NHS England

Evidence Review:

Renal denervation for Resistant Hypertension

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Prepared by	Turnkey Clinical Evidence Review Team on behalf of NHS England specialised commissioning

Contents

1. Introduction

Hypertension, also known as high blood pressure, is a chronic medical condition in which the blood pressure in the arteries is persistently elevated. This puts extra strain on the arteries and heart, which can lead to serious conditions such as heart attack, heart failure, kidney disease, stroke, or dementia.

There are several ways to reduce blood pressure. For most people, changes in lifestyle such as eating less salt or losing weight can be sufficient to reduce the risks. Some individuals however, will require medication with one or more antihypertensive medications.

There are a small number of people who will still not be able to reduce their blood pressure to normal levels (a "clinic" systolic blood pressure of <160 mm Hg). At the point where they have tried three or more of the conventional antihypertensive agents they will be diagnosed with resistant hypertension.

It is known that the renal nerves (sympathetic nerves) can be a main cause of hypertension when they become overactive. The renal denervation procedure inserts a device through the groin to deliver radiofrequency energy to deaden the nerves associated with the renal arteries. There is clinical interest as to whether renal denervation may be effective as a treatment option for individuals with drug-resistant hypertension.

2. Summary of results

This evidence review has sought to address the following research questions:

Research question 1: Is renal denervation clinically effective in patients with resistant hypertension (RH)?
Research question 2: Is renal denervation cost effective in patients with resistant hypertension (RH)?

In summary, the current evidence base is inconclusive for the clinical effectiveness of renal denervation (RDN) over current standard of care treatments for resistant hypertension with the more recent randomised control trial and meta-analysis indicating nil to modest impact of RDN on lowering blood pressure.

Question 1. Is renal denervation clinically effective in patients with resistant hypertension?

Early studies from 2010 onwards suggested that renal denervation (RDN) was a more clinically effective method of treatment than standard of care pharmacological interventions for patients with resistant hypertension (RH) (Bhatt et al., 2011, Esler et al., 2011). Meta-analyses based on such studies therefore found a significant effect in RH patients treated with RDN, which, added to the high levels of safety reported, resulted in general support for the use of this technology (Howard et al., 2013, Davis et al., 2013). More recently, Azizi et al., (2015) also showed a significant result in RDN patients against a control population that received stepped-care anti-hypertensive treatment).

The effectiveness of RDN was most recently challenged by the PRAGUE-15 trial (Rosa et al., 2015), which reported no significant benefits of RDN over an intensified pharmacological regimen including spironolactone. However, these RCTs were non-blinded, which made it difficult to ascertain the extent of the placebo effect (Jin et al., 2014). Therefore, SYMPLICITY HTN-3, a blinded RCT with a control group that received a placebo procedure (angiogram in lieu of renal denervation), was much anticipated.

In 2014, the 6-month results from the SYMPLICITY HTN-3 trial were published (Bhatt et al., 2014), and it reported that RDN produced insignificant reductions in both office and ambulatory systolic blood pressure. This data, however, was not immediately conclusive. Howard et al. (2013) concluded that even if results from this blinded RCT were to report lower blood pressure reductions than expected, a significant clinical impact would still be felt as long as blood pressure drops were in the region of 10 - 16 mm Hg.

Recently, the 12-month ambulatory blood pressures from the SYMPLICITY HTN-3 trial were published (Bakris et al., 2015). Ambulatory blood pressures are regarded as a more accurate measure compared to office blood pressure due to elimination of the white coat effect and averaging over 24 hours. The 6-month and 12-month results together paint an inconclusive story. Interestingly, the blinded trial produced no significant difference from the placebo - the difference in systolic blood pressure (SBP) reduction at 12 months was −2.39 mm Hg, which

would itself suggest that the RDN procedure is not clinically effective (Bhatt et al., 2014, Bakris et al., 2015). However, unlike previous trials, patients in the placebo group actually responded to the control (placebo) procedure, with systolic blood pressure (SBP) drops of −11.74±25.94 mm Hg in the sham control group at 6 months (Bhatt et al., 2014). This could be due to the Hawthorne effect, where patient medication adherence is improved in both study arms (Kwok et al., 2014). Meanwhile, the RDN group registered an SBP drop of −14.13±23.93 mm Hg at 6 months (Bhatt et al., 2014) and 15.5 +/- 24.1 mm Hg at 12 months (Bakris et al., 2015). Although the differences were not significant between the RDN and placebo group the magnitude of the drop falls within the range that Howard et al. (2013) indicated would be clinically meaningful.

Siagian et al. (2014) stated that the limitations of SYMPLICITY HTN-3 trial included the regression-to-mean phenomenon, a lower baseline blood pressure than other studies in the past (159.1 mm Hg vs 180 mm Hg), and that there were no measurements taken to affirm the extent of the renal denervation and that the operators were inexperienced, although the authors of the study (Bhatt et al., 2014) claimed that operators who had operated five times on patients did not produce better blood pressure results in the last operation compared to the first.

