NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

Cutting nerve supplies to the kidneys to reduce blood pressure
Hypertension (or chronic high blood pressure) raises the risk of having events such as heart attack, stroke or death. It is usually treated with lifestyle changes or medication to reduce the heart rate, but sometimes these treatments are not enough to reduce a person's blood pressure. Nerves located in the renal artery wall communicate information from the kidney to the brain to control blood pressure. In this procedure, a device is inserted through the groin to deliver heat energy to the renal nerves with the aim of reducing blood pressure.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2011 and updated in September 2011.

Procedure name

- Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

Specialty societies

- British Society of Interventional Radiology
- British Hypertension Society
- The Renal Association
- British Cardiovascular Society.

Description

Indications and current treatment

Hypertension (high blood pressure) is considered one of the most common and preventable causes of premature morbidity and mortality in the UK. It is a major but modifiable risk factor for cardiovascular disease (including stroke and myocardial infarction) and chronic renal disease. The cause of primary hypertension (the most common form) is not fully understood. However, it is likely to be multifactorial and include an increase in sodium retention and a reduction in renal blood flow mediated by the sympathetic nervous system. Secondary hypertension (much rarer) is caused by conditions affecting the kidneys, arteries, heart or endocrine system.

First-line treatment usually involves lifestyle changes, such as diet and exercise. Antihypertensive medications are used if high blood pressure persists.

What the procedure involves

Renal artery denervation aims to lower the blood pressure of patients who remain hypertensive despite pharmacological treatment. Radiofrequency energy is used to disrupt the sympathetic nerve fibres in the renal arteries to interrupt both local and central neurogenic reflexes that have a major role in the regulation of blood pressure through sodium reabsorption, renin production, and renal blood flow.

The procedure is usually performed with the patient under local anaesthesia with conscious sedation. Anticoagulation is generally used during the procedure. A temperature-controlled radiofrequency catheter connected to a generator is delivered through the femoral artery and advanced into renal artery under fluoroscopic control. Low-power radiofrequency treatments are given in 2-minute applications to the endoluminal lining in a spiral fashion at 4 to 6 points along each renal artery.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. Searches were conducted of the following databases, covering the period from their commencement to 27 July 2011: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or

resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with resistant hypertension.
Intervention/test	Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 309 patients from 1 randomised controlled trial (RCT)[1] and 2 case series[2, 3] (but it is likely that there is some overlap in patients reported in these studies).

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Symplicity HTN-2 Investigators (2010)[1]

Randomised controlled trial
Europe, Australia and New Zealand
Recruitment period: 2009–10
Study population: high blood pressure unsuccessfully controlled with antihypertensive drugs
n = 106 (52 renal denervation vs 54 control)
Age: 58 years
Sex: 35% vs 50% female
Patient selection criteria: age 18 to 85 years, baseline systolic blood pressure ≥ 160 mm Hg (≥ 150 mm Hg for those with type 2 diabetes), tried 3 or more antihypertensive drugs.
Exclusion criteria: estimated glomerular filtration rate of less than 45 mL/min per 1.73 m^2, type I diabetes, contraindications to MRI, renal artery stenosis, previous renal artery intervention, unsuitable renal artery anatomy (< 4 mm diameter, < 20 mm length or more than one main renal artery), substantial stenotic valvular heart disease, pregnancy or planned pregnancy, history of MI, unstable angina or cerebrovascular accident in previous 6 months.
Technique: renal artery denervation</td>
<td>Number of patients analysed: 100 (49 renal denervation vs 51 control)
Change in systolic blood pressure as measured in the office (primary effectiveness endpoint)
<table>
<tr><th></th><th colspan="2">Blood pressure (mm Hg)</th><th>p value</th></tr>
<tr><th></th><th>Baseline</th><th>Reduction at 6 months</th><th></th></tr>
<tr><td>Renal denervation</td><td>178/96 (SD 18/16)</td><td>32/12 (SD 23/11)</td><td>< 0.0001 (both diastolic and systolic)</td></tr>
<tr><td>Control</td><td>178/97 (SD 17/16)</td><td>1/0 (SD 21/10)</td><td>0.77 (diastolic) 0.83 (systolic)</td></tr>
</table>
(based on averages of triplicate measurements)
Reduction of 33/11 mm Hg in renal denervation compared with control (p < 0.0001 for both systolic and diastolic blood pressure).
Change in home-based blood-pressure measurements from baseline to 6 months (n = 32 vs 40)
<table>
<tr><th></th><th>Change in blood pressure (mm Hg)</th></tr>
<tr><td>Renal denervation</td><td>20/12 decrease (SD 17/11)</td></tr>
<tr><td>Control</td><td>Rise of 2/0 (SD 13/7)</td></tr>
</table>
(based on averages of 3 measurements in the morning and 3 in the evening at both baseline and 6 months)
Absolute difference was 22/12 mm Hg (p < 0.0001) for both systolic and diastolic blood pressure.
Change in average blood pressure from 24-hour</td>
<td>Minor periprocedural events in those treated with renal denervation
<table>
<tr><th>Event</th><th># of patients</th></tr>
<tr><td>Femoral artery pseudoaneurysm treated with manual compression</td><td>1.9% (1/52)</td></tr>
<tr><td>Postprocedural drop in blood pressure requiring drop in antihypertensive drugs</td><td>1.9% (1/52)</td></tr>
<tr><td>Urinary tract infection</td><td>1.9% (1/52)</td></tr>
<tr><td>Extended hospital admission for assessment of paraesthesias</td><td>1.9% (1/52)</td></tr>
<tr><td>Back pain treated with analgesia and resolving after 1 month</td><td>1.9% (1/52)</td></tr>
<tr><td>Transient intraprocedural bradycardia requiring atropine with no sequelae</td><td>13.5% (7/52)</td></tr>
<tr><td>Possible progression of underlying atherosclerotic lesion*</td><td>1.9% (1/52)</td></tr>
</table>
*not located near location where radiofrequency energy was delivered
Serious adverse events requiring hospital admission in those treated with renal denervation
<table>
<tr><th>Event</th><th># of patients</th></tr>
<tr><td>Nausea and oedema (site</td><td>1.9%</td></tr>
</table></td>
<td>Follow-up issues:
Follow-up at 1, 3 and 6 months.
3 in each group lost to follow-up because of withdrawal of consent (n = 3) or missed visit (n = 3).
Study design issues:
24 centres (16 were considered hypertension centres of excellence)
Of 190 patients (56%) screened for eligibility.
Randomisation from sealed envelopes at each clinical site in a one-to-one ratio.
No blinding.
50 patients per group was the figure calculated to be necessary for 80% power (with primary endpoint of at least 12 mm Hg difference in systolic blood pressure [SD: 21 mm Hg] from baseline to 6</td>
</tr>
</table>

