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Renal denervation and blood pressure reduction in resistant hypertension: a systematic review and meta-analysis

Chun Shing Kwok,[1] Yoon K Loke,[2] Shiva Pradhan,[3] Bernard Keavney,[1] Magdi El-Omar,[4] Mamas A Mamas[1,3]

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[1]Cardiovascular Institute, University of Manchester, Manchester, UK
[2]Norwich Medical School, University of East Anglia, Norwich, Norfolk, UK
[3]Leeds General Infirmary, Great George Street, Leeds, UK
[4]Manchester Heart Centre, Manchester Royal Infirmary, Manchester, UK

Correspondence to
Dr Chun Shing Kwok;
shingkwok@doctors.org.uk

ABSTRACT

Objective: The objective of this study is to evaluate the efficacy and safety of renal denervation in patients with resistant hypertension.

Methods: We searched MEDLINE and EMBASE for studies that evaluated the use of catheter-based renal sympathetic denervation compared to a control group and reported blood pressure results at follow-up. Data was extracted from relevant studies and pooled estimates for blood pressure were determined using the inverse variance method for meta-analysis with mean difference.

Results: We identified 12 studies (three randomised controlled trials (n=688), eight prospective observational studies (n=478) and one observational study with matched controls (n=310)). Data from SYMPLICITY HTN-3, the only high-quality blinded randomised control trial suggests that there is no significant difference in change in systolic (−2.30 95% CI −6.90 to 2.30 mm Hg) or diastolic (−1.96 95% CI −4.98 to 1.06 mm Hg) blood pressure at 6 months. The pooled data from two unblinded trials of lower quality showed significant reduction in change in systolic (−27.36 95% CI −37.08 to −24.61 mm Hg) and diastolic blood pressure (−9.62 95% CI −14.51 to −4.72 mm Hg). In terms of safety, SYMPLICITY HTN-3 found no significant differences between treatment and control group in terms of death, myocardial infarction, new onset renal disease, stroke and hypertensive emergencies.

Conclusions: In conclusion, while poor quality unblinded studies provide evidence that renal denervation using catheter-based systems is effective in reducing systolic and diastolic blood pressure in resistant hypertension, the largest randomised controlled trial to date (SYMPLICITY HTN-3) failed to demonstrate any benefit.

KEY MESSAGES

What is already known about the subject?

- Renal denervation has generate significant interest as a method for the treatment of systemic hypertension.
- Several non-blinded studies of renal denervation have shown favourable reductions in blood pressure.

What does this study add?

- The high quality SIMPLICITY HTN-3 trial, failed to demonstrate any significant improvement in blood pressure compared to control, whereas meta-analysis of two RCTs without sham control or blinding found significant reduction in BP with renal denervation.
- Other non-blinded observational studies which are at risk of bias appear to suggest that there are significant reduction in blood pressure with renal denervation.

How might this impact on clinical practice?

- Current evidence provides insufficient evidence to support the use of renal denervation in the treatment of resistant hypertension as the highest quality trial failed to demonstrates this relationship.

INTRODUCTION

Hypertension is an important risk factor for mortality worldwide, causing an estimated 7.5 million deaths per year.[1] Despite receiving hypertensive medications, only 53% of patients with hypertension achieve the recommended blood pressure targets,[2] with a proportion of these patients developing resistant hypertension. Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes, with one of the three agents being a diuretic.[3]

There has been significant interest in targeting the renal sympathetic nervous system in treatment of systemic hypertension. Evidence suggests that sympathetic nervous system over-activity is responsible for the development and maintenance of hypertension.[4] Historical observations have shown that surgical sympathectomy can achieve good blood pressure reduction.[5] More

recently, catheter-based renal denervation that applies low-level radiofrequency (RF) energy to disrupt renal sympathetic nerves within the renal artery wall has emerged as a promising minimally invasive treatment for hypertension. There is growing clinical evidence to suggest that this method effectively and safely reduces blood pressure in patients with resistant hypertension.[6 7] Most recently, however, the SYMPLICITY HTN-3 single blind randomised controlled study reported a failure to reach its primary efficacy endpoint of a reduction in office-based systolic blood pressure from baseline to 6 months.[8 9]

In view of the renewed interest around renal denervation, particularly in light of the SYMPLICITY HTN-3 trial data, we report a systematic review and meta-analysis, which aims to evaluate the efficacy of renal denervation in the treatment of resistant hypertension over time.

METHODS

Study eligibility

Studies were considered for inclusion if they evaluated the use of catheter-based renal sympathetic denervation compared to a control group and reported blood pressure results at follow-up. Single arm studies, case reports, case series, letters and editorials were excluded, but relevant reviews were retrieved to identify additional studies.

Search strategy

Our search was carried out using the OvidSP interface covering MEDLINE and EMBASE from inception until April 2014. Brown search terms were used to reduce likelihood of missing relevant studies (see online supplementary appendix 1).

Two reviewers (CSK and SP) independently checked retrieved titles and abstracts for eligibility, and the relevant abstracts were checked by the other reviewers (YKL and MAM). Finally, two reviewers manually searched bibliographies of included studies, as well as full-text review articles identified from the search (CSK and YKL).