Patients in the SYMPLICITY HTN-3 trial also consumed higher amounts of the antihypertensive medication spironolactone (Kwok et al., 2014), which acts mechanistically similar to RDN (Pancholy et al., 2014). Such vasodilators have been shown to be a predictor for non-response in renal denervation procedures (Siagian et al., 2014). In addition, no urine test was taken to verify patient medication adherence, and results from this trial are only strictly applicable to catheters using the same radiofrequency-based technology found in the Simplicity catheters manufactured by Medtronic, and may not be directly translatable for ultrasound ablation catheters such as PARADISE (ReCor Medical, Ronkoma, New York) due to the unipolar nature of the SYMPLICITY system, which makes it more technically difficult to ensure circumferential ablation compared to more modern multipolar systems (Kwok et al., 2014).

Fadl et al., 2015 have reported a high quality meta-analysis of the data from 7 recently published randomized controlled trials (SYMPLICITY HTN-2 SYMPLICITY HTN-3 OSLO RDN PRAGUE-15 DENERHTN SYMPLICITY-FLEX SYMPLICITY HTN-Japan) which provides conclusive evidence that RDN is effective in a carefully selected patient sub-populations (stage I–II hypertension, low risk factor profile and evidence of sympathetic overactivity). The BP-lowering effect of RDN on top of continued or optimized antihypertensive drug treatment is modest, averaging 4.9 mmHg systolic and 3.5 mmHg diastolic on office measurement, and 2.8 mmHg systolic and 1.5 mmHg diastolic on 24 h ambulatory monitoring in the short term.

The current evidence base therefore fails to provide conclusive evidence in favour of RDN's clinical effectiveness over current standard of care treatments for resistant hypertension.

Question 2. Is renal denervation cost effective in patients with resistant hypertension?

There is only one paper in the literature search that provided evidence for the cost effectiveness of renal denervation in the context of resistant hypertension. Gladwell et al., 2014 concluded that RDN resulted in a greater health benefit to the patient compared to standard of care pharmacological intervention alone, extending QALYs from 12.16 to 12.77. This added health benefit came at a cost of £4805 per QALY. However, Gladwell et al., 2014 published their findings in the same year as the publication of SYMPLICITY HTN-3 trial results but were not able to include these results in their economic model. Given the reported lack of clinical effectiveness in SYMPLICITY HTN-3 (Bhatt et al., 2014, Bakris et al., 2015), the cost effectiveness of this treatment likely to impact the cost-effectiveness analysis. An updated model including results from this blinded RCT is needed before the cost effectiveness of RDN for RH can be accurately ascertained.

3. Research questions

Is renal denervation clinically effective in patients with resistant hypertension?

Is renal denervation cost effective in patients with resistant hypertension?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Level	Study design and intervention			Outcomes					Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1++	Systematic + Meta Analysis	5652 patients screened, 985 qualified. 397 randomised to control group and 588 to RDN intervention	RDN with SYMPLICITY™ catheter system	Clinical effectiveness of the intervention compared to existing interventions	Systolic/diastolic blood pressure (SBP and DBP) at office and 24 hour ambulatory	Office SBP reduction at 6-month follow up. RDN: -16.5 mm Hg (CI: -24.0 to -9.0 mm Hg, p=0.002), Control: -11.6 mm Hg (CI: -20.3 to -2.8 mm Hg, p=0.09). In summary the BP-lowering effect of RDN on top of continued or optimized antihypertensive drug treatment is modest, averaging 4.9 mmHg systolic and 3.5 mmHg diastolic on office measurement, and 2.8 mmHg systolic and 1.5 mmHg diastolic on 24 h ambulatory monitoring.	-	-	Fadl Elmula, Fadl Elmula M.; Jin, Yu; Yang, Wen-Yi; Thijs, Lutgarde; Lu, Yi-Chao; Larstorp, Anne C.; Persu, Alexandre; Sapoval, Marc; Rosa, Ján; Widimský, Petr; Jacobs, Lotte; Renkin, Jean; Petrák, Ondřej; Chatellier, Gilles; Shimada, Kazuyuki; Widimský, Jiři; Kario, Kazuomi; Azizi, Michel; Kjeldsen, Sverre E.; Staessen, Jan A.; European Network Coordinating Research On Renal Denervation (ENCOReD) Consortium. Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension. Blood Press. 2015;24(5):263-274.	-	-	Population: Systolic/ diastolic office and 24 h BP 168.5/93.3 mmHg and 151.8/86.1 mmHg, respectively, and estimated glomerular filtration rate (eGFR) 79.3 ml/min/1.73 m². Average age of enrolment was 58.1 years (range 18-85). Control (n=397) and RDN with SYMPLICITY catheters (n=588). Comments: Robust methodology. The pooled analysis was limited to randomised trial. The patient population was tetsed for heterogeneity and sensitivity analysis included impact of exclusion of each trial. Authors highlight that RDN can be effective in a carefully selected patient sub-population (stage I–II hypertension, low risk factor profile and evidence of sympathetic overactivity). The key limitation of the analysis was short follow-up time hence leaving verdict open on the sustained a benefit on BP reduction.
1+	RCT	535 in total; 364 in RDN group, 171 in control group	RDN delivered by the Symplicity Renal Denervation System (Medtronic, Santa Rosa, California)	Clinical effectiveness of the intervention compared to existing interventions	Mean change in office and ambulatory SBP at 6 and 12 months	12-month office SBP = 15.5 +/- 24.1 mm Hg, 6 month office SBP = 18.9 +/- 25.4 mm Hg (p=0.025). 24-h SBP change was not significantly different at 12 months (p=0.2249)	-	-	Bakris, George L.; Townsend, Raymond R.; Flack, John M.; Brar, Sandeep; Cohen, Sidney A.; D'Agostino, Ralph; Kandzari, David E.; Katzen, Barry T.; Leon, Martin B.; Mauri, Laura; Negoita, Manuela; O'Neill, William W.; Oparil, Suzanne; Rocha-Singh, Krishna; Bhatt, Deepak L.; SYMPLICITY HTN-3 Investigators. 12-month blood pressure results of catheter-based renal artery denervation for resistant hypertension: the SYMPLICITY HTN-3 trial. J. Am. Coll. Cardiol. 2015;65(13):1314-1321.	-	-	Population: Subjects were required to have a seated office SBP of at least 160 mm Hg at their first screening visit, and a 24-h ambulatory SBP of at least 135 mm Hg. Mean age of RDN group: 57.9 years +/- 10.4. Mean age of sham control group: 56.2 years +/- 11.2. Comments: This is a set of results from the SYMPLICITY HTN-3 trial, a very well-conducted blinded RCT for RDN on RH patients. This publication reports office systolic and diastolic blood pressure at 12 months. The results suggest that RDN is not more effective than the sham procedure in reducing blood pressure in patients with resistant hypertension.

