NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of implanting a baroreceptor stimulation device for resistant hypertension

Hypertension (or high blood pressure) raises the risk of having a heart attack or stroke, which can lead to early death. Resistant hypertension is when blood pressure stays high despite drug treatment. In this procedure, a small device is implanted beside the carotid artery in the neck. It sends signals to baroreceptors (sensors that measure blood pressure) that are in the carotid artery, which activate the body's natural blood pressure control system to lower blood pressure.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared in October 2014 and updated in August 2015.

Procedure name

- Implanting a baroreceptor stimulation device for resistant hypertension
- Baroreflex activation therapy

Specialist societies

- British Hypertension Society
- The Vascular Society of Great Britain and Ireland
- British Pharmacological Society.

Description

Indications and current treatment

Hypertension is usually asymptomatic, but it is a common and preventable cause of premature morbidity and death. It is a major, but modifiable, risk factor for cardiovascular disease (including stroke and myocardial infarction) and chronic kidney disease. The cause of primary hypertension, which is the most common form, is not fully understood. However, it is likely to involve multiple factors including an increase in sodium retention and a reduction in renal blood flow mediated by the sympathetic nervous system. Secondary hypertension, which is less common, is caused by conditions affecting the kidneys, arteries, heart or endocrine system.

The NICE guideline on hypertension defines resistant hypertension as blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-II receptor blocker (ARB) plus a calcium-channel blocker (CCB) plus a diuretic. First-line treatment of hypertension includes lifestyle changes, such as diet and exercise. Antihypertensive medications are used if high blood pressure persists. Implanting a baroreceptor stimulation device may be considered if hypertension fails to respond adequately to these measures.

What the procedure involves

Implanting a baroreceptor stimulation device for resistant hypertension aims to lower blood pressure by electrically stimulating the carotid baroreflex, which controls blood pressure by regulating autonomic nervous activity. The device consists of an electrode placed on 1 of the carotid sinuses and a battery-powered implantable generator. Device programming allows the frequency, amplitude and pulse-width of stimulation to be adjusted and it is programmable by time of day.

The procedure is usually done with the patient under general anaesthesia or conscious sedation. The pulse generator is implanted under the skin near the clavicle. A button electrode is sutured to the carotid sinus and a thin wire conducts electrical energy from the implantable pulse generator to the carotid sinus. Intraoperative testing is used to determine the optimal placement of the electrode for the best haemodynamic response.

The device is usually activated about a month after implantation. Clinic staff adjust therapy settings, such as the frequency, amplitude and pulse-width of stimulation, using wireless communication when the patient attends hospital for follow-up appointments. The device can be turned off by clinic staff if necessary.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to implanting a baroreceptor stimulation device for resistant hypertension. The following databases were searched, covering the period from their start to 24 February 2015: 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	Implanting a baroreceptor stimulation device.
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 IP overview

This IP overview is based on approximately 377 patients treated by a bilateral baroreceptor stimulation device from 1 randomised controlled trial (reported in 2 papers), 1 cohort study that was an open label follow-up of the randomised controlled trial, 1 case series[1–5] and 99 patients treated by a unilateral baroreceptor stimulation device from 2 case series and 1 non-randomised comparative study[6–8] .

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 2a Summary of key efficacy and safety findings on implanting a bilateral baroreceptor stimulation device for resistant hypertension

Study 1 Bisognano JD (2011)

Details

Study type	**Randomised controlled trial (Rheos pivotal trial)**
Country	USA (49 centres)
Recruitment period	2007–9
Study population and number	**n=265 (181 immediate baroreceptor stimulation versus 84 deferred baroreceptor stimulation)** Patients with resistant hypertension
Age and sex	61% (162/265) male Mean age (years): 54 (immediate stimulation) and 52 (deferred stimulation)
Patient selection criteria	Resistant hypertension was defined as at least 1 outpatient in-office systolic blood pressure ≥160 mmHg with diastolic blood pressure ≥80 mmHg taken per protocol using a standardised automated device, designed to minimise the 'white coat' effect. This measurement was taken after at least 1 month of maximally tolerated therapy with at least 3 appropriate antihypertensive medications, including a diuretic. Additional enrolment criteria were an ambulatory systolic blood pressure ≥135 mmHg for a 24-hour average, and an absence of clinically significant orthostatic blood pressure changes. Patients with carotid stenosis were excluded.
Technique	The Rheos System (CVRx Inc, Minnesota) was implanted by a vascular, cardiothoracic or neurosurgeon. The device consisted of a pulse generator and leads that were separately tunnelled subcutaneously to attach to each carotid sinus. The device was activated 1 month after implantation and stimulation parameters were adjusted according to a protocol-defined algorithm, including the option of unilateral or bilateral stimulation, such that optimal therapy was achieved by 4 months.
Follow-up	**Mean 21±8 months.**
Conflict of interest/source of funding	Study was funded by CVRx Inc., Minnesota (manufacturer of the Rheos system). All the authors are consultants/advisers for CVRx. One author is an investigator for Relapysa and Medtronic; a consultant for Abbott, Takeda, Lilly, and Servier; a board member of the National Kidney Foundation and the president of the American Society of Hypertension.