Data extraction

Two reviewers (CSK and SP) extracted data on study, design, patient characteristics, treatment, follow-up and results, and performed quality assessment of included studies. This was checked by the other reviewers (MAM and YKL).

Data synthesis

We planned to perform meta-analysis using RevMan V.5.1.2 (Nordic Cochrane Centre) using the inverse variance method for mean difference if there was not more than a moderate degree of heterogeneity. The random effects model was used because it considers study heterogeneity when generating an average estimate. Statistical heterogeneity was evaluated through the I^2 statistic where values of 30–60% were representing moderate heterogeneity.[10]

Validity assessment

Validity assessment was performed by considering use of blinding, outcome ascertainment, baseline differences, loss to follow-up and selective reporting. A subjective overall risk of bias was also assigned for each study based on these factors. In addition, we planned to conduct asymmetry testing for publication bias provided that there were >10 studies in the meta-analysis and if statistical heterogeneity was <50%.[11]

RESULTS

Twelve studies met the inclusion criteria (study selection is shown in online supplementary appendix 2). These studies included three randomised controlled trials,[7–9 12] eight prospective observational studies[6 13–19] and one observational study with matched controls[20] with a total of 1556 participants (table 1). In general, the participant selection criteria were similar across all but one study that randomised patients with atrial fibrillation to renal denervation and pulmonary isolation versus pulmonary isolation alone.[12]

The risk of bias assessment is shown in online supplementary appendix 3. All included studies were non-blinded except for SYMPLICITY HTN-3. The majority of studies were deemed to be of at least moderate risk of bias. Two studies were only available in abstract form and were deemed to be at high risk of bias.

The renal denervation procedures, control group, follow-up and results are shown in table 2. The majority of studies used the SYMPLICITY catheter system by Medtronic with multiple ablations in both renal arteries. All except two studies did not describe in detail the management received by the control group. In the matched observational study,[20] normotensive and controlled blood pressure controls from the Australian Diabetes, Obesity and Lifestyle database were used. In another randomised trial of patients with atrial fibrillation, patients were randomised to pulmonary vein isolation alone or in combination with renal denervation. All studies included reported increased reductions in systolic and diastolic blood pressure with renal denervation therapy, compared to controls.

Three randomised controlled trials were considered for meta-analysis. However, there was significant statistical heterogeneity when pooling the three randomised controlled trials and it was decided that the two unblinded trials (of moderate-high risk of bias) would be considered separately from the higher quality trial that had used a sham procedure as placebo. Data from SYMPLICITY HTN-3, the only high-quality blinded randomised control trial, suggests that there was no significant difference in change in systolic (−2.30 95% CI −6.90 to 2.30 mm Hg) or diastolic (−1.96 95% CI −4.98 to 1.06 mm Hg) blood pressure at 6 months. The pooled

Table 1 Study design, patient characteristics of parallel group studies of renal denervation versus control in resistant hypertension

	Design	Year	Country	Number of participants (treatment, control)	Mean age	Per cent male	Selection criteria and management
Clinical trials							
Pokushalov *et al*[12]	Randomised trial	NA	Russia, The Netherlands and USA	27 (13, 14)	56 and 57 years	78	Drug-refractory AF or paroxysmal AF, with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs and eGFR ≥45 mL/min/1.73m^2. Diuretics were used in 96% of patients. Patients with secondary causes of hypertension were excluded
SYMPLICITY HTN-2[7]	Randomised trial	June 2009 to January 2010	Europe, Australia and New Zealand	106 (52, 54)	58 years	58	Age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. Diuretics were used in 90% of patients. Patients with significant renal artery stenosis or renal artery anatomy that precluded treatment were excluded
SYMPLICITY HTN-3[8 9]	Randomised trial	September 2011 to January 2014	International	535	57 years	61	Age ≥18 and ≤80 years on stable medical regimen of ≥3 antihypertensives. Office BP ≥160 mm Hg on average of 3 readings on initial screening and confirmatory screening. Exclusions: eGFR<45 mL/min/1.73 m^2, ambulatory blood pressure monitoring average <135 mm Hg, type 1 diabetes, chronic oxygen support, mechanical ventilation, primary pulmonary hypertension or pregnancy
Observational studies							
Brandt *et al*[14]	Prospective observational study	October 2009 to January 2011	Austria and Germany	64 (46, 18)	63 years in both groups	67 and 61	Patients age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. All patients were on diuretic treatment. Patients with secondary causes of hypertension were excluded
Brandt *et al*[15]	Prospective observational study	October 2009 to September 2011	Austria and Germany	120 (110, 10)	64 and 65 years	70 and 80	Patients age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. Diuretics were used in 83% of patients. Patients with secondary causes of hypertension were excluded
Fatum *et al*[16]		NA	Germany	21 (15, 6)	67 and 61 years	59 and 60	Patients age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at