2+	Cohort	998	RDN	Clinical effectiveness of the intervention	Office SBP and DBP after 6 months	At 6 months, the changes in office and 24-hour systolic BPs were −11.6±25.3 and −6.6±18.0 mm Hg for all patients (P<0.001 for both) and −20.3±22.8 and −8.9±16.9 mm Hg for those with severe hypertension (P<0.001 for both)	-	-	Böhm, Michael; Mahfoud, Felix; Ukena, Christian; Hoppe, Uta C.; Narkiewicz, Krzysztof; Negoita, Manuela; Ruilope, Luis; Schlaich, Markus P.; Schmieder, Roland E.; Whitbourn, Robert; Williams, Bryan; Zeymer, Uwe; Zirlik, Andreas; Mancia, Giuseppe; GSR Investigators. First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Hypertension 2015;65(4):766-774.	-	-	Population: 323 adult patients (>18 years) with severe hypertension. Mean baseline office systolic BP was 163.5±24.0 mm Hg for all patients and 179.3±16.5 mm Hg for the severe cohort. The corresponding baseline 24-hour mean systolic BPs were 151.5 ± 17.0 and 159.0 ± 15.6 mm Hg. Comments: The study was based on the Global SYMPLICITY registry, a prospective, open-label, multicenter registry. However, this registry-based study was limited by the lack of clear inclusion criteria and no standardised follow-up procedures; hence, adverse events could be underreported. There was no control group undergoing a sham procedure.
3	Cohort	29	RDN	Clinical effectiveness of the intervention	SBP decrease after 6 and 12 months	Mean 24-hour BP decreased by 6±12/5±7 mm Hg 12 months after RDN	-	-	Verloop, Willemien L.; Spiering, Wilko; Vink, Eva E.; Beeftink, Martine M. A.; Blankestijn, Peter J.; Doevendans, Pieter A.; Voskuil, Michiel. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. Hypertension 2015;65(4):751-757.	-	-	Population: Thirty-four percent (n=10) of patients did not use any antihypertensive drugs at baseline, 74% of patients (n=25) did not use any antidiabetic drugs at baseline. >18 years, mean age of 60 ± 9 years. Comments: This study was a pilot study with only 29 patients, which is its biggest limitations. In addition, the study only observed results from RDN intervention, and did not have a control group to compare the effects of RDN against.