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>vs control (no change – patients remaining on same anti-hypertensive mediation)
Follow-up: 6 months

Conflict of interest/source of funding: funded by Ardian (previous manufacturer of Symplicity Catheter System, now owned by Medtronic)</td>
<td>
ambulatory blood-pressure recordings from baseline to 6 months (n = 20 vs 25)
<table>
<tr><th></th><th>Decrease in blood pressure (mm Hg)</th><th>p value</th></tr>
<tr><td>Renal denervation</td><td>11/7 (SD 15/11)</td><td>0.006 (systolic)
0.014 (diastolic)</td></tr>
<tr><td>Control</td><td>3/1 (SD 19/12)</td><td>0.51 (systolic)
0.75 (diastolic)</td></tr>
</table>
(based on 24-hour average from measurements taken every 15 minutes during the day and every 30 minutes in the evening)
Proportion of patients with no decrease in systolic blood pressure at 6 months
<table>
<tr><th>Proportion</th><th>Renal denervation</th><th>Control</th></tr>
<tr><td>No decrease</td><td>10% (5/49)</td><td>47% (24/51)</td></tr>
<tr><td>Greater than or equal to 10 mm Hg</td><td>84% (41/49)</td><td>35% (18/51)</td></tr>
<tr><td>Less than 140 mm Hg</td><td>39% (19/49)</td><td>6% (3/51)</td></tr>
</table>
p < 0.0001 for all between-group comparisons
</td>
<td>
<table>
<tr><td>not identified)</td><td>(1/52)</td></tr>
<tr><td>Hypertension crisis after clonidine abruptly stopped</td><td>1.9% (1/52)</td></tr>
<tr><td>Transient ischaemic attack</td><td>1.9% (1/52)</td></tr>
<tr><td>Hypotensive episode resulting in reduction of antihypertensive drugs</td><td>1.9% (1/52)</td></tr>
<tr><td>Coronary stent required for angina</td><td>1.9% (1/52)</td></tr>
</table>
(no more details such as timing of events were reported)
Serious adverse events requiring hospital admission in control group
<table>
<tr><td>Event</td><td># of patients</td></tr>
<tr><td>Transient ischaemic attack</td><td>3.7% (2/54)</td></tr>
<tr><td>Coronary stent required for angina</td><td>1.9% (1/54)</td></tr>
</table>
(no more details such as timing of events were reported)
Renal function
No loss of renal function, renal stenosis, or anomalies in the location of the treatment was observed on renal angiography studies.
<table>
<tr><th></th><th>Mean change for denervation (SD)</th><th>Mean change for control (SD)</th><th>p value</th></tr>
<tr><td>eGFR (ml/min per 1.73 m^2)</td><td>0.2 (11)</td><td>0.9 (12)</td><td>0.76</td></tr>
</table>
</td>
<td>
months).
• Intention-to-treat analysis not performed.
• Both groups were not allowed changes in anti-hypertensive medications, but there were some changes in medication judged medically necessary (reduction in 20% [10/49] vs 6% [3/51], p = 0.04 and increase in 8% [4/49] vs 12% [6/51], p = 0.74).
Study population issues:
• Patients treated with renal denervation had lower baseline renal function than the control group (77 mL/min per 1.73 m2 vs 86 mL/min per 1.73 m2, p = 0.013) but did not vary in other characteristics.
Other issues:
• Screening consisted of patient-recorded automated blood pressure twice daily and drug
</td>
</tr>
</table>

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
		Serum creatinine (µmol/L): 0.2 (17.6); –1.1 (10.3); 0.67 Cystatin C (mg/L): 0.1 (0.2); 0.0 (0-1); 0.31 (p value for difference in mean value)	compliance for 2 weeks (this was also done 2 weeks before 6-month follow-up); and renal artery anatomical screening with renal duplex-computer tomography, MRI or renal angiography to confirm anatomical eligibility.

