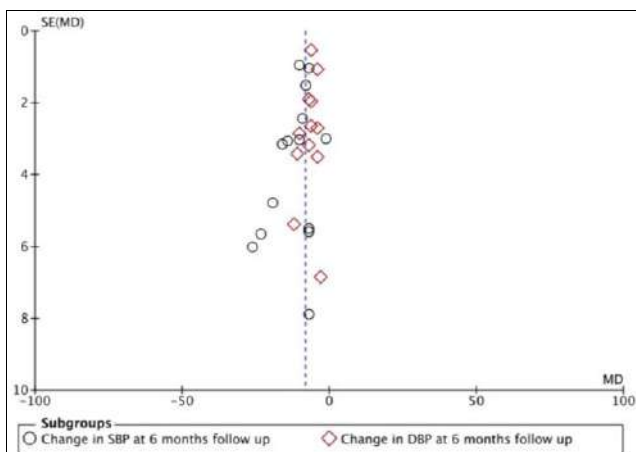
Detailed data on the impact of RND intervention 6-month post-RND 24 hours ambulatory blood pressure after intervention (table 5); 6-month Post-RND meta-analysis of 24-hour ambulatory blood pressure after intervention (Analysis 4).

**Table 5:** Influence of RND on 24h-ABPM at 6-months after RND

Author/Year	Journal	Arm	Size	Method	Baseline	6 Month
Benjamin K 2013	CCI	RND	20	24-h ABPM	147/80 ± 10/10	146/76 ± 9/7
Christian Ott 2013	CJASN	RND	19	24-h ABPM	159/84 ± 17/13	152/80 ± 17/8
Christian Ott MD 2013	JACC	RND	54	24-h ABPM	150/83 ± 16/10	136/76 ± 16/10
Christine S 2012	FIP	RND	11	24-h ABPM	149/82 ± 19/17	142/79 ± 18/15
Costas Tsioufis 2014	IJC	RND	31	24-h ABPM	151/90 ± 16/15	135/80 ± 15/13
Deepak L B 2014	NEJM	RND Sham	364 171	24-h ABPM	159 ± 13 160 ± 15	-7 ± 15(n=353) -7 ± 17 (n=171)
Drik Prochnau 2012	IJC	RND	30	24-h ABPM	166/88 ± 22/13	142/77 ± 20/11 (n=20)
Felix Mahfoud 2013	Circulation	RND	346	24-h ABPM	150/85 ± 20/13	142/81 ± 17/13 (n=236)
Humar Ahmed 2012	JACC CI	RND	10	24-h ABPM	158/88 ± 16/15	135/76 ± 8/8
Jan Rosa 2015	Hypertension	RND	52	24-h ABPM	149/86 ± 12/10	140/80 ± 13/10
Kazuomi Kario 2015	Circulation	RND	22	24-h ABPM	164 ± 18	157 ± 19
M G Kiuchi 2013	EHJ	RND	24	24-h ABPM	151/92 ± 18/11	132/85 ± 15/11
Michel Azizi 2014	Lancet	RND	53	24-h ABPM	151/90 ± 16/15	135/80 ± 15/13 (n=48)
Stephen G 2013	EHJ	RND	46	24-h ABPM	150/83 ± 5/3	140/77 ± 4/2 (n=44)



**Analysis 4:** Influence of RND on 24h-ABPM at 6-month post-RND



**Fig 5:** Assessment of publication bias of 24h-ABPM at 6-months post-RND

**Discussion**

**The results of the current meta-analysis**

Through the RND clinical meta-analysis we found:

1. Major results of this meta-analysis of RND can reduce systolic blood pressure of 22.50mmHg; can reduce the diastolic blood pressure of 8.99 mmHg (follow-up period of 6 months);
2. For Randomized Controlled Trials, RND can lower systolic blood pressure (SBP) 15.07 mmHg
3. For observational studies with control group, RND can reduce systolic blood pressure of 26.36 mmHg
4. For observational studies without control group, RND can reduce systolic blood pressure of 26.27mmHg
5. For 24 hours ambulatory blood pressure monitoring over all clinical research. RND can reduce the systolic blood pressure of 10.44 mmHg; RND can also reduce the diastolic blood pressure of 5.88 mmHg.