Continued

Table 1 Continued

	Design	Year	Country	Number of participants (treatment, control)	Mean age	Per cent male	Selection criteria and management
	Prospective observational study						least 3 antihypertensive drugs. Unclear use of diuretics. Unclear if patients with secondary causes of hypertensions were included
Franzen *et al*[13]	Prospective observational study	NA	Germany	27 (21, 6)	63 years	NA	Patients with BP ≥150 mm Hg with at least 3 antihypertensive drugs. All patients were on diuretic treatment. Patients with secondary causes of hypertensions were excluded
Krum *et al*[6]	Prospective observational study	June 2007 to November 2008	Australia and Europe	50 (45, 5)	57 years	58	Patients age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. Diuretics were used in 96% of patients. Patients with secondary causes of hypertensions were excluded
Lambert *et al*[20]	Observational study with match controls	NA	Australia	62 treatment, 248 controls	62 years	65	Patients with resistant hypertension. Diuretics were used in 85% of patients. Unclear if patients with secondary causes of hypertension were excluded
Mahfoud *et al*[17]	Prospective observational study	March 2009 to May 2010	Australia and Germany	50 (37, 13)	60 years	74	Patients with age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. All patients were taking diuretics. Patients with renal artery abnormality or stenosis were excluded
Mahfoud *et al*[18]	Prospective observational study	January 2010 to February 2011	Australia and Germany	100 (88, 12)	62 years	61	Patients with age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. All patients had received diuretics. Patients with renal artery abnormality or stenosis were excluded
Ukena *et al*[19]	Prospective observational study	March 2009 to October 2010	Germany, Australia, USA	46 (37, 9). 28 from SYMPLICITY HTN-2	60 years	70	Patients with age >18 years with BP ≥160 mm Hg (≥150 mm Hg with type 2 diabetes) with at least 3 antihypertensive drugs. Diuretics were used in 87% of patients. Patients with secondary causes of hypertension were excluded

AF, atrial fibrillation; BP, blood pressure; eGFR, estimated-glomerular filtration rate; NA, not available.

Table 2 Treatment, follow-up and results of parallel group studies of renal denervation versus control in resistant hypertension

Clinical trials	RD group	Control group	Duration of follow-up	Efficacy results
Pokushalov *et al*[12]	RFA of 8–10 W for 2 min up to 6 lesions and pulmonary vein isolation	Pulmonary vein isolation alone	12 months	Reduction at 6 months Systolic BP Denervation: −28±7 mm Hg Control: −5±5 mm Hg Diastolic BP: Denervation: −10±6 mm Hg Control: −3±6 mm Hg
SYMPLICITY HTN-2[7]	Catheter-based RD with SYMPLICITY Catheter System	Continuation of anti-hypertensive drugs	1, 3 and 6 months	Systolic BP RD group (n=52): Baseline 178±18/96±16 mm Hg. Change at 1 months −20, 3 months −24, 6 months −32 ±23 mm Hg. Control group (n=54): Baseline mm Hg. Change at 1 months 0, 3 months −4, 6 months 1 ±21 mm Hg Diastolic BP RD group (n=52): Baseline 178±17/98±16 mm Hg. Change at 1 months −7, 3 months −8, 6 months −12 ±11 mm Hg. Control group (n=54): Baseline mm Hg. Change at 1 months 0, 3 months −2, 6 months 0 ±10 mm Hg
SYMPLICITY HTN-3[8 9]	Catheter-based RD with SYMPLICITY Catheter System	Sham procedure	1, 6 months	Systolic BP RD group (n=364): Baseline office 179.7±16.1. Value at 6 months: 165.6±23.7. Change from baseline:−14.13±23.93 mm Hg Baseline ambulatory: 159.1±13.2. Value at 6 months: 151.8±16.0. Baseline home: 169.0±15.9. Value at 6 months: 161.1±19.2. Control group (n=171): Baseline office 180.2 ±16.8. Value at 6 months: 168.4±28.6. Change from baseline −11.74±25.94 mm Hg Baseline ambulatory: 159.5±13.5. Value at 6 months: 153.9±19.1. Baseline home: 169.1±16.3. Value at 6 months: 162.8±21.1 Diastolic BP RD group (n=364): Baseline office 96.5±16.6. Value at 6 months: 89.5±16.9