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Symplicity HTN-1Investigators (2011)[2]

Case series
Australia, Europe, USA
Recruitment period: 2007–10
Study population: resistant hypertension
n = 153
Mean age: 57 years
Sex: 61% male
Average number of antihypertensive drugs: 5.1

Patient selection criteria: resistant hypertension defined as office systolic blood pressure ≥ 160 mm Hg despite being on 3 or more antihypertensive medications (including a diuretic) at a target or maximal tolerated dose, at least 18 years old, not pregnant, no known secondary cause of hypertension.
Exclusion criteria: estimated glomerular filtration rate < 45 ml/min/1.73 m^2, type I diabetes, known secondary cause of hypertension other than sleep apnoea or chronic kidney disease, significant renovascular abnormalities (such as haemodynamically significant artery stenosis, short length main renal artery, or known multiple main renal arteries).
Technique: percutaneous radiofrequency catheter-based renal</td>
<td>Number of patients analysed: 153
Reduction in office-measured blood pressure
92% had office BP reduction of ≥ 10 mm Hg.
<table>
<tr><th></th><th colspan="2">Reduction in blood pressure mm Hg</th></tr>
<tr><th></th><th>Uncensored</th><th>Censored (including those with increased medications)</th></tr>
<tr><td>Baseline</td><td>176/98 ± 17/15 (n = 153)</td><td>-</td></tr>
<tr><td colspan="3">Mean reduction in blood pressure</td></tr>
<tr><td>1 month</td><td>20/10 (n = 138)</td><td>20/10 (n = 134)</td></tr>
<tr><td>3 months</td><td>24/11 (n = 135</td><td>24/11 (n = 127)</td></tr>
<tr><td>6 months</td><td>25/11 (n = 86)</td><td>25/11 (n = 75)</td></tr>
<tr><td>12 months</td><td>23/11 (n = 64)</td><td>23/11 (n = 52)</td></tr>
<tr><td>18 months</td><td>26/14 (n = 36)</td><td>26/14 (n = 29)</td></tr>
<tr><td>24 months</td><td>32/14 (n = 18)</td><td>30/14 (n = 13)</td></tr>
</table>
Within patient changes in both systolic and diastolic blood pressure from baseline to each time point was p < 0.0001 for all changes except at 24 months where it was p = 0.002 (using ANOVA and pairwise comparison).

Baseline predictors of BP response
Multivariate analysis showed that significant independent predictors of greater systolic blood pressure response were higher baseline systolic blood pressure (p < 0.0001) and use</td>
<td>Periprocedural complications
10% (15/153) had bradycardia during the procedure (managed with atropine).
1 case of renal artery dissection before delivery of radiofrequency energy requiring treatment with renal artery stent and aborting treatment. No further sequelae.
3 cases of pseudoaneurysm/haematoma at the femoral access site in patients treated with an 8F guide. These were treated successfully without subsequent complications.
Renal vascular safety
Minor focal renal artery irregularities attributed to minor spasm and/or oedema were noted immediately after the energy delivery but none limited flow.
No evidence of renal artery stenosis or abnormality in any treatment location on short-term follow-up angiogram (n = 20) or in magnetic resonance angiogram, computer tomography angiography or duplex evaluation 6 months after the procedure (n = 81).
Renal function (available in 25 patients)
<table>
<tr><th></th><th></th><th colspan="3">Change at:</th></tr>
<tr><th></th><th>Baseline</th><th>6 months (n = 102)</th><th>1 year (n = 64)</th><th>2 years (n = 10)</th></tr>
<tr><td>eGFR (mL/ min /1.73m^2)</td><td>83 (SD 20)</td><td>–0.1 (95% CI –4.3 to 1.1)</td><td>–2.9 (95% CI –6.2 to +0.3)</td><td>–16</td></tr>
</table>
In the 10 available for follow-up at 2 years, 5 had spironolactone or other diuretic added after the first</td>
<td>Follow-up issues:
• Follow-up at 1, 3, 6, 12, 18 and 24 months. Renal angiography again at 14–30 days after.
• 2 patients lost to follow-up between 3 and 6 months.
Study design issues:
• 19 centres in prospective, proof-of-principle trial.
• Appears to include patients reported in Krum[3]; not clear if patients in treatment arm of Symplicity HTN-2 study[1] were included here.
• The first 10 patients had staged procedures (denervating each artery with 1-month interval).
• Renal angiography used before and immediately after the procedure.
• Despite instructions not to change medications during follow-up (applied more strictly in first year), 27 had a reduction in number</td>
</tr>
</table>

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
sympathetic denervation with Symplicity catheter system (Ardian Inc) (55 patients had a 6F guide and 98 had an 8F guide). Follow-up: **up to 24 months (18 patients)** Conflict of interest/source of funding: funded by Ardian Inc (2 authors are employees and all other authors received per-patient payment for study involvement)	of central sympatholytic agents (p = 0.018).	year of follow-up. In these 5, eGFR changed –7.8 mL/min/1.73m^2 for annualised change of –3.9 mL/min/1.73m^2. ***Postural hypotension and oedema*** None had symptomatic orthostatic hypotension 6 had transient dizziness across the entirety of the study period (but none had lost consciousness). 3 had pitting oedema considered to be related to medication adjustment (treated with conservative care, use of diuretics and/or reduction in minoxidil dose). ***Pain*** 1 patient had bilateral flank pain. Despite extensive diagnostic evaluation, the cause was not identified. Ibuprofen was effective at alleviating the pain over a number of months but then it completely resolved. 3 patients had intermittent or transient flank or kidney pain which resolved with or without analgesic intervention. ***Death*** 2 died during the follow-up period but neither was considered to be related to the device or the procedure: - 1 patient with known coronary artery disease died from a myocardial infarction (clopidogrel was stopped after episode of reversible cerebral ischaemia, which was thought to have occurred secondary to atrial fibrillation with rapid ventricular response) - 1 patient with gastrointestinal disease and coronary artery bypass grafting was thought to have sudden death.	of medications, 18 had an increase (10 after drops in blood pressure) but overall number of medications did not change significantly (from 5.1 to 5.0, p = 0.11). **Study population issues**: • 31% had type 2 diabetes mellitus, 22% coronary artery disease • 91% were on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 82% on beta blockers, 75% on calcium-channel blockers, 19% on vasodilators, 95% on diuretics.