2-	Systematic	883	Renal sympathetic nerve ablation	Clinical effectiveness of the intervention compared to existing interventions	SBP and DBP change	Change in SBP after 6 months of RDN ranged from -10 to -37 mmHg Change in DBP after 6 months of RDN ranged from -7.4 to -12.4 mmHG	-	-	Siagian, Minarma; Ferly, Aldo; Irianti, Arinna; Kurniati, Arky; Low, Florence; Riza, Ras A.. Effectiveness of renal denervation for treatment of resistant hypertension: an evidence-based case report. Acta Med Indones 2014;46(4):341-347.	-	-	Population: not stated. Comments: The authors did not have a robust conclusion backed by statistical analysis. The results were not rigorously cross-compared, and the authors drew a conclusion against the presented statistical evidence on the basis of "superior methodology" in one trial, suggesting heavy bias. However, they were correct to point out that the one trial (Bhatt et al., 2014) was a high quality blinded RCT with a large patient sample size
1+	RCT	1416, 106 of those were randomly assigned to treatment (53 patients in each group, intention-to-treat population) and 101 analysed because of patients with missing endpoints (48 in the renal denervation group, 53 in the control group, modified intention-to-treat population	RDN delivered by the Symplicity Renal Denervation System (Medtronic, Santa Rosa, California)	Clinical effectiveness of the intervention	Mean change in daytime ambulatory systolic blood pressure from baseline to 6 months.	Systolic blood pressure at 6 months was −15·8 mm Hg (95% CI −19·7 to −11·9) in the renal denervation group and −9·9 mm Hg (−13·6 to −6·2) in the group receiving SSAHT alone, a baseline-adjusted diff erence of −5·9 mm Hg (−11·3 to −0·5; p=0·0329).	Mean changes in all other blood pressure variables from baseline to 6 months assessed by ambulatory, home, and office blood pressure; proportion of patients with controlled blood pressure at 6 months (<135/85 mm Hg by daytime, <120/70 mm Hg by night-time, and <130/80 mm Hg by 24-h ABPM); adherence to antihypertensive medication by three categories according to the MMAS-8	Daytime ambulatory systolic blood pressure: mean baseline-adjusted difference between the two groups of −5·9 mm Hg (95% CI −11·3 to −0·5 mm Hg, p=0·0329. night-time and 24-h ambulatory systolic blood pressure. The daytime ambulatory systolic blood pressure levels achieved at 6 months did not differ significantly between the two groups.	Azizi, Michel; Sapoval, Marc; Gosse, Philippe; Monge, Matthieu; Bobrie, Guillaume; Delsart, Pascal; Midulla, Marco; Mounier-Véhier, Claire; Courand, Pierre-Yves; Lantelme, Pierre; Denolle, Thierry; Dourmap-Collas, Caroline; Trillaud, Hervé; Pereira, Helena; Plouin, Pierre-François; Chatellier, Gilles; 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.	-	-	Population: 1416 patients screened for eligibility, 101 patients reported: RDN (n=48) and SSAH control group (n=53). Average age: 55.2 years. Comments: This is the set of results from the DENERHTN trial. This is a high-quality study with a very large patient sample size, but is limited by the fact that it was not blinded, and that the control was not a sham procedure, but a treatment procedure.

3	Cohort	43	RDN using the EnlighHTN ablation catheter (multi-electrode) (St. Jude Medical)	Clinical effectiveness of the intervention compared to existing interventions	SBP change	At 6 months post-RDN, office BP and 24-hour BP were reduced by 25.6/10.3mmHg and by 10.2/6mmHg (p b 0.001 for all cases), respectively; The rates of systolic and diastolic 24-hour BP variation were decreased 6 months after RDN, (from 0.40/0.30 to 0.34/0.24, p = 0.030/0.006, respectively)	-	-	Tsioufis, Costas; Papademetriou, Vasilios; Tsiachris, Dimitris; Kasiakogias, Alexandros; Kordalis, Athanasios; Thomopoulos, Costas; Dimitriadis, Kyriakos; Tousoulis, Dimitrios; Stefanadis, Christodoulos; Parati, Gianfranco; Worthley, Stephen. 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.	-	-	Population: 31 patients with drug-resistant uncontrolled hypertension, 6 months after RDN. 12 patients resistant hypertensives matched for office BP as control group. Average age 61.1 ± 10 years. Comments: Authors conclude that a multi-frequency catheter does not decrease blood pressure variability. A strength of this study was that 24-h ambulatory blood pressure was taken, which ought to minimise biases due to the white coat effect and the regression-to-mean.phenomenon. But this study was non-randomised and had a small sample size and should be treated as a pilot study, so limited conclusions can be drawn. There were also only two data points on BP; one at baseline and one at 6 months. It would be ideal for 3 month follow-ups to be conducted up to a minimum of 12 months.
1+	RCT	106 patients were randomised to renal denervation (n=52), or intensified pharmacological treatment (n=54)	RDN delivered by the Symplicity Renal Denervation System (Medtronic, Santa Rosa, California)	Clinical effectiveness of the intervention compared to existing interventions	SBP at 6 months, office and ambulatory	RDN: systolic office blood pressure: −12.4 [95% confidence interval: −17.0, −7.8] mm Hg. Pharmacological group: −14.3 [95% confidence interval: −19.7, −8.9] mm Hg. 24-hour average systolic blood pressure after 6 months: −8.6 [95% confidence interval: −11.8, −5.3]; in renal denervation versus −8.1 [95% confidence interval: −12.7, −3.4] mm Hg in pharmacological group	-	-	Rosa, Ján; Widimský, Petr; Toušek, Petr; Petrák, Ondřej; Čurila, Karol; Waldauf, Petr; Bednář, František; Zelinka, Tomáš; Holaj, Robert; Štrauch, Branislav; Šomlóová, Zuzana; Táborský, Miloš; Václavík, Jan; Kociánová, Eva; Branny, Marian; Nykl, Igor; Jiravský, Otakar; Widimský, Jiří. 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.	-	-	Population: Systolic blood pressure of 159±17 and 155±17 mm Hg and average number of drugs 5.1 and 5.4, respectively. Subgroups were: 1. a catheter-based RDN plus optimal antihypertensive treatment group 2. an intensified pharmacological treatment group (PHAR), including spironolactone if tolerated and not contraindicated. Comments: Results from the Prague-15 study. The patient sample size was comparable to the SYMPLICITY HTN-2 trial, so it was a moderately-sized trial. No sham control procedure was introduced, which may affect the variability of results and also patient adherence due to the Hawthorne effect. This study used experienced clinicians who were familiar with the SYMPLICITY catheters, which should minimise operator error.