The above results can be summarized as the results of this meta-analysis. Results of this meta-analysis were also compared with Symplicity HTN-3 RCT results, including the comparison of different studies types and comparison of 24-hours ambulatory systolic blood pressure.

1. All three studies types in this meta-analysis shows systolic blood pressure decreased significantly compared to Simplicity HTN-3 RCT (table 6).
2. Comparison between different studies types, in randomized controlled trials blood pressure decreases was found to be minimum degree.

3. Comparison between the meta-analysis and Simplicity HTN-3 for 24-hour ambulatory systolic blood pressure also shows significant decrease of systolic blood pressure in meta-analysis compare to Simplicity HTN-3 RCT (table 7)

These results suggest that RND treatment for resistant hypertension, regardless of the clinical design, whether it is the office blood pressure or 24 hours ambulatory blood pressure, RND has a significant antihypertensive effect.

**Table 6:** Comparison of SBP at 6-month follow-up between HTN-3 and Meta-analysis

Research	No of Research	Sample	Heterogeneity test	SBP (mmHg)
<b>HTN-3</b>				
RND	1	364	P > 0.05	14.00
Sham Procedure	1	171	P > 0.05	11.00
<b>Meta-analysis</b>				
Over all Meta Outcome	33	2313	P <0.05	22.50
RCT	6	537	P <0.05	15.07
Studies with Control	8	545	P <0.05	26.36
Studies without Control	19	997	P <0.05	26.27

**Table 7:** Comparison of 24h ABPM at 6-month follow-up between HTN-3 and Meta-analysis

Research	No. Of Research	Sample	Heterogeneity test	SBP (mmHg)
HTN-3 RND Group	1	364	P > 0.05	7.00
HTN-3 (Sham Procedure group)	1	171	P > 0.05	5.00
Meta-analysis	14	944	P <0.05	10.44

**Authors Conclusion**

Hypertension is most common cardiovascular risk factor all over the world including developed, developing and third world countries. Several clinical research and trials have proved sympathetic nerve activity is increased in all types of hypertension. RND intervention technique may provide new treatment options for resistant hypertensive patients. Indeed, several recent trials and studies result suggest that renal nerve denervation decreases sympathetic nerves activity and thus reduces office blood pressure and ABPM. In contrary to Symplicity HTN-1 and HTN-2, blinded sham controlled Symplicity HTN-3 compared with sham intervention failed to reach statistical significance in office BP and ABPM between RND group and Sham group.

Although the results from Symplicity HTN-3 suggested that the effectiveness of RND is still controversial but still 58% of patient in RND group and 48% of patient in the sham group shows the decrease in BP of 10 mmHg or more at 6-month follow up. Symplicity HTN-3 involving 535 patients at 88 centers, 364 RND interventions done by 111 physicians, large number of operating physicians performed only one procedure. This is important as RND procedure may be technically easy procedure but still good exposure is needed to achieve denervation of renal afferent and efferent nerves. Variability in target anatomy also plays a causative role in achieving effective treatment, which may bring difference in clinical results.

Above meta-analysis results suggest that the RND for patients with resistant hypertension can play a hypotensive effect; RND could exert protective effect on patients with resistant high blood pressure through its antihypertensive effect. Catheter based renal nerve denervation for treatment of resistant hypertension is still a technique in its very early development. Despite promising preliminary results, several

uncertainties remain which needs future large scale studies in such patients, as well as examining the effects of RND treatment on mortality and cardiovascular events. Such data could produce helpful recommendations regarding their future us

**Limitations of this meta-analysis**

The main limitations of this meta-analysis: (1) most of the studies were small sample, non-randomized controlled study. According to the inclusion and exclusion criteria, we screened 44 clinical studies of RND, after careful verification, 6 articles were excluded because of no blood pressure data; Finally, this meta-analysis included 38 articles related to the RND clinical study evaluating the effect of RND on blood pressure. A review of the 38 RND clinical studies, 6 studies are of a randomized controlled trial, 10 studies are of prospective observational studies with control group, and the remaining 22 studies are prospective observational studies with no control group. Therefore, although many clinical research results of RND show that RND can effectively reduce the blood pressure of patients with resistant hypertension, blood pressure was significantly higher than that of the sham operated control group (HTN-3 test). However, most of the studies on RND done so far is for small sample and mostly non-randomized study, so the antihypertensive efficiency of RND, still need more researches in future. (2) There is heterogeneity between studies. 38 studies included in the analysis, there are different kinds of heterogeneity, which may leads, to decline in reliability of this meta-analysis. In order to reduce the meta-analysis results significant risk of bias (statistical estimation results is relatively conservative), increase the credibility meta-analysis using a random effects model to estimate the effect.