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Krum H (2009)[3]

Case series
Australia and Europe
Recruitment period: 2007–8
Study population: resistant hypertension
n = 50
Age: 58 years
Sex: 58% male
Number of antihypertensive drugs: 4.7

Patient selection criteria: resistant hypertension defined as systolic blood pressure ≥ 160 mm Hg and being on 3 or more antihypertensive medications (including a diuretic) or confirmed intolerance to medications, at least 18 years old, not pregnant, no known secondary cause of hypertension, glomerular filtration rate of 45 ml/min/1.73 m^2 or more estimated (estimated with modification of diet in renal disease formula).
Exclusion criteria: type I diabetes, haemodynamically significant valvular disease, implanted pacemakers or implantable cardioverter defibrillator, on treatment including clonidine, moxonidine, rilmenidine, or warfarin, renovascular abnormalities (including severe artery stenosis, previous renal stenting or angioplasty or known dual renal arteries).
Technique: percutaneous</td>
<td>Number of patients analysed: 45
Reduction in office-measured blood pressure
<table>
<tr><th></th><th colspan="2">Blood pressure mm Hg (95% CI)</th></tr>
<tr><th></th><th>Uncensored</th><th>Censored (including those with increased medications)</th></tr>
<tr><td>Baseline</td><td>177/101 (n = 40)</td><td>-</td></tr>
<tr><td colspan="3">Mean reduction in blood pressure</td></tr>
<tr><td>1 month</td><td>–14/–10 (4/3) (n = 41)</td><td>–14/–10 (4/3)</td></tr>
<tr><td>3 months</td><td>–21/–10 (7/4) (n = 39)</td><td>–22/–11 (7/4)</td></tr>
<tr><td>6 months</td><td>–22/–11 (10/5) (n = 26)</td><td>–22/–10 (7/4)</td></tr>
<tr><td>9 months</td><td>–24/–11 (9/5) (n = 20)</td><td>–26/–11 (7/5)</td></tr>
<tr><td>12 months</td><td>–27/–17 (16/11) (n = 9)</td><td>–28/–17 (22/18)</td></tr>
</table>
Repeated measures ANOVA showed both systolic and diastolic was significantly lower after the procedure (p = 0.026 systolic and p = 0.027 diastolic).
At each point of follow-up, both systolic and diastolic blood pressure were significantly lower with p < 0.001, except at 12 months when p = 0.02 for diastolic blood pressure.
The 5 patients which were ineligible for the procedure had mean increases of +3/–2, +2/+3, +14/+9, and +26/+17 mm Hg at 1, 3, 6, and 9 months follow-up.
Proportion considered non-responders
13% (6/45) had systolic blood pressure reductions of less than 10 mm Hg, so were considered non-responders.</td>
<td>Complications
All patients reported diffuse visceral non-radiating abdominal pain during the procedure requiring narcotics and sedative drugs but this did not persist after the radiofrequency energy application was finished.
1 case of renal artery dissection before delivery of radiofrequency energy requiring treatment with renal artery stent and aborting treatment. No further sequelae.
1 case of pseudoaneurysm at the femoral access site treated successfully with antibiotics and analgesics (timing of event not reported).

Renal function (available in 25 patients)
No evidence of renal artery stenosis or abnormality in any treatment location on short-term follow-up angiogram (14–30 days, n = 18) or in magnetic resonance angiogram 6 months after the procedure (n = 14).
<table>
<tr><th></th><th>Baseline</th><th>6 months</th></tr>
<tr><td>eGFR (ml/min/1.73m^2)</td><td>79 (SD 21)</td><td>83 (SD 25)</td></tr>
</table>
In 6 patients this increased by ≥ 20% and 1 patient with a substantial drop in systolic blood pressure (below 70 mm Hg) had a reduction of > 20%.</td>
<td>Follow-up issues:
• Follow-up at 1, 3, 6, 9, and 12 months. Renal angiography again at 14–30 days after.
• 2 patients lost to follow-up between 3 and 6 months.
Study design issues:
• 5 centres in prospective, proof-of-principle trial.
• Patients likely to be included in Symplicity HTN-1 above[2] (see ‘Validity and generalisability of the studies’ on page 16 for explanation of why both were included in this table’)
• 5 patients were excluded for anatomical reasons but followed up for duration of trial.
• The first 10 patients had staged procedures (denervating each artery with 1-month interval).
• Renal angiography used before and</td>
</tr>
</table>

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>radiofrequency catheter-based renal sympathetic denervation with Symplicity catheter system (Ardian Inc, Palo Alto, CA, USA)

Follow-up: up to 1 year (in 9 patients)