3	RCT	-	RDN	Clinical effectiveness of the intervention compared to existing interventions	Difference in office systolic blood pressure (SBP) change at 6 months	Non-African-American patients receiving RDN: –15.2+23.5 mm Hg, sham treatment group: –8.6+24.8 mmHg, (P = 0.012)	-	-	Kandzari, David E.; Bhatt, Deepak L.; Brar, Sandeep; Devireddy, Chandan M.; Esler, Murray; Fahy, Martin; Flack, John M.; Katzen, Barry T.; Lea, Janice; Lee, David P.; Leon, Martin B.; Ma, Adrian; Massaro, Joseph; Mauri, Laura; Oparil, Suzanne; O'Neill, William W.; Patel, Manesh R.; Rocha-Singh, Krishna; Sobotka, Paul A.; Svetkey, Laura; Townsend, Raymond R.; Bakris, George L.. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur. Heart J. 2015;36(4):219-227.	-	-	Population: Resistant hypertension were randomized 2 : 1 to RDN (n=364) or sham (n=171). Comments: Analysis of results from the SYMPLICITY HTN-3 trial. The paper mainly aimed to run a multivariate analysis to better understand why the SYMPLICITY HTN-3 trial failed to produce the anticipated positive results supporting RDN efficacy.
1+	Systematic + Meta Analysis	1476 patients over 12 studies; controlled trials (n=688controlled trials (n=688), prospective observational studies (n=478), observational study with matched controls (n=310)	Renal sympathetic nerve ablation	Clinical effectiveness of the intervention compared to existing interventions	Systolic blood pressure, diastolic blood pressure	At 6 months follow up: SYMPLICITY HTN-3: SBP = −2.30 mm Hg (95% CI −6.90 to 2.30), DBP = −1.96 mm Hg (95% CI −4.98 to 1.06)	-	-	Kwok, Chun Shing; Loke, Yoon K.; Pradhan, Shiva; Keavney, Bernard; El-Omar, Magdi; Mamas, Mamas A.. Renal denervation and blood pressure reduction in resistant hypertension: a systematic review and meta-analysis. Open Heart 2014;1(1):e000092.	-	-	Population: Not stated. Comments: The authors dedicated much of their discussion to SYMPLICITY HTN-3, the blinded, randomised controlled trial considered to provide the highest-quality data. A meta-analysis was conducted on the other two unblinded randomised controlled trials for comparison. Little analysis was done on the remaning 9 papers; blood pressure results were summarised in a table.