## Summary

The meta-analysis observed RND could effectively reduce the blood pressure of 22.50 mmHg of office systolic blood pressure and 10.44 mmHg of 24-hour ambulatory systolic blood pressure in cases of resistant hypertension. Subgroup analysis showed that (I) all three subgroup randomized controlled trials, prospective observational studies with control group and prospective observational studies with no control group systolic blood pressure decreased significantly greater than the Symplicity HTN-3 RCT in the experimental group. In a variety of different design types, the blood pressure drop was the minimum in the randomized controlled trial, while there was no significant difference in the systolic blood pressure drop between the control groups. These results suggest that the RND for patients with resistant hypertension can play a hypotensive effect; RND could exert protective effect on patients with resistant high blood pressure through its antihypertensive effect.

## References

- Ruilope LM, Schmieder R. Current status of renal denervation in resistant hypertension. *J Am Soc Hypertens*,2012;6(6):414-146. doi: 10.1016/j.jash.2012.10.001. Epub 2012 Oct 30.
- Pathak A, Girerd X, Azizi M, Benamer H, Halimi JM, Lantelme P, *et al*: French Society of Hypertension: French Society of Cardiology: Working Group on Atheroma, Interventional Cardiology: French Society of Radiology. Expert consensus: renal denervation for the treatment of arterial hypertension. *Arch Cardiovasc Dis*,2012;105(6-7):386-393.
- Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*,2010;376(9756):1903-1909. doi: 10.1016/S0140-6736(10)62039-9. Epub 2010 Nov 17.
- Bertog SC, Sobotka PA, Sievert H. Renal denervation for hypertension. *JACC Cardiovasc Interv*,2012;5(3):249-258. doi: 10.1016/j.jcin.2011.12.011.
- Tellez A, Rousselle S, Palmieri T, Rate WR 4th, Wicks J, Degrange A, *et al*. Renal artery nerve distribution and density in the porcine model: biologic implications for the development of radiofrequency ablation therapies. *Transl Res*,2013;162(6):381-389. doi: 10.1016/j.trsl.2013.07.002. Epub 2013 Jul 30.
- Myat A, Redwood SR, Qureshi AC, Thackray S, Cleland JG, Bhatt DL, *et al*. Renal sympathetic denervation therapy for resistant hypertension: a contemporary synopsis and future implications. *Circ Cardiovasc Interv*,2013;6(2):184-197. doi: 10.1161/CIRCINTERVENTIONS.112.000037.
- Burke GM, Sica DA, Frishman WH. Renal sympathetic denervation for the treatment of systemic hypertension. *Cardiol Rev*,2012;20(6):274-28. doi: 10.1097/CRD.0b013e3182651f91.
- Doumas M, Faselis C, Papademetriou V. Renal sympathetic denervation and systemic hypertension. *Am J Cardiol*,2010;105(4):570-576. doi: 10.1016/j.amjcard.2009.10.027.
- Bruno RM, Ghiadoni L, Seravalle G, Dell'oro R, Taddei S, Grassi G. Sympathetic regulation of vascular function in health and disease. *Front Physiol*,2012;3:284. doi: 10.3389/fphys.2012.00284. eCollection 2012.
- Katholi RE, Rocha-Singh KJ. The role of renal sympathetic nerves in hypertension: has percutaneous renal denervation refocused attention on their clinical significance? *Prog Cardiovasc Dis*,2009;52(3):243-248. doi: 10.1016/j.pcad.2009.09.003.
- Papademetriou V, Rashidi AA, Tsioufis C, Doumas M. Renal nerve ablation for resistant hypertension: how did we get here, present status, and future directions. *Circulation*,2014;129(13):1440-1451. doi: 10.1161/CIRCULATIONAHA.113.005405.
- Pokushalov E, Romanov A, Corbucci G, *et al*. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol*,2012;60(13):1163-1170.
- Bhatt DL, Kandzari DE, O'Neill WW, *et al*. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*,2014;370(15):1393-1401.
- Kario K, Ogawa H, Okumura K, Okura T, Saito S, Ueno T, *et al*: SYMPLICITY HTN-Japan Investigators. SYMPLICITY HTN-Japan - First Randomized Controlled Trial of Catheter-Based Renal Denervation in Asian Patients. *Circ J*,2015;79(6):1222-1229. doi: 10.1253/circj.CJ-15-0150. Epub 2015 Apr 24.
- Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, *et al*: Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet*,2015::385(9981):1957-1965. doi: 10.1016/S0140-6736(14)61942-5. Epub 2015 Jan 26.
- Rosa J, Widimský P, Toušek P, Petrák O, Čurila K, Waldauf P, *et al*. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension*,2015;65(2):407-413. doi: 10.1161/HYPERTENSIONAHA.114.04019. Epub 2014 Nov 24.
- Krum H, Schlaich M, Whitbourn R, *et al*. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*,2009;373(9671):1275-1281.
- Ukena C, Mahfoud F, Kindermann I, *et al*. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol*,2011;58(11):1176-1182.
- Mahfoud F, Cremers B, Janker J, *et al*. Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. *Hypertension*,2012;60(2):419-424.
- Esler MD, Krum H, Schlaich M, *et al*. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. *Circulation*,2012;126(25):2976-2982.