Conflict of interest/source of funding: funded by Ardian Inc (also, one author was an employee and another a paid consultant)</td>
<td>Of those who responded, univariate analysis failed to show associations between ≥ 10 mm Hg reduction and a number of different patient characteristics or number of ablations.
24-hour ambulatory blood-pressure monitoring (measured in 12 patients at 1 centre)
<table>
<tr><th></th><th>Change from baseline to 30 days</th></tr>
<tr><td>Responders (n = 9)</td><td>–11 mm Hg (95% CI 7) [office measurement in these patients was –27 mm Hg]</td></tr>
<tr><td>Non-responders (n = 3)</td><td>10 mm Hg (95% CI 16) [office measurement in these patients was 3 mm Hg]</td></tr>
</table>
Correlation between office and mean ambulatory blood pressure: $r^2 = 0.62$ ($p = 0.002$)
Subgroup of patients tested for renal noradrenaline spillover (measured in 10 patients)
Mean reduction in renal noradrenaline spillover was 47% (95% CI 28–65%) from before the procedure to 15–30 days after the procedure (all patients had mean 6-month office blood-pressure reduction of 22/12 mm Hg).</td>
<td></td>
<td>immediately after the procedure. The first 10 also had one at 2 weeks, the next 8 at 1 month, but the last 27 patients did not have a follow-up angiogram until 6 months when all had a follow-up angiogram.
• A patient was considered a responder if they had a ≥ 10 mm Hg reduction in systolic blood pressure.
• Test for noradrenaline spillover used because overflow of noradrenaline in venous drainage of an organ is thought to be proportional to sympathetic activity, providing a measure of sympathetic activity where microneurography is not possible or difficult.
• Despite instructions not to change medications during follow-up, 9 had an increase (5 of these had ≥ 10 mm Hg</td>
</tr>
</table>

Abbreviations used: ANOVA, analysis of variance; CI, confidence interval; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			reduction in systolic blood pressure before change in medication) and 4 had a reduction from 4 to 3 medications (1 of these was a non-responder but the others had optimal blood pressure control). **Study population issues**: • 32% (16/50) had type 2 diabetes mellitus, 22% (11/50) coronary artery disease94% (47/50) were on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 78% (39/50) on beta blockers, 72% (36/50) on calcium-channel blockers, 16% (8/50) on vasodilators, 92% (46/50) on diuretics.

Efficacy

A randomised controlled trial (RCT) reported that office-based measurements of blood pressure decreased by 32/12 mm Hg in the 49 patients treated with renal denervation compared with an increase of 1/0 mm Hg for the 51 patients in the control group, from baseline to 6 months ($p < 0.0001$ for both systolic and diastolic blood pressure in treatment group compared with $p = 0.77$ and $p = 0.83$ for diastolic and systolic blood pressure in the control)[1].

The RCT recorded 24-hour ambulatory blood pressure from baseline to 6 months in 20 patients treated with renal denervation and 25 in the control group based on an average of measurements taken every 15 minutes during the day and every 30 minutes in the evening. The decrease in blood pressure in the renal denervation group was 11/7 mm Hg ($p = 0.006$ for systolic blood pressure and $p = 0.014$ for diastolic blood pressure). This compares with a decrease of 3/1 mm Hg for the control group ($p = 0.51$ for systolic blood pressure and $p = 0.75$ for diastolic blood pressure)[1].

A case series of 153 patients treated with the procedure reported a reduction in blood pressure from 176/98 mm Hg at baseline by 25/11 mm Hg at 6 months (n = 86), by 23/11 mm Hg at 12 months (n = 64), by 26/14 mm Hg at 18 months (n = 36) and by 32/14 mm Hg at 24 months (n = 18) (within-patient changes in both systolic and diastolic blood pressure from baseline to each time point were $p < 0.0001$ for all changes except at 24 months where it was $p = 0.002$).

A case series of 50 patients including 45 patients treated with the procedure, reported a significant reduction in blood pressure by –14/–10 mm Hg at 1 month (n = 41), –22/–11 mmHg at 6 months (n = 26), and –27/–17 mm Hg (n = 9) at 12 months ($p < 0.001$ for both systolic and diastolic at each time point, except for diastolic blood pressure at 12 months where $p = 0.02$)[3].

Safety

The case series of 153 patients reported renal artery dissection in 1 patient before the delivery of radiofrequency energy. Renal denervation was stopped and the patient was successfully treated with a renal artery stent with no further sequelae[2].

The same study reported periprocedural pseudoaneurysm or haematoma at the femoral access site in 3 patients which was treated successfully[2].

The RCT reported transient ischaemic attack in 2% (1/52) of patients treated with renal denervation compared with 4% (2/54) in the control group and angina requiring a coronary stent in 1 patient in each treatment group (timing of events not reported)[1].

The same study reported the following additional events (requiring hospitalisation) in the treatment group in 1 patient each: nausea and oedema, hypertensive crisis after clonidine was abruptly stopped, and a hypotensive episode resulting in a reduction in antihypertensive medication (timing not reported)[1].

The same study reported the following periprocedural events which were considered minor in 1 patient each: femoral artery pseudoaneurysm treated with manual compression, postprocedural drop in blood pressure requiring drop in antihypertensive drugs, urinary tract infection, extended hospital admission for assessment of paraesthesias, back pain treated with analgesia and resolving after 1 month, transient intraprocedural bradycardia requiring atropine with no sequelae, and possible progression of underlying atherosclerotic lesion (this was not located near location where radiofrequency energy was delivered)[1].