Continued

Table 2 Continued

Clinical trials	RD group	Control group	Duration of follow-up	Efficacy results
				Change from baseline −6.75±15.11 mm Hg Baseline ambulatory:88.0±14.0. Value at 6 months: 83.1±13.7. Baseline home: 89.6±15.9. Value at 6 months: 86.0±16.6. Control group (n=171): Baseline office 98.9 ±15.8. Value at 6 months: 94.1±17.7 Change from baseline −4.79±17.25 mm Hg. Baseline ambulatory: 90.9±14.4. Value at 6 months: 87.4±14.6. Baseline home: 92.9±16.4. Value at 6 months: 90.0±16.4
Observational studies				
Brandt *et al*[14]	RD with SYMPLICITY or Flex catheter (Ardian) with up to 6 ablations at 8 W for 2 min each were performed for both renal arteries	Details of control group not specified	1 and 6 months	Resting systolic BP RD group (n=46): Baseline 180.7±18.3, 1 month 158.2±17.6, 6 months 152.9±22.4 mm Hg. Control group (n=18): Baseline 184.5±22.1, 1 month 181.6±26.3, 6 months 182.8 ±24.6 mm Hg. Resting diastolic BP RD group (n=46): Baseline 95.8±10.1, 1 month 88.6±10.9, 6 months 87±12.9 mm Hg. Control group (n=18): Baseline 98.2±13.6, 1 month 98±12.7, 6 months 99.8±16.5 mm Hg. The average number of antihypertensives was constant for control group 4.8±2.5 while in RD group it deceased in seven patients (15%) which led to a change from 4.7±0.5 to 4.5±1.6 antihypertensives
Brandt *et al*[15]	RD with catheter (SYMPLICITY and Flex by Ardian) with up to 6 ablations at 8 W for 2 min each were performed for both renal arteries	Details of control group not specified	1, 3 and 6 months	Resting systolic BP RD group (n=110): Baseline 181±24.7, 1 month 161.1±22.8, 3 month 159.1±22.1, 6 months 152.1±20 mm Hg. Control group (n=10): Baseline 183.9±21.6, 1 month 181.3±18.5, 3 month 190.6±16.9, 6 months 193.9 ±15.4 mm Hg. Resting diastolic BP RD group (n=110): Baseline 91.4±12.8, 1 month 87±14, 3 months 84±13.1, 6 months 83.7 ±13.5 mm Hg. Control group (n=10): Baseline

Continued

Table 2 Continued

Clinical trials	RD group	Control group	Duration of follow-up	Efficacy results
				95.3±11.5, 1 month 97.1±18.9, 3 months 104.6 ±15.6, 101.5±17.9 mm Hg
Fatum *et al*[16]	Catheter-based bilateral RD	Untreated controls	6 months	At 6 months, office BP reduced by −26/ −7 mm Hg in the RD group (n=15) and no significant changes in the control group (n=6). Baseline 170/89 mm Hg for RD group and 172/ 93 mm Hg for control group
Franzen *et al*[13]	Percutaneous RD with a RFA catheter system	Details of control group not specified	3 and 6 months	Systolic BP RD group (n=21): Baseline 156±13, 3 months 145±13, 6 months 148±17 mm Hg. Control group (n=6): Values did not change significantly
Krum *et al*[6]	RD with catheter (SYMPLICITY) with ablations at 8 W for 2 min each were performed for both renal arteries	Patients with renovascular abnormalities such as severe renal artery stenosis, previous renal stenting/ angioplasty or known dual renal arteries	1, 3, 6, 9 and 12 months	Mean reduction in office blood pressures for treatment group were −14/−10 (95% CI 4/3), −21/−10 (7/4), −22/−11 (10/5), −24/−11 (9/5) and −27/−17 at 1, 3, 6, 9 and 12 months. Mean reduction in office blood pressures were +3/−2, +2/+3, +14/+9, +26/+17 at 1, 3, 6 and 9. At baseline average of 4.7 hypertensive medications and 96% had diuretics. This did not change at follow-up
Lambert *et al*[20]	Bilateral renal nerve ablation by a radiofrequency catheter (SYMPLICITY by Ardian)	Matched normotensive and controlled blood pressure controls from the Australian Diabetes, Obesity, and Lifestyle database	3 months	Post RD BP had reduced by −16±4 and −6 ±2 mm Hg. Baseline BP was 166±3 and 88 ±2 mm Hg in RD group (n=62)
Mahfoud *et al*[17]	Treatment catheter (SYMPLICITY and Flex by Ardian) with RFA lasting up to 2 min with low power of 8 W to obtain up to 6 ablations	Medical therapy	1 and 3 months	Systolic BP RD group (n=37): Baseline 177±3.Change at 1 month −28±2, 3 months −32±4 mm Hg. Control group (n=13): Baseline 184±5. Change at 1 month −8±6, 3 months −5±5 mm Hg. Diastolic BP RD group (n=37): Baseline 96±6. Change at 1 month −10±2, 3 months −12±2 mm Hg. Control group (n=13): Baseline 94±4. Change at 1 month −4±4, 3 months −3±3 mm Hg. While patients were instructed not to change their medications, 13 patients in the treated group had to reduce antihypertensives because of symptoms of hypotension
Mahfoud *et al*[18]	Treatment catheter (SYMPLICITY and Flex by Ardian) with ablations in both	Details of control group not specified	3 and 6 months	Systolic BP RD group (n=88): Baseline 174±2 mm Hg.