Analysis

Follow-up issues:

- 1 patient in the immediate stimulation group was lost to follow-up before the 12-month visit.

Study design issues:

- Randomised, double blind study. 322 patients had a baroreceptor stimulation device implanted and 265 were randomised 1 month later to immediate baroreceptor stimulation or deferred stimulation after the 6-month visit. 2 patients had the device explanted because of infection and were not randomised; the remaining 55 patients were treated in an open-label arm. 4 additional patients did not exhibit an acute testing response during surgery and were not implanted with the device. Patients and investigators remained blinded to treatment until after the 12-month visit.
- Investigators were permitted to change antihypertensive medications during the course of the trial.
- Efficacy analyses were done on an intention-to-treat basis, with results from unblinded and withdrawn patients treated as failures.
- Safety analyses were done using the assessment of an independent adverse events committee. All patients in the randomised portion of the trial were included in the safety evaluation.
- The trial did not have a run-in period to allow for several blood pressure measurements to be made on separate days; the trial assumed a standard deviation of 15 mmHg in the reduction of systolic blood pressure but the observed standard deviation of the difference exceeded 27 mmHg. In addition, the reduction in systolic blood pressure for the control group was larger than expected.
- The implant procedure safety did not meet the pre-specified 82% event-free objective performance criterion that was based on historic implant safety of implantable cardioverter defibrillators; the authors noted that the adverse event profile compares favourably with endarterectomy, which is more like the dissection used for this procedure.

Study population issues:

- The 2 groups were well matched for clinical baseline and demographic characteristics. The mean number of antihypertensive medications at baseline was 5.2 and over 90% of patients were on a diuretic.

Key efficacy and safety findings

Efficacy	Safety

Number of patients analysed: **265 (181 vs 84)**
 	
Response at 6 months (≥10 mmHg drop in SBP at month 6 compared with month 0, defined as the blood pressure obtained at the randomisation visit 1 month after implant):
• Immediate stimulation=54%
• Deferred stimulation=46%, p=0.97 (superiority margin=20%)
 	
88% of patients who responded at 6 months maintained the response at 12 months (p<0.001; the reduction at 12 months had to remain at least 50% of that seen at month 6)
 	
Mean decrease in SBP at 6 months from month 0:
• Immediate stimulation=16±29 mmHg
• Deferred stimulation=9±29 mmHg (p=0.08)
Mean decrease in SBP at 12 months from month 0:
• Immediate stimulation=25±32 mmHg (12 months of stimulation)
• Deferred stimulation=25±31 mmHg (6 months of stimulation)
 	
Proportion of patients with SBP≤140 mmHg at 6 months:
• Immediate stimulation=42%
• Deferred stimulation=24% (p=0.005)
Proportion of patients with SBP≤140 mmHg at 12 months (estimated from graphical presentation):
• Immediate stimulation=53%
• Deferred stimulation=51% (p=0.70)
 	
Post-hoc analysis (done using pre-implant BP measure rather than month 0 because of the unexpected differences between the pre-implant and month 0 SBP values)
Mean decrease in SBP at 6 months from pre-implant:
• Immediate stimulation=26±30 mmHg
• Deferred stimulation=17±29 mmHg (p=0.03)
 	