The case series of 153 patients reported that 6 patients had transient dizziness for the entirety of the study period (but none had lost consciousness) and that 3 patients had pitting oedema considered to be related to medication adjustment (treated with conservative care, use of diuretics and/or reduction in minoxidil dose)[2].

The same study reported that 1 patient had idiopathic bilateral flank pain which was successful controlled with ibuprofen over a number of months when it resolved completely. An additional 3 patients had intermittent or transient flank or kidney pain which resolved with or without analgesic intervention[2].

Validity and generalisability of the studies

- There is very little literature published on this procedure. The first was a proof-of-concept study (Krum et al)[3], and the Symplicity HTN-2 RCT[1] was performed subsequently, followed by the Symplicity HTN-1 case series with longer follow-up[2]. It appears that most of the patients reported in Krum et al[3] are probably included in the Symplicity HTN-1 study[2], but it is not clear whether those in the treatment arm of the RCT were included in the non-randomised study.
- Despite the likely overlap of patients in Krum et al[3] and Symplicity HTN-1[2], both were included in the main data extraction table because they appear to report some different information:
  - Krum et al[3] reports 2 patients lost to follow-up at 3 and 6 months (none reported in the later Symplicity HTN-1 study[2]),
  - Two additional efficacy outcomes were reported in Krum et al[3] (ambulatory blood pressure and noradrenaline spillover).
  - Exclusion criteria appeared to be broadly the same except that Krum et al[3] also reported to exclude patients with previous renal stenting or angioplasty, valvular disease, implanted pacemakers or implantable cardioverter defibrillator, on treatment including clonidine, moxonidine, rilmenidine or warfarin.

  - Krum et al[3] reports on 5 patients excluded for anatomical reasons.
- It is interesting to note the presence of RCT data in the absence of more observational studies. See 'Issues for consideration by IPAC' below for a description of some studies underway.
- All studies were funded by the manufacturer and performed by largely the same authors.
- There was an additional case report, but it was not clear if this was published in a peer-reviewed journal.
- Follow-up is limited with only 18 patients followed-up for 2 years so it is unclear if the results are sustained in the long term.

Existing assessments of this procedure

The Australia and New Zealand Horizon Scanning Network published a prioritising summary in March 2010 which stated that it considered renal sympathetic denervation investigational. It has recommended that further information from clinical trials be assessed in 24 months' time.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Clinical guidelines

- Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). This guidance is currently under partial review and is expected to be updated in August 2011. For more information, see www.nice.org.uk/guidance/CG34

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Prof Mark Caulfield, Dr Charles Knight, Dr Melvin Lobo, Prof Neil Poulter (British Hypertension Society), Prof Jon Moss (British Society of Interventional Radiology).

- Four advisers consider this procedure the first in a new class of procedure.
- Patients with treatment-resistant hypertension have no comparator currently (as, by definition of the resistant nature of their hypertension, maximal antihypertensive therapy has not been successful).
- One adviser commented that there are few patients with severe resistant hypertension in specialist hypertension clinics.

- Anecdotal adverse events include femoral access site complications (such as groin haematoma, bruising in leg, access site trauma/pseudoaneurysm), hypotension, and transient pain from the delivery of radiofrequency energy. Renal artery dissection and renal artery perforation have also occurred but only rarely.
- Long-term safety is unknown. Theoretical events include late stenosis of the renal artery, renal artery infarction, promotion of atheromatous disease in the renal artery in the long term, other renal artery damage, sodium depletion and hypotension. Long-term follow-up is necessary to be more certain about the safety of this procedure.
- The key efficacy outcome is a reduction in blood pressure but regression in left ventricular mass and improvement in parameters of renal function could also be considered outcomes. One adviser considered reduction in cardiovascular morbidity and mortality to be an efficacy outcome.
- The advisers commented that it is clear that some patients do not benefit from this procedure, but it is not clear what the characteristics are between responders and non-responders.
- The advisers have commented that the HTN-3 trial is to be performed in the USA to support FDA approval and it will be similar in design to the HTN-2 trial.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- There are a number of trials underway:
  - Controlled studies:
    - ◊ A randomised controlled trial comparing atrial fibrillation ablation alone or combined with percutaneous renal denervation (NCT01117025, based in Greece, estimated enrolment of 150 patients, due to complete in August 2012 with 2-year timeframe).
  - A number of small (n < 75) uncontrolled studies.
- Equality and diversity: in addition to the differences between the groups highlighted in the scope, blood pressure has a strong association with alcohol intake, high salt intake, obesity, and psychosocial stress which may be more prevalent in individuals with a lower socioeconomic status.
- The current procedure title does not distinguish the procedure from open sympathectomy. The Committee could consider:
  - Adding 'percutaneous' or 'transluminal' to the title.
  - Including 'radiofrequency energy' in the title (in case a procedure to denervate the renal arteries with another form of energy is introduced).

References

1. Symplicity HTN-2 Investigators. (2010) Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 376:1903–9.

2. Symplicity HTN-1 Investigators. (2011) Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension: Epub ahead of print March 14, 2011.

3. Krum HK, Schlaich M, Whitbourn R et al. (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 373:1275–81.

Appendix A: Additional papers on percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	**Number of patients/ follow-up**	**Direction of conclusions**	**Reasons for non-inclusion in table 2**
Mahfoud F, Schlaich M, Kindermann I et al. (2011) Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: A pilot study. Circulation 123: 1940–1946.	Non-randomised comparative study n = 50 Follow-up = 3 months	Renal denervation improves glucose metabolism and insulin sensitivity in addition to significantly reducing blood pressure.	The main focus of the paper was to assess glucose metabolism and insulin sensitivity.