Continued

Table 2 Continued

Clinical trials	RD group	Control group	Duration of follow-up	Efficacy results
	renal arteries with up to 8 ablations for 2 min with a maximum of 8 W			Change at 3 month −22.7±2.3, 6 months −26.6 ±2.5 mm Hg. Control group (n=12): Baseline 184 ±7 mm Hg. Change at 3 month −7.2±7.6, 6 months −4.4±6.2 mm Hg. Diastolic BP RD group (n=88): Baseline 95±2 mm Hg. Change at 3 month −7.7±1.3, 6 months −9.7 ±1.5 mm Hg. Control group (n=12): Baseline 97 ±5 mm Hg. Change at 3 month −4.1±4.7, 6 months −3.0±4.3 mm Hg. Number of antihypertensives was 5.7±0.2. At 3 months follow-up 18 patients (18%) had reduced antihypertensives use and 7 (7%) had increased antihypertensive use
Ukena *et al*[19]	Catheter-based RD with SYMPLICITY Catheter System	Details of control group not specified	3 months	Systolic BP RD group (n=37): Baseline 172±24, 3 months 141±21 mm Hg. Change at 3 months 31 ±13 mm Hg. Control group (n=9): Baseline 166 ±23, 3 months 166±25 mm Hg. Change at 3 months 0±17 mm Hg. Diastolic BP RD group (n=37): Baseline 94±19, 3 months 85 ±16 mm Hg. Change at 3 months: −9 ±13 mm Hg. Control group (n=9): Baseline 90±7, 3 months 89±9 mm Hg. Change at 3 months −1 ±5 mm Hg

BP, blood pressure; RD, renal denervation; RFA, radiofrequency ablation.

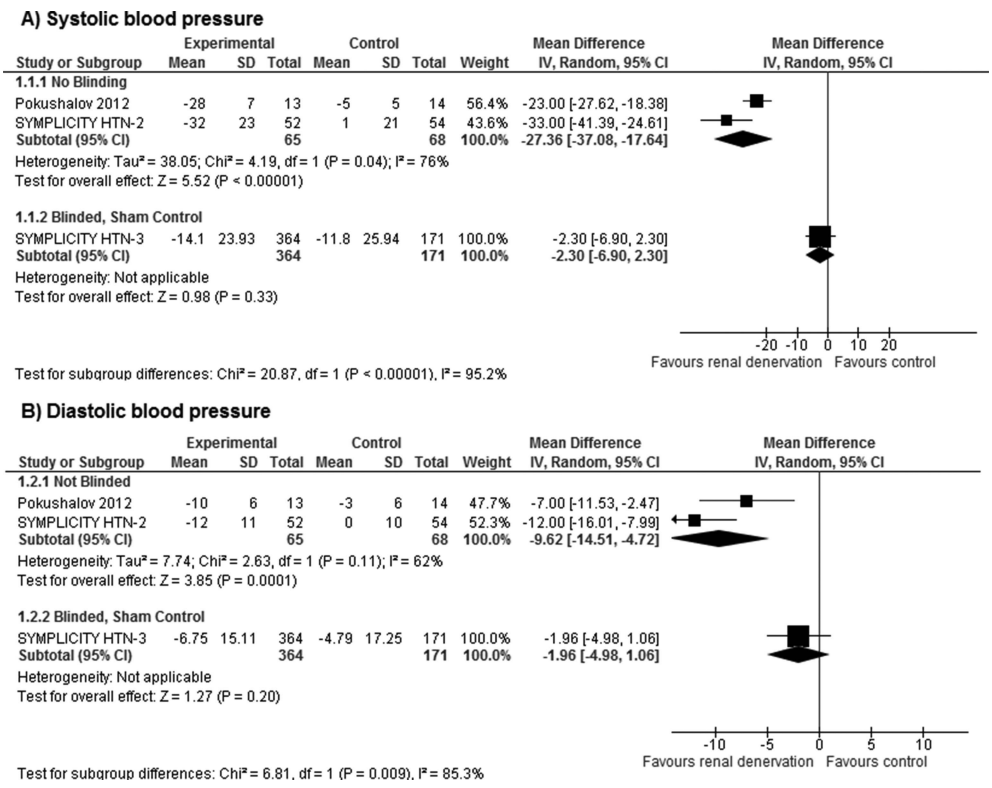

Figure 1 Mean difference in systolic and diastolic blood pressure for the three randomised controlled trials at follow-up postrenal denervation.

data from two unblinded trials of lower quality showed significant reduction in change in systolic (−27.36 95% CI −37.08 to −24.61 mm Hg) and diastolic blood pressure (−9.62 95% CI −14.51 to −4.72 mm Hg). The subgroup testing proves significant differences between the two data set and confirms that moderate-high risk of bias studies give significant effects while low risk of bias studies do not. The results are presented in figure 1.

Results from other observational studies are shown in table 2. Systolic and diastolic blood pressure reductions with renal denervation were reported by all of these studies.[6 13–20]

Only a few studies reported adverse events associated with renal denervation (see online supplementary appendix 4). The SYMPLICITY HTN-3 trial was the only study to report cardiovascular events at 6 months follow-up. There was no significant difference between treatment and control group in terms of death, myocardial infarction, new onset renal disease, stroke and hypertensive crisis or emergency. The most commonly reported adverse event was a pseudoaneurysm at the femoral access site and this was reported in four studies.[6 7 17 18] Other adverse events reported included renal artery dissection,[6] contrast medium allergic reaction,[18] postprocedural hypotension,[7] intraprocedural bradycardia[7] and five cases of hypertensive emergencies requiring admission to hospitalisation (three in the renal denervation group and two in the control group).[7]

DISCUSSION

Our systematic review of three randomised controlled trials with 688 participants has suggested a wide range of reported outcomes associated with the treatment of drug-resistant hypertension by renal denervation. Data derived from the highest quality single-blind, randomised, sham-controlled trial (SYMPLICITY HTN-3) suggests that renal denervation does not produce significant reductions in systolic blood pressure and diastolic blood pressure while lower quality non-blinded randomised controlled trials and observational studies suggest that there are significant reductions in blood pressure with renal denervation. These latter studies are confounded by significant bias.