3	Cohort	126	RDN; bilaterally via femoral access with a dedicated radiofrequency catheter (Symplicity)	Clinical effectiveness of the intervention	6 month office and ambulatory SBP and DBP	In the CH group, office SBP and DBP at 3-, 6-, and 12-month follow-up were significantly reduced by 28/27/30±25/21/24 mm Hg (P<0.001 for all) and by 13/16/18±13/12/15 mm Hg (P<0.001 for all), respectively. In patients with ISH at 3-, 6-, and 12-month follow-up a significant reduction in SBP by 17/18/17±21/24/25 mm Hg (P<0.001 for all) and DBP by 5/4/4±9/11/10 mm Hg (P<0.001 after 3 months, P=0.004 after 6 months, and P=0.003 after 12 months); Mean 24-hour ambulatory SBP and DBP after 3, 6, and 12 months were significantly reduced by 10/13/15 and 6/6/9 mm Hg in CH, diastolic ambulatory blood pressure after 3, 6, and 12 months, respectively.	-	Non-responder rate: after 6 months was 37% in ISH and 21% in CH	Ewen, Sebastian; Ukena, Christian; Linz, Dominik; Kindermann, Ingrid; Cremers, Bodo; Laufs, Ulrich; Wagenpfeil, Stefan; Schmieder, Roland E.; Böhm, Michael; Mahfoud, Felix. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. Hypertension 2015;65(1):193-199.	-	-	Population: SBP ≥140 mm Hg despite treatment with ≥3 antihypertensive drugs of different classes, including a diuretic at maximum or highest tolerated dose. 126 patients divided into 63 patients with (isolated systolic hypertension) ISH and 63 patients with combined hypertension. Aged ≥18 years; mean age was 66.7 ± 8.4 years. Comments: Authors reported that RDN is able to reduce systolic blood pressure in patients with combined hypertension (CH) and isolated systolic hypertension (ISH). There was no control or sham procedure, so a Hawthorne effect cannot be excluded, and the extent of a placebo effect also could not be assessed.
1+	Other	-	RDN	Other	-	-	-	-	Gladwell, Daniel; Henry, Thea; Cook, Mark; Akehurst, Ron. Cost effectiveness of renal denervation therapy for the treatment of resistant hypertension in the UK. Appl Health Econ Health Policy 2014;12(6):611-622.	-	-	Population: Baseline SBP of 178 mm Hg, average of had taken on average 5 types of antihypertensive medication. Mean age 58 years. Comments: Authors conclude that RDN resulted in a greater health benefit to the patient compared to only standard of care pharmacological intervention alone, extending QALYs from 12.16 to 12.77. This added health benefit came at a cost of £4805 per QALY. The biggest weakness of this study was that these calculations were baesd on the SYMPLICITY HTN-2 trial, which is an unblinded RCT. Due to the large discrepancies found in clinical effectiveness between SYMPLICITY HTN-2 and SYMPLICITY HTN-3, the cost effectiveness of RDN is likely to change should the latest blinded RCT be taken into account

1+	Systematic + Meta Analysis	-	RDN	Cost effectiveness	SBP and DBP at 6 months (Pulse pressure endpoint not included here)	RDN patients at 6 months: systolic BP mean -24.7 mm Hg, 95% CI -32.5 to -16.8, p = 0.001, I2 = 90%), diastolic BP mean -8.4 mm Hg, 95% CI -10.6 to -6.4, p= 0.001, I2= 22%). MMT patients at 6 months: systolic BP (WMD - 6.1 mm Hg, 95% CI 11.3 to 0.8, p=0.02, I2=68%), diastolic BP (WMD 3.1 mm Hg, 95% CI 5.2 to 0.9 mm Hg, p =0.005, I2= 0%)	-	-	Pancholy, Samir B.; Shantha, Ghanshyam Palamaner Subash; Patel, Tejas M.; Sobotka, Paul A.; Kandzari, David E.. Meta-analysis of the effect of renal denervation on blood pressure and pulse pressure in patients with resistant systemic hypertension. Am. J. Cardiol. 2014;114(6):856-861.	-	-	Population: RDN (n=534) vs. maximum medical therapy (MMT) . Comments: There is significant lowering of systolic and diastolic blood pressure in the RDN group compared to the MMT group, supporting the claim that RDN is a more clinically effective therapy compared to existing pharmacological interventions in the treatment of RT. However, the lower of blood pressure was much less marked when only RCTs were considered.
1+	RCT	70 CHECK THIS FIGURE - SHOULD BE 110?	RDN	Clinical effectiveness of the intervention	SBP and DBP change	Systolic blood pressure decreased 34 mmHg (95% CI: -40, -27, P, 0.01) and diastolic blood pressure decreased 13 mmHg (95% CI: -16, -10, P, 0.01). The systolic and diastolic blood pressure reduction at 36 months for the initial renal denervation group was -33 mmHg (95% CI: -40, -25, P, 0.01) and -14 mmHg (95% CI: 217, 210, P, 0.01), respectively	-	-	Esler, Murray D.; Böhm, Michael; Sievert, Horst; Rump, Christian L.; Schmieder, Roland E.; Krum, Henry; Mahfoud, Felix; Schlaich, Markus P.. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur. Heart J. 2014;35(26):1752-1759.	-	-	Population: Average age = 58 years. Comments: SYMPLICITY HTN-2 trial. The biggest limitation is the the control group did not undergo a sham procedure.