21. Brandt MC, Reda S, Mahfoud F, *et al.* Effects of renal sympathetic denervation on arterial stiffness and central hemodynamics in patients with resistant hypertension. *J Am Coll Cardiol*,2012;60(19):1956-1965.
22. Hering D, Lambert EA, Marusic P, *et al.* Renal nerve ablation reduces augmentation index in patients with resistant hypertension. *J Hypertens*,2013;31(9):1893-1900.
23. Hering D, Lambert EA, Marusic P, *et al.* Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension*,2013;61(2):457-464.
24. Tsioufis C, Papademetriou V, Tsiachris D, Kasiakogias A, Kordalis A, Thomopoulos C, *et al.* Impact of multi-electrode renal sympathetic denervation on short-term blood pressure variability in patients with drug-resistant hypertension. Insights from the EnligHTN I study. *Int J Cardiol*,2015;180:237-242. doi: 10.1016/j.ijcard.2014.11.121. Epub 2014 Nov 26.
25. Mahfoud F, Urban D, Teller D, Linz D, Stawowy P, Hassel JH, *et al.* Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. *Eur Heart J*,2014 Sep 1;35(33):2224
26. Ewen S, Mahfoud F, Linz D, Pöss J, Cremers B, Kindermann I, *et al.* Effects of renal sympathetic denervation on exercise blood pressure, heart rate, and capacity in patients with resistant hypertension. *Hypertension*,2014;63(4):839-845. doi: 10.1161/HYPERTENSIONAHA.113.01985. Epub 2014 Jan 13.
27. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension*,2011;57(5):911-917.
28. Witkowski A, Prejbisz A, Florczak E, *et al.* Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension*,2011;58(4):559-565.
29. Hering D, Mahfoud F, Walton AS, *et al.* Renal denervation in moderate to severe CKD. *J Am Soc Nephrol*,2012;23(7):1250-1257.
30. Mortensen K, Franzen K, Himmel F, *et al.* Catheter-based renal sympathetic denervation improves central hemodynamics and arterial stiffness: a pilot study. *J Clin Hypertens (Greenwich)*,2012;14(12):861-870.
31. Zuern CS, Rizas KD, Eick C, *et al.* Effects of renal sympathetic denervation on 24-hour blood pressure variability. *Front Physiol*,2012;3:134.
32. Ahmed H, Neuzil P, Skoda J, *et al.* Renal sympathetic denervation using an irrigated radiofrequency ablation catheter for the management of drug-resistant hypertension. *JACC Cardiovasc Interv*,2012;5(7):758-765.
33. Prochnau D, Lucas N, Kuehnert H, *et al.* Catheter-based renal denervation for drug-resistant hypertension using a standard electrophysiology catheter. *EuroIntervention*,2012;7(9):1077-1080.
34. Lambert GW, Hering D, Esler MD, *et al.* Health-related quality of life after renal denervation in patients with treatment-resistant hypertension. *Hypertension*,2012 Dec;60(6):1479-1484.
35. Davies JE, Manisty CH, Petraco R, *et al.* First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Eur Heart J*,2014;35(4):276-284.
36. Dorenkamp M, Bonaventura K, Leber AW, *et al.* Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. *Eur Heart J*,2013 Feb;34(6):451-461.