Appendix B: Related NICE guidance for percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

Guidance	Recommendations
Clinical guidelines	**Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006)** 1.2 Lifestyle interventions 1.2.1 Ascertain patients' diet and exercise patterns because a healthy diet and regular exercise can reduce blood pressure. Offer appropriate guidance and written or audiovisual materials to promote lifestyle changes. • *Education about lifestyle on its own is unlikely to be effective.* • *Healthy, low-calorie diets had a modest effect on blood pressure in overweight individuals with raised blood pressure, reducing systolic and diastolic blood pressure on average by about 5−6 mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 40% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.* • *Taking aerobic exercise (brisk walking, jogging or cycling) for 30–60 minutes, three to five times each week, had a small effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 2–3 mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 30% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg or more in the short term, up to 1 year.* • *Interventions actively combining exercise and diet were shown to reduce both systolic and diastolic blood pressure by about 4–5 mmHg in trials. About one-quarter of patients receiving multiple lifestyle interventions were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.* • *A healthier lifestyle, by lowering blood pressure and cardiovascular risk, may reduce, delay or remove the need for long-term drug therapy in some patients.* 1.2.2 Relaxation therapies* can reduce blood pressure and individual patients may wish to pursue these as part of their treatment. However, routine provision by primary care teams is not currently recommended. * *Examples include: stress management, meditation, cognitive therapies, muscle relaxation and biofeedback.* • *Overall, structured interventions to reduce stress and promote relaxation had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3–4 mmHg in trials. There is variation in the reduction in blood pressure achieved in trials and it is unclear why. About one-third of patients receiving*

	relaxation therapies were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year. • *The current cost and feasibility of providing these interventions in primary care has not been assessed and they are unlikely to be routinely provided.* 1.2.3 Ascertain patients' alcohol consumption and encourage a reduced intake if patients drink excessively, because this can reduce blood pressure and has broader health benefits. • *Excessive alcohol consumption (men: more than 21 units/week; women: more than 14 units/week) is associated with raised blood pressure and poorer cardiovascular and hepatic health.* • *Structured interventions to reduce alcohol consumption, or substitute low alcohol alternatives, had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3–4 mmHg in trials. Thirty percent of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.* • *Brief interventions by clinicians of 10–15 minutes, assessing intake and providing information and advice as appropriate, have been reported to reduce alcohol consumption by one-quarter in excessive drinkers with or without raised blood pressure, and to be as effective as more specialist interventions.* • *Brief interventions have been estimated to cost between £40 and £60 per patient receiving intervention. The structured interventions used in trials of patients with hypertension have not been costed.* 1.2.4 Discourage excessive consumption of coffee and other caffeine-rich products. • *Excessive consumption of coffee (five or more cups per day) is associated with a small increase in blood pressure (2/1 mmHg) in participants with or without raised blood pressure in studies of several months duration.* 1.2.5 Encourage patients to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce blood pressure. • *Advice to reduce dietary salt intake to less than 6.0 g/day (equivalent to 2.4 g/day dietary sodium) was shown to achieve a modest reduction in systolic and diastolic blood pressure of 2–3 mmHg in patients with hypertension, at up to 1 year in trials. About one-quarter of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.* • *Long-term evidence over 2–3 years from studies of normotensive patients shows that reductions in blood pressure tend to diminish over time.* • *One trial suggests that reduced sodium salt, when used as a replacement in both cooking and seasoning, is as effective in reducing blood pressure as restricting the use of table salt.* 1.2.6 Do not offer calcium, magnesium or potassium supplements as a

	method for reducing blood pressure. • *The best current evidence does not show that calcium, magnesium or potassium supplements produce sustained reductions in blood pressure.* • *The best current evidence does not show that combinations of potassium, magnesium and calcium supplements reduce blood pressure.* 1.2.7 Offer advice and help to smokers to stop smoking. • *There is no strong direct link between smoking and blood pressure. However, there is overwhelming evidence of the relationship between smoking and cardiovascular and pulmonary diseases, and evidence that smoking cessation strategies are cost effective.* • *See: Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, NICE technology appraisal no. 39, March 2002. www.nice.org.uk/TA039* 1.2.8 A common aspect of studies for motivating lifestyle change is the use of group working. Inform patients about local initiatives by, for example, healthcare teams or patient organisations that provide support and promote healthy lifestyle change. 1.4 Pharmacological interventions 1.4.1 Drug therapy reduces the risk of cardiovascular disease and death. Offer drug therapy to: • patients with persistent high blood pressure of 160/100 mmHg or more • patients at raised cardiovascular risk (10-year risk of CVD of 20% or more, or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg. • *In placebo-controlled trials, blood pressure management beginning with a low-dose thiazide-type diuretic or beta-blocker has been shown to reduce mortality, myocardial infarction and stroke (relative risk reductions of 8%, 15% and 25%, respectively).* 1.4.2 Provide appropriate guidance and materials about the benefits of drugs and the unwanted side effects sometimes experienced in order to help patients make informed choices. 1.4.3 Offer drug therapy, adding different drugs if necessary, to achieve a target of 140/90 mmHg, or until further treatment is inappropriate or declined. Titrate drug doses as described in the 'British national formulary' noting any cautions and contraindications. • *In trials aiming to reduce blood pressure to below 140/90 mmHg using stepped medication regimens, between one-half and three-quarters of patients achieved target blood pressure.* • *In these trials about one-half of patients needed treatment with more than one drug.* 1.4.4 In hypertensive patients aged 55 or older or black patients of any age, the first choice for initial therapy should either be a calcium-channel blocker or a thiazide-type diuretic. For this recommendation, black patients are considered to be those of African or Caribbean descent, not mixed-race, Asian or Chinese. 1.4.5 In hypertensive patients younger than 55, the first choice for initial