1+	RCT	535 in total; 364 in RDN group, 171 in control group	RDN delivered by the Symplicity Renal Denervation System (Medtronic, Santa Rosa, California)	Clinical effectiveness of the intervention compared to existing interventions	Mean change in office and ambulatory SBP at 6 and 12 months	At 6 months, the 24-h ambulatory SBP changed 6.8 +/- 15.1 mm Hg in the denervation group and 4.8 +/- 17.3 mm Hg in the sham group: difference of 2.0 mm Hg (95% confidence interval [CI]: -5.0 to 1.1; p =0.98	-	-	Bakris, George L.; Townsend, Raymond R.; Liu, Minglei; Cohen, Sidney A.; D'Agostino, Ralph; Flack, John M.; Kandzari, David E.; Katzen, Barry T.; Leon, Martin B.; Mauri, Laura; Negoita, Manuela; O'Neill, William W.; Oparil, Suzanne; Rocha-Singh, Krishna; Bhatt, Deepak L.; SYMPLICITY HTN-3 Investigators. Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. J. Am. Coll. Cardiol. 2014;64(11):1071-1078.	-	-	Population: Subjects were required to have a seated office SBP of at least 160 mm Hg at their first screening visit, and a 24-h ambulatory SBP of at least 135 mm Hg. RDN group: 57.9 +/- 10.4 years. Sham control group: 56.2 +/- 11.2 years. Comments: This is a set of results from the SYMPLICITY HTN-3 trials, a very well-conducted blinded RCT for RDN on RH patients. Results did not demonstrate a benefit of renal artery denervation on reduction in ambulatory BP in either the 24-h or day and night periods compared with the sham control group
1-	RCT	-	RDN	Clinical effectiveness of the intervention	-	-	-	-	Jin, Yu; Jacobs, Lotte; Baelen, Marie; Thijs, Lutgarde; Renkin, Jean; Hammer, Frank; Kefer, Joelle; Petit, Thibault; Verhamme, Peter; Janssens, Stefan; Sinnaeve, Peter; Lengelé, Jean-Philippe; Persu, Alexandre; Staessen, Jan A.; investigator-steered project on intravascular renal denervation for management of drug-resistant hypertension (INSPiRED) investigators. Rationale and design of the Investigator-Steered Project on Intravascular Renal Denervation for Management of Drug-Resistant Hypertension (INSPiRED) trial. Blood Press. 2014;23(3):138-146.	-	-	No results provided yet; only trial design presented
1-	Systematic + Meta Analysis	146 eligible, 60 excluded to give a final 86 patients, moderate resistant (n=48), severe resistant (n=38)	Pulmonary vein isolation (PVI) and RDN vs. PVI only	Clinical effectiveness of the intervention compared to existing interventions	SBP and DBP change at 12 months	SBP amd DBP for moderate resistant hypertension: –12.5 +/- 7.8/7.8 +/- 2.9 mmHg (P<0.001 vs baseline), for severe resistant hypertension: -29.1 +/- 14.6/–12.2 +/- 7.7 mmHg (P<0.001 vs baseline)	-	-	Pokushalov, Evgeny; Romanov, Alexander; Katritsis, Demosthenes G.; Artyomenko, Sergey; Bayramova, Sevda; Losik, Denis; Baranova, Vera; Karaskov, Alexander; Steinberg, Jonathan S.. Renal denervation for improving outcomes of catheter ablation in patients with atrial fibrillation and hypertension: early experience. Heart Rhythm 2014;11(7):1131-1138.	-	-	Population: Not stated. Comments: Only 2 meta-analyses were considered. This study supports the claim that RDN is a clinically effective methodology in treating hypertension, with more marked results for patients suffering from severe resistant hypertension.

1++	RCT	1441 assessed; 535 eligible	RDN delivered by the Symplicity Renal Denervation System (Medtronic, Santa Rosa, California)	Clinical effectiveness of the intervention compared to existing interventions	Mean change in office systolic blood pressure from baseline to 6 months in the denervation group, as compared with the mean change in the sham control group, with a superiority margin of 5 mm Hg	−14.13±23.93 mm Hg in the denervation group as compared with −11.74±25.94 mm Hg in the sham-procedure group (P<0.001 for both comparisons of the change from baseline), for a difference of −2.39 mm Hg (95% confidence interval [CI], −6.89 to 2.12; P = 0.26 for superiority with a margin of 5 mm Hg)	Change in mean 24-hour ambulatory systolic	24-hour ambulatory systolic blood pressure was −6.75±15.11 mm Hg in the denervation group and −4.79±17.25 mm Hg in the sham-procedure group, for a difference of −1.96 mm Hg (95% CI, −4.97 to 1.06; P = 0.98 for superiority with a margin of 2 mm Hg)	Bhatt, Deepak L.; Kandzari, David E.; O'Neill, William W.; D'Agostino, Ralph; Flack, John M.; Katzen, Barry T.; Leon, Martin B.; Liu, Minglei; Mauri, Laura; Negoita, Manuela; Cohen, Sidney A.; Oparil, Suzanne; Rocha-Singh, Krishna; Townsend, Raymond R.; Bakris, George L.; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N. Engl. J. Med. 2014;370(15):1393-1401.	-	-	Population: Patients with resistant hypertension, defined as SBP of 160 mm Hg or higher. On average receiving 5 of more types of antihypertensive treatments. Ages 18-80 years. Comments: A robust and reliable blinded RCT with a large population size. Authors concluded that RDN did not show a significant of reduction of systolic blood pressure in patients with resistant hypertension (RH) at 6 months. Limitations or biases could be introduced by inexperience of the operators. Furthermore, no confirmation was done to affirm that the renal sympathetic nerve was denervated due to the lack of procedure that can be done in a large trial
1-	RCT	-	RDN	Clinical effectiveness of the intervention compared to existing interventions	-	-	-	-	Vink, Eva E.; de Beus, Esther; de Jager, Rosa L.; Voskuil, Michiel; Spiering, Wilko; Vonken, Evert-Jan; de Wit, G. Ardine; Roes, Kit C. B.; Bots, Michiel L.; Blankestijn, Peter J.. The effect of renal denervation added to standard pharmacologic treatment versus standard pharmacologic treatment alone in patients with resistant hypertension: rationale and design of the SYMPATHY trial. Am. Heart J. 2014;167(3):308-314.e3.	-	-	No results provided; only trial design presented