Mean decrease in SBP at 12 months from pre-implant:
• Immediate stimulation=35±28 mmHg
• Deferred stimulation=33±30 mmHg (p=0.57)
At 12 months, the SBP of 81% of patients had dropped ≥10 mmHg from pre-implant. Patients who responded had a mean reduction of 44 mmHg and 63% of these patients had SBP≤140 mmHg.
	Procedural adverse events
	• **Total=25.7% (68/265)**
	• Surgical complications=4.9% (13/265)
	• Nerve injury with residual deficit=4.9% (13/265)
	• Transient nerve injury=4.5% (12/265)
	• Respiratory complication=2.6% (7/265)
	• Wound complication=2.6% (7/265)
	Event-free rate=74.8%
	
	Adverse events related to baroreceptor stimulation:
	• Hypertensive crisis
	  ○ immediate stimulation=5.0% (9/181)
	  ○ deferred stimulation=8.3% (7/84)
	
	Adverse events related to the device
	• **Total=12.8% (34/265)**
	• Hypertension-related stroke=2.3% (6/265)
	
	Adverse events that occurred at a rate <2% were not described separately in the paper.
	
	Management of the adverse events was not described in the paper.
	
	There were a total of 7 deaths, none of which were related to either the procedure or the device. The causes of death were 3 intracerebral haemorrhages, 2 cardiopulmonary arrests, 1 ruptured abdominal aortic aneurysm, and 1 drug overdose.

Abbreviations used: SBP, systolic blood pressure	

Study 2 Bakris GL (2012)

Details

Study type	**Cohort study (single-arm open-label continuation of Rheos pivotal trial)**
Country	USA
Recruitment period	2010
Study population and number	**n=322 (244 were classified as clinically significant responders after the initial trial phase)** All patients who had a device implanted as part of the Rheos pivotal trial were included, regardless of whether they were subsequently randomised. The original trial recruited patients with resistant hypertension.
Age and sex	Not reported
Patient selection criteria	Resistant hypertension was defined as at least 1 outpatient in-office systolic blood pressure ≥160 mmHg with diastolic blood pressure ≥80 mmHg taken per protocol using a standardised automated device, designed to minimise the 'white coat' effect. This measurement was taken after at least 1 month of maximally tolerated therapy with at least 3 appropriate antihypertensive medications, including a diuretic. Additional enrolment criteria for the Rheos pivotal trial were an ambulatory systolic blood pressure ≥135 mmHg for a 24-hour average, and an absence of clinically significant orthostatic blood pressure changes. Patients with carotid stenosis were excluded.
Technique	The Rheos System (CVRx Inc, Minnesota) was implanted by a vascular, cardiothoracic or neurosurgeon. The device consisted of a pulse generator and leads that were separately tunnelled subcutaneously to attach to each carotid sinus. The device was activated 1 month after implantation and stimulation parameters were adjusted according to a protocol-defined algorithm, including the option of unilateral or bilateral stimulation.
Follow-up	**Mean 28±9 months (maximum 53 months)**
Conflict of interest/source of funding	One author is an employee of CVRx, Inc. One author is a former employee and a current paid consultant of CVRx, Inc. 3 authors have received grant support from CVRx, Inc. and are paid consultants or advisers of CVRx Inc. One author is an investigator for Relapysa and Medtronic; a consultant for Abbott, Takeda, Lilly, and Servier; a board member of the National Kidney Foundation and the president of the American Society of Hypertension.

Analysis

Follow-up issues: At each biannual scheduled visit, patient medications, vital signs and blood pressure were collected.

Study design issues:

- Blood pressure was measured using an automated system. At each follow-up visit, treatment parameters could be changed and investigators were allowed to adjust concomitant pharmacotherapy.
- The pre-implant blood pressure measurements were used as the baseline rather than the 1-month post-implantation measurements that were used in the original Rheos pivotal trial.
- The US Food and Drug Administration (FDA) established rigorous criteria to identify patients whose blood pressure response was clinically significant (called 'responders') so that these patients could have the device replaced after battery depletion and continue to receive long-term therapy. A patient's blood pressure response qualified as clinically significant if, in a sustained manner, goal systolic blood pressure had been reached (≤140 mmHg or ≤130 mmHg in patients with diabetes or renal disease) or if systolic blood pressure dropped by 20 mmHg or more from device activation. Alternatively, a patient's blood pressure response could be assessed through deactivation of the device: the patient was blinded to the date and time of deactivation and then monitored for 30 days after deactivation. A response was defined as an increase in systolic blood pressure by 20 mmHg or more at 2 of 3 assessments at 24 hours or more apart, as well as at the mean of the 3 assessments. If the patient had been free of hypertensive crises for the 3 months before deactivation but experienced 1 crisis needing hospitalisation with systolic blood pressure ≥220 mmHg the patient was deemed to have a clinically significant response.