37. Ukena C, Mahfoud F, Spies A, *et al.* Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. *Int J Cardiol*,2013 Nov;167(6):2846-2851.
38. Kiuchi MG, Maia GL, de Queiroz Carreira MA, *et al.* Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood pressure and renal function in patients with chronic kidney disease and resistant hypertension. *Eur Heart J*,2013 Dec;34(28):2114-2121.
39. Id D, Kaltenbach B, Bertog SC, *et al.* Does the presence of accessory renal arteries affect the efficacy of renal denervation? *JACC Cardiovasc Interv*,2013;6(10):1085-1091.
40. Worthley SG, Tsioufis CP, Worthley MI, *et al.* Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur Heart J*,2013;34(28):2132-2140.
41. Dorr O, Liebetau C, Mollmann H, *et al.* Influence of renal sympathetic denervation on quality of life. *J Interv Cardiol*,2013;26(5):536-541.
42. Ukena C, Mahfoud F, Kindermann I, *et al.* Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol*,2011;58(11):1176-1182.
43. Mahfoud F, Ukena C, Schmieder RE, *et al.* Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation*,2013;128(2):132-140.
44. Ott C, Janka R, Schmid A, *et al.* Vascular and renal hemodynamic changes after renal denervation. *Clin J Am Soc Nephrol*,2013;8(7):1195-1201.
45. Manakshe G, Chakravarthi R, Hussaini S, *et al.* Renal sympathetic denervation for treatment of resistant hypertension - indigenous technique. *Indian Heart J*,2013;65(3):239-242.
46. Kaltenbach B, Franke J, Bertog SC, *et al.* Renal sympathetic denervation as second-line therapy in mild resistant hypertension: a pilot study. *Catheter Cardiovasc Interv*,2013;81(2):335-339.
47. Ott C, Mahfoud F, Schmid A, *et al.* Renal denervation in moderate treatment-resistant hypertension. *J Am Coll Cardiol*,2013;62(20):1880-1886.
48. Lenski M, Mahfoud F, Razouk A, *et al.* Orthostatic function after renal sympathetic denervation in patients with resistant hypertension. *Int J Cardiol*,2013;169(6):418-424.
49. Fadl Elmula FE, Hoffmann P, Fossum E, *et al.* Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. *Hypertension*,2013;62(3):526-532.
50. Schlaich MP, Bart B, Hering D, *et al.* Feasibility of catheter-based renal nerve ablation and effects on

- sympathetic nerve activity and blood pressure in patients with end-stage renal disease. *Int J Cardiol*,2013;168(3):2214-2220.
51. Krum H, Schlaich MP, Sobotka PA, *et al*. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*,2014;383(9917):622-629.
  52. Ezzahti M, Moelker A, Friesema EC, *et al*. Blood pressure and neurohormonal responses to renal nerve ablation in treatment-resistant hypertension. *J Hypertens*,2014;32(1):135-141.
  53. Poss J, Mahfoud F, Ukena C, *et al*. Association of vitamin D status and blood pressure response after renal denervation. *Clin Res Cardiol*,2014;103(1):41-47.
  54. Schirmer SH, Sayed MM, Reil JC, *et al*. Improvements in left ventricular hypertrophy and diastolic function following renal denervation: effects beyond blood pressure and heart rate reduction. *J Am Coll Cardiol*,2014 May 13;63(18):1916-1923.