The choice of control arm is an important consideration when evaluating studies of renal denervation. The SYMPLICITY HTN-3 trial was the first randomised controlled trial to use both a sham-control group and blinding. This raises the issue of possible bias during outcome assessment in the other two randomised controlled trials and non-blinded observational studies where there may have been major differences in the subsequent monitoring and follow-up, or medication adherence and use of cointerventions among patients who had undergone renal denervation. Inadequate blinding may cause bias through differences in recording blood pressure. Interestingly, in the SYMPLICITY studies, the magnitude of reduction in blood pressure following renal

denervation was also significantly greater if recorded through office measurements compared to ambulatory measurements. For example, the decrease in systolic blood pressure at 6 months following renal denervation was between 25 and 30 mm Hg for office blood pressure measurements while on 24 h ambulatory monitoring, it was approximately 10 mm Hg.[6 7 21] The reasons for these differences in magnitude of benefit depending on the modality by which blood pressure is measured remain unclear although ambulatory blood pressure monitors operate in a blinded fashion whereas office blood pressure measurements as in the SYMPLICITY studies are recorded in an unblinded fashion and were therefore subject to bias. The failure of the SYMPLICITY HTN-3 trial to meet the primary blood pressure end point is of interest. The blinded, sham nature of the study would remove many of the biases included in unblinded denervation studies, such as the possibility of decreased medication adherence in patients randomised to the medical treatment arm with improved adherence in the treatment arm. Office-based blood pressure measurements are a significant source of major bias,[22] with significant potential for regression towards the mean. Patients enrolled in hypertension studies have a better chance of meeting the inclusion criteria of the study on a day when their blood pressure is above their own long-term mean. If the patient's blood pressure is then followed up, its average will tend to return to that individual's true mean pressure, even if there was no intervention introducing bias.[22] One aspect that has drawn comment regarding the failure of the SYMPLICITY HTN-3 trial to show efficacy in the treatment of drug-resistant hypertension relates to whether or not participants achieved optimal renal denervation and the potential for different subgroups of patients to respond differently to the denervation procedure.[23–25] Reductions in blood pressure were observed in specific subgroups of patients particularly in non-black patient cohorts and in younger patients, although the absolute reduction in BP in these subgroups was small with an order of magnitude around 5–6 mm Hg. Whether this represents differences in the importance of the sympathetic nerve system in the pathophysiology of drug-resistant hypertension in these cohorts or the efficacy of the procedure in disrupting neural pathways in these patients remains unclear.

While angiographic markers of successful delivery of energy causing vascular disruption (notching) can be seen during the denervation procedure, no reliable markers of renal denervation are available, hence the completeness and extent of renal nerve disruption is uncertain. The unipolar nature of the SYMPLICITY system used in this trial makes it more technically challenging to ensure true circumferential ablation, compared to more contemporary multipolar systems, hence the efficacy of the treatment will be highly operator dependent. Interestingly, the SYMPLICITY HTN-3 trial reported that outcomes between operators performing five or more procedures and those performing fewer than five procedures were similar, with no evidence of a learning curve for high-volume operators when earlier procedures were compared with later ones. It remains unclear whether similar results will be seen with other multipolar systems currently on the market, which have been designed to enable the delivery of a circumferential ablation to the renal artery, or whether the lack of efficacy reported with the SYMPLICITY system represents a class effect. An interesting finding of the SYMPLICITY HTN-3 was that major reductions in blood pressure, which were not present in the previous SYMPLICITY trials, were observed in the control group. One explanation for this was that there was greater exposure to spironolactone in SYMPLICITY HTN-3.[25] The other explanations may relate to the difference in control arm and the use of sham operation, which may lead to improved adherence to medication and the placebo effect.

Despite renal denervation being undertaken predominantly in patients with drug-resistant hypertension who are at significant risk from future cardiovascular events, the very nature of an invasive procedure itself may predispose to potential cardiovascular complications. SYMPLICITY HTN-3 is the first high-quality study to demonstrate the safety of the procedure in terms of cardiovascular disease and mortality end points, with no significant increases in major adverse events, defined as death from any cause, end-stage renal disease, embolic events resulting in end-organ damage, renal-artery or other vascular complications, hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months following the denervation procedure. A few other studies have described procedure-related complications, the most common of which being access site related complications at the femoral access such as haematomas, pseudoaneurysms, etc (approximately 2%), with two reported cases of renal artery dissection (<1%) that needed renal artery stenting.[6 21 26] Furthermore, concerns have been raised regarding the impact of renal denervation on renal function.[27] There is limited long-term evidence from the SYMPLICITY HTN-1, that there was a decrease in estimated-glomerular filtration rate after renal denervation but it is unclear if this is related to changes in medication after the procedure.[28]

Our systematic review has a few strengths. We were able to identify studies that reported mean differences and SDs that enable statistical pooling of results. We have considered studies of different design that varied in their risk of bias. Our systematic review relies on the most up-to-date evidence, including data derived from the largest, highest quality randomised controlled trial.