	therapy should be an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated). 1.4.6 New If initial therapy was with a calcium-channel blocker or a thiazide-type diuretic and a second drug is required, add an ACE inhibitor (or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated). If therapy was initiated with an ACE inhibitor (or angiotensin-II receptor antagonist), add a calcium-channel blocker or a thiazide-type diuretic. 1.4.7 If treatment with three drugs is required, the combination of ACE inhibitor (or angiotensin-II receptor antagonist), calcium-channel blocker and thiazide-type diuretic should be used. 1.4.8 If blood pressure remains uncontrolled on adequate doses of three drugs, consider adding a fourth and/or seeking expert advice. 1.4.9 If a fourth drug is required, one of the following should be considered: • a higher dose of a thiazide-type diuretic or the addition of another diuretic (careful monitoring is recommended) or • beta-blockers or • selective alpha-blockers. 1.4.10 If blood pressure remains uncontrolled on adequate doses of four drugs, and expert advice has not yet been obtained, this should now be sought. 1.4.11 Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly: • those with an intolerance or contraindication to ACE inhibitors and angiotensin-II receptor antagonists or • women of child-bearing potential or • people with evidence of increased sympathetic drive. In these circumstances, if therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-type diuretic to reduce the patient's risk of developing diabetes. 1.4.12 In patients whose blood pressure is not controlled (that is, above 140/90 mmHg) despite a treatment regimen that includes a beta-blocker, treatment should be revised according to the treatment algorithm on page 45 (see also 1.4.14). 1.4.13 In patients whose blood pressure is well controlled (that is, 140/90 mmHg or below) with a regimen that includes a beta-blocker, long-term management should be considered as part of their routine review. In these patients there is no absolute need to replace the beta-blocker with an alternative agent. 1.4.14 When a beta-blocker is withdrawn, the dose should be stepped down gradually. Beta-blockers should not be withdrawn in patients who have compelling indications for beta-blockade, for example those who have symptomatic angina or who have had a myocardial infarction. 1.4.15 Offer patients with isolated systolic hypertension (systolic BP 160 mmHg or more) the same treatment as patients with both raised systolic and diastolic blood pressure.

	• *Patients with isolated systolic hypertension received similar benefits from treatment to other patients with raised blood pressure.* 1.4.16 Offer patients over 80 years of age the same treatment as other patients over 55, taking account of any comorbidity and their existing burden of drug use. • *Patients over 80 years of age are poorly represented in clinical trials and the effectiveness of treatment in this group is less certain. However, it is reasonable to assume that older patients will receive worthwhile benefits from drug treatment, particularly in terms of reduced risk of stroke.* 1.4.17 Where possible, recommend treatment with drugs taken only once a day. • *A meta-analysis found that patients adhered to once-daily blood pressure lowering regimens better than to regimens requiring two or more doses a day (91% versus 83%). Similarly, once-daily regimens were better adhered to than twice-daily regimens (93% versus 87%).* 1.4.18 Prescribe non-proprietary drugs where these are appropriate and minimise cost. • *Drug treatment beginning with either a non-proprietary thiazide-type diuretic or beta-blocker minimises cost.* • *From a model of lifetime costs and effects, based on the findings of trials, treatment using stepped care including thiazide-type diuretics, beta-blockers, ACE-inhibitors/angiotensin receptor blockers and calcium-channel blockers is estimated to be cost effective.*

Appendix C: Literature search for percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	27/07/2011	Issue 3 of 4, Jul 2011
Database of Abstracts of Reviews of Effects – DARE (CRD website)	27/07/2011	n/a
HTA database (CRD website)	27/07/2011	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	27/07/2011	Issue 3 of 4, Jul 2011
MEDLINE (Ovid)	27/07/2011	1948 to July Week 2 2011
MEDLINE In-Process (Ovid)	27/07/2011	July 25, 2011
EMBASE (Ovid)	27/07/2011	1980 to 2011 Week 29
CINAHL (NLH Search 2.0/EBSCOhost)	27/07/2011	n/a
Zetoc (for update searches only)	27/07/2011	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

hypertension/
exp hypertension renal/
(hypertension or hypertensive).tw.
((high or raise*) adj3 blood adj3 pressure).tw.
1 or 2 or 3 or 4
exp Sympathectomy/
*sympathetic nervous system/
denervation/
Catheter Ablation/

6 or 7 or 8 or 9
exp Kidney/
renal artery/
(kidney or renal).tw.
11 or 12 or 13
10 and 14
5 and 15
((renal or kidney) adj3 sympathe* adj3 (denervat* or ablation* or activ*)).tw.
rsd.tw.
symplicity.tw.
(catheter* adj3 (renal or kidney) adj3 (denervat* or ablation*)).tw.
17 or 18 or 19 or 20
5 and 21
16 or 22
animals/ not humans/
23 not 24