Other issues:

- There is patient overlap between this study and the previous study (Bisognano et al. 2011). This study includes all patients who had a device implanted in the previous study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **322**

76% (244/322) of patients had a clinically significant response; 10% (32/322) had an indeterminate response (patients who have not yet needed device replacement and do not presently fulfil responder criteria); 14% (46/322) were withdrawn from the trial (10 with a clinically significant response and 36 who had an indeterminate response or who did not respond)

Baseline and follow-up characteristics

	Responders			**Indeterminate**			**Withdrawn**		
	Pre-implant n=244	Month 12 n=233	Last visit n=239	Pre-implant n=32	Month 12 n=30	Last visit n=32	Pre-implant n=46	Month 12 n=31	Last visit n=29
Systolic BP (mmHg)	177 (22)	139 (27)^	142 (29)^	177 (27)	155 (27)^	157 (22)^	187 (22)	161 (33)^	152 (33)^
Diastolic BP (mmHg)	102 (15)	85 (16)^	86 (18)^	105 (18)	95 (21)^	95 (19)^	108 (14)	92 (18)^	91 (23)^
Heart rate	73 (15)	71 (14)	72 (14)	79 (12)	75 (13)	75 (14)	74 (15)	73 (15)	74 (14)
Number of BP medications	5.3 (1.9)	4.7 (2.1)*	5.0 (2.0)**	6.2 (1.9)	5.4 (1.9)	5.9 (2.2)	5.2 (1.6)	5.0 (2.0)	4.8 (2.0)
≥5 BP medications	155 (64)	115 (49)	131 (55)	25 (78)	22 (73)	24 (75)	26 (57)	19 (61)	15 (52)
ACE inhibitor	130 (53)	115 (49)*	114 (48)	17 (53)	14 (47)	16 (50)	28 (61)	18 (58)	16 (62)
Alpha blocker	34 (14)	23 (10)*	27 (11)	7 (22)	5 (17)	4 (13)	5 (11)	4 (13)	3 (10)
Angiotensin receptor blocker	120 (49)	100 (43)*	108 (45)	18 (56)	15 (50)	16 (50)	21 (46)	15 (48)	13 (45)
Beta-blocker	207 (85)	170 (73)*	184 (77)	26 (81)	26 (87)	27 (84)	40 (87)	27 (87)	26 (90)
Calcium channel blocker	157 (64)	138 (59)*	155 (65)**	28 (88)	25 (83)	27 (84)	31 (67)	21 (68)	20 (69)
Diuretic	229 (94)	205 (88)*	216 (90)	32 (100)	25 (83)*	28 (88)	43 (93)	26 (84)	22 (76)**
Minoxidil	37 (15)	25 (11)*	25 (10)	10 (31)	4 (13)	8 (25)	5 (11)	3 (10)	4 (14)
Other sympatholytic	116 (48)	74 (32)*	75 (31)	14 (44)	14 (47)	17 (53)	21 (46)	12 (39)	8 (28)

values are mean (sd) or n (%)

^All BP reductions were significant ($p<0.001$).

*significant change in medication at month 12 relative to pre-implant ($p<0.05$)

**significant change in medication at most recent follow-up relative to month 12 ($p<0.05$) At the most recent follow-up, the use of calcium channel blockers had increased significantly relative to month 12 ($p=0.03$).

55% of patients who had a clinically significant response reached goal pressures throughout follow-up.

Abbreviations used: ACE, angiotensin-converting enzyme; BP, blood pressure; sd, standard deviation

Safety

There were a total of 13 deaths throughout the course of the trial. 9 occurred before approval of the long-term follow-up study, 2 occurred in patients who had not yet enrolled in the long-term study (1 unclassified death during sleep and 1 ischaemic encephalopathy) and 2 occurred in patients considered to have a clinically significant response (2 cardiopulmonary arrests). None of the deaths were considered to be related to either the procedure or the device.