Study limitations

The major limitations of our review stem from only one high-quality study; the majority were underpowered and longer follow-up is needed. Furthermore, there may have been overlap of some of the studies, for example,

both the Ukena[19] and Mahfoud[17 18] analyses contained a small number of patients that were enrolled as part of the SYMPLICITY HTN-1 and/or SYMPLICITY HTN-2 studies. The sample sizes of studies included were as small as 20 patients, which are insufficient to capture safety events. Non-blinded studies have a risk of bias in outcome assessment and the heterogeneity and lack of management description of the control group is another limitation. These studies lack a standardised diagnostic work-up to exclude secondary hypertension and do not include ambulatory out-of-the-office blood pressure measurement to exclude white coat hypertension or a formal assessment of adherence. Finally, there is the potential for publication bias and selective outcome reporting, particularly with a new technology such as renal denervation where investigators who found no benefit from renal denervation may have decided either to not publish the data or to only report selected significant findings.

In summary, evidence for the efficacy of renal denervation using catheter-based systems in reducing blood pressure in resistant hypertension is derived from unblinded studies that are at risk of bias. The highest quality single blinded randomised controlled trial did not show efficacy in office blood pressure reduction, although it did meet its safety end point. Future studies investigating the efficacy of renal denervation in the treatment of drug-resistant hypertension should be undertaken in a blinded manner, with sham procedures in the control group and ambulatory monitoring to reduce the potential for bias.

Contributors CSK and MAM conceptualised the review and developed the protocol. CSK and YKL analysed the data. CSK, YKL and MAM wrote the manuscript. BK and ME-O contributed to the writing of the manuscript. CSK and SP abstracted the data, which was checked by YKL and MAM. CSK and MAM will act as guarantors for the paper.

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Appendix 1: Search strategy
Ovid SP

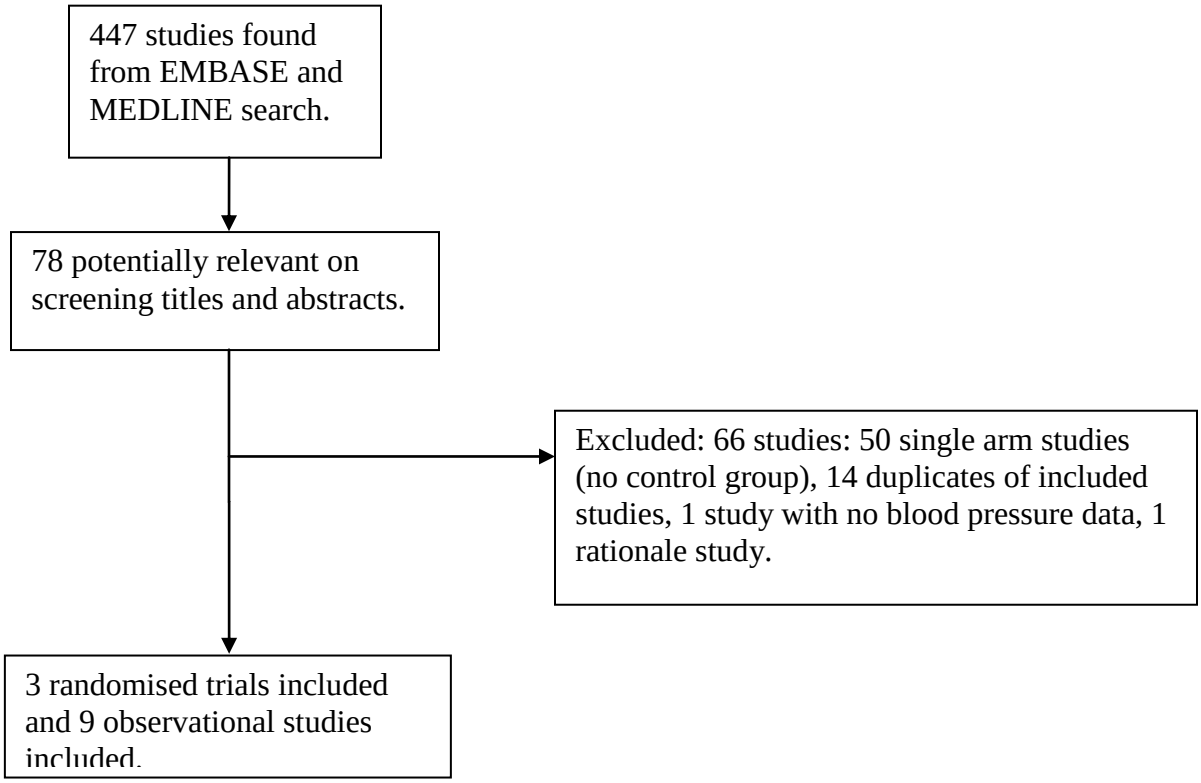
EMBASE, MEDLINE

renal denervation.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, uk] AND. hypertension.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, an, uk]