1++	Systematic + Meta Analysis	Drug trials (n=4121), RDN trials (n=720)	RDN	Clinical effectiveness of the intervention compared to existing interventions	SBP and DBP change	In drug trials without randomisation or blinding, pressure reductions are 5.6 mm Hg (95% CI 2.98 to 8.22 mm Hg) larger on office measurements than ambulatory blood pressure monitoring (p<0.0001). By contrast, with randomisation and blinding, office reductions are identical to ambulatory reductions (difference −0.88 mm Hg, 95% CI −3.18 to -1.43, p=0.45). In unblinded trials, office pressure drops were 27.6 mm Hg versus pretreatment, and 26.6 mm Hg versus unintervened controls. By contrast, ambulatory pressure drops averaged 15.7 mm Hg across all trials.	-	-	Howard, James P.; Nowbar, Alexandra N.; Francis, Darrel P.. Size of blood pressure reduction from renal denervation: insights from meta-analysis of antihypertensive drug trials of 4,121 patients with focus on trial design: the CONVERGE report. Heart 2013;99(21):1579-1587.	-	-	Population: Patients who had resistant hypertension, as defined by individual trials. Comments: This meta-analysis was extremely comprehensive in scope, including a large number of studies covering both drug (n=31) and RDN (n=23) trials. The author set out to explore the discrepancy between office and ambulatory blood pressure based on different variables, and through the data presented, a mean of all office BP data was calculated for both drug-only and RDN procedures, and compared. The data shows that RDN is clinically more effective, but the biggest weakness would be that SYMPLICITY HTN-3, a high-quality blinded RCT, had not been completed yet at the point of writing so was not included in the study.

1++	Systematic + Meta Analysis	579 in total, of which 561 were included. Controlled studies (n=183), uncontrolled studies (n=396)	RDN	Clinical effectiveness of the intervention compared to existing interventions	Mean systolic and idastolic BP reduction at 3 months and 6 months	In controlled studies, there was a reduction in mean systolic and diastolic blood pressure (BP) at 6 months of –28.9 mm Hg (95% confidence interval [CI]: –37.2 to –20.6 mm Hg) and –11.0 mm Hg (95% CI: –16.4 to –5.7 mm Hg), respectively, compared with medically treated patients (for both, $p < 0.0001$). In uncontrolled studies, there was a reduction in mean systolic and diastolic BP at 6 months of –25.0 mm Hg (95% CI: –29.9 to –20.1 mm Hg) and –10.0 mm Hg (95% CI: –12.5 to –7.5 mm Hg), respectively, compared with pre-RDN values (for both, $p < 0.00001$).	1. Nonresponder rate; (decrease in systolic BP of <10mm Hg), 2. mean BP reduction stratified by catheter type, 3. Reported procedural complications and adverse outcomes	Non-responder rate was 13%	Davis, Mark I.; Filion, Kristian B.; Zhang, David; Eisenberg, Mark J.; Afilalo, Jonathan; Schiffrin, Ernesto L.; Joyal, Dominique. Effectiveness of renal denervation therapy for resistant hypertension: a systematic review and meta-analysis. J. Am. Coll. Cardiol. 2013;62(3):231-241.	-	-	Population: Not stated. Comments: The data shows that RDN is a safe procedure. The biggest weakness of this study, similar to Howard et al. 2013, is that the results from the high-quality SYMPLICITY HTN-3 clinical trial had not been published yet and was therefore not included in this meta-analysis.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	The NICE IPG overview contains good background information and a rapid literature review. This review will need updating with new publications and any systematic reviews
Updated search terms - Population	Hypertension Blood pressure
Updated search terms - Intervention	Renal denervation Kidney denervation
Updated search terms - Comparator	None
Updated search terms - Outcome	None
Inclusion criteria	General inclusion criteria
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Title/Abstract Publish date: since date of last literature reviewed as part of 2013 Renal Denervation for Resistant Hypertension Clinical Commissioning Policy Statement (Reference: NHSCB/A09/PS/d) English language

Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	None