AND

1. exp research design/
2. exp clinical trial/
3. comparative study/ or placebos/
4. multicenter study.pt.
5. clinical trial$1.pt.
6. random$.ti,ab.
7. (double blind$ or triple blind$3).ti,ab.
8. placebo$.ti,ab.
9. (clinicaladj trial$1).ti,ab.
10. exp epidemiologic research design/
11. (controlled clinical trial or randomized controlled trial).pt.
12. practice guideline.pt.
13. feasibility studies/
14. clinical protocols/
15. exp treatment outcome/
16. or/1-15

Appendix 2: Flow diagram of study selection



Appendix 3: Quality assessment of included parallel group studies of renal denervation versus control in resistant hypertension

Clinical trials	Blinding	Outcome ascertainment	Baseline differences	Lost to follow up	Selective reporting	Risk of bias
Pokushalov 2012 [12]	None.	Unclear but done according tothe standard Joint National Committee VII guidelines.	No significant differences.	No loss to follow up.	Yes, this was a secondary outcome and not the main objective of the trial	Moderate-High
SymplicityHTN-2 2010 [7]	None.	Office blood pressure using automatic oscillometric Omron HEM-705 monitor	No significant differences.	6 lost to follow up.	No.	Moderate-High
Symplicity HTN-3 2014 [8-9]	Sham procedure in control arm. Both the patient and the outcome assessor were blinded.	Office BP using automatic oscillometric Omron monitor	No significant differences.	12 lost to follow-up	No	Low.
Observational studies	Blinding	Outcome ascertainment	Baseline differences	Lost to follow up	Selective reporting	Risk of bias
Brandt 2012a [14]	None.	Automated blood pressure.	No significant differences.	No loss to follow up.	No.	Moderate, full paper.
Brandt 2012b [15]	None.	Automated blood pressure.	No significant differences.	No loss to follow up.	No.	Moderate, full paper.
Fatum 2012 [16]	None.	Unclear.	Not reported.	No loss to follow up.	Abstract. Not full reporting.	High, abstract only.
Franzen 2012 [13]	None.	Automated blood pressure.	Not reported.	No loss to follow up.	Abstract. Not full reporting.	High, abstract only.
Lambert 2012 [20]	None.	Automated blood pressure.	Use of matching but unclear if there are baseline differences.	No loss to follow up.	Study of quality of life. Not full reporting.	Moderate, full paper.

Krum 2009 [6]	None.	Automated blood pressure.	Some baseline differences were present.	2 lost to follow up.	No.	Moderate, full paper.
Mahfoud 2011 [17]	None.	Unclear but done according to the standard Joint National Committee VII guidelines.	No significant differences.	No loss to follow up.	No.	Moderate, full paper.
Mahfoud 2012 [18]	None.	Unclear but done according to the standard Joint National Committee VII guidelines.	No significant differences.	No loss to follow up.	No.	Moderate, full paper.
Ukena 2011 [19]	None.	Manual blood pressure.	No significant differences	No loss to follow up.	No.	Moderate, full paper.

Appendix 4: Adverse events associated with renal denervation

Clinical trials	Safety results
Pokushalov 2012 [12]	No procedural-related complications occurred with regard to either pulmonary vein isolation or renal ablation.
SymplicityHTN-2 2010 [7]	There were no serious complications related to the device or procedure. Minor periprocedural events included one femoral artery pseudoaneurysm, one post-procedure hypotension, one urinary tract infection and one case of back pain. Seven patients (13%) had transient intraprocedural bradycardia requiring atropine. Renal function was unchanged at 6 months. There were 5 hypertensives emergencies 3 patients in RD group and 2 in control group. Other events requiring admission included one case of nausea and oedema, one hypertensive crisis, one TIA, one hypotensive episode and one coronary stent for angina.
Symplicity HTN-3 2014 [8-9]	Major adverse events: 5/361 vs 1/171. Composite safety end point at 6 months: 14/354 vs 10/171. Death: 2/352 vs 1/171. Myocardial infarction 6/352 vs 3/171. New-onset end-stage renal disease 0/352 vs 0/171. Increase in serum creatinine of >50% from baseline. Embolic event resulting in end-organ damage: 1/352 vs 0/171. Renal-artery intervention: 0/352 vs 0/171. Vascular complication requiring treatment: 1/352 vs 0/171. Hypertensive crisis or emergency: 9/352 vs 9/171. Stroke: 4.352 vs 2/171. Hospitalization for new-onset heart failure: 9/352 vs 3/171. Hospitalization for atrial fibrillation: 5/352 vs 1/171. New renal-artery stenosis of >70% 1/332 vs 0/165.
Observational studies	Safety results
Krum 2009 [6]	Two adverse events out of 45 patients one was renal artery dissection upon placement of catheter before delivery of radiofrequency energy and patients was treated with a stent and the other was a pseudoaneurysm at the femoral access site.
Mahfoud 2011 [17]	One patient developed a pseudoaneurysm at femoral access site that was treated without further sequelae.
Mahfoud 2012 [18]	Two patient developed pseudoaneurysm at the femoral access site which was treated with compression. One patient had contrast medium allergic reaction.