Study 3 Scheffers IJM (2010)

Details

Study type	**Prospective case series (feasibility study [DEBut-HT trial])**
Country	The Netherlands, Switzerland, Germany, Czech Republic, Poland
Recruitment period	2004–7
Study population and number	**n=45** Patients with resistant hypertension
Age and sex	58% (26/45) male Mean age=54 years
Patient selection criteria	Age >21 years, blood pressure ≥160/90 mmHg despite receiving at least 3 antihypertensive agents, including a diuretic. Carotid bifurcations were assessed by ultrasound to be at or below the C3 to C4 level to ensure operative suitability. Exclusions included baroreflex failure, significant orthostatic hypotension, cardiac arrhythmias, chronic atrial fibrillation, clinically significant cardiac valvular disease or hypertension secondary to a treatable cause, carotid artery atherosclerosis with >50% stenosis, prior implant or radiation in the carotid sinus region, currently implanted electrical medical devices, dialysis, and pregnancy or contemplating pregnancy.
Technique	The Rheos System (CVRx Inc, Minnesota) was implanted. The device was activated 1 month after implantation. Therapy was adjusted at each follow-up visit to achieve an optimal reduction in blood pressure.
Follow-up	**3 months–2 years**
Conflict of interest/source of funding	The study was funded by CVRx, Inc.

Analysis

Follow-up issues:

- The first 3 patients enrolled were excluded from the safety and efficacy analyses per protocol. There were 4 dropouts and 1 missed visit, resulting in 37 patients evaluable. At the time of the report, 26 patients had completed 1 year of therapy and 17 had completed 2 years.

Study design issues:

- Multicentre, prospective study.
- Medications were kept constant for 2 months before trial entry and during the first 3 months of therapy, except when medically necessary.
- Blood pressure was measured with a validated electronic device, and readings were repeated when 2 consecutive measurements varied by >5 mmHg. The recorded blood pressure was the mean of the last 2 readings. In addition, ambulatory blood pressure measurements were done with at least 40 measurements during 24 hours using a validated device.
- The study baseline time point was 1 month after device implantation (the time point of device activation).
- An independent committee assessed adverse events to determine the severity and relationship to the procedure or device. The following were considered to be serious adverse events: death, life-threatening situation, inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability.
- 10 eligible patients who declined participation in the trial were followed up by regular care.

Study population issues:

- The median number of antihypertensive medications at baseline was 5 (range 3–9).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 37

Mean change in blood pressure from baseline (±standard error)
<table>
<tr><td></td><td>3 months</td><td>1 year</td><td>2 years</td></tr>
<tr><td colspan="4">Office blood pressure</td></tr>
<tr><td></td><td>n=37</td><td>n=26</td><td>n=17</td></tr>
<tr><td>SBP (mmHg)</td><td>-21±4 (p<0.001)</td><td>-30±6 (p<0.001)</td><td>-33±8 (p=0.001)</td></tr>
<tr><td>DBP (mmHg)</td><td>-12±2 (p<0.001)</td><td>-20±4 (p<0.001)</td><td>-22±6 (p=0.002)</td></tr>
<tr><td>Heart rate (beats/min)</td><td>-8±2 (p<0.001)</td><td>-8±2 (p=0.001)</td><td>-11±4 (p=0.008)</td></tr>
<tr><td colspan="4">Ambulatory blood pressure</td></tr>
<tr><td></td><td>n=26</td><td>n=15</td><td>n=8</td></tr>
<tr><td>SBP (mmHg)</td><td>-6±3 (p=0.102)</td><td>-13±3 (p<0.001)</td><td>-24±8 (p=0.017)</td></tr>
<tr><td>DBP (mmHg)</td><td>-4±2 (p=0.041)</td><td>-8±2 (p=0.001)</td><td>-13±5 (p=0.049)</td></tr>
<tr><td>Heart rate (beats/min)</td><td>-5±2 (p=0.001)</td><td>-6±2 (p=0.012)</td><td>-11±34 (p=0.005)</td></tr>
</table>
The intensity of antihypertensive drug treatment was unchanged.

There was no significant change in blood pressure in the cohort of patients who declined to participate in the trial, and the mean number of antihypertensive medications was slightly increased.

At each visit, the device was temporarily turned off and blood pressure immediately increased to its baseline levels, only to fall again when the device was reactivated.
</td><td>
Procedure-related serious adverse event=16.7% (7/42)
Device-related serious adverse event=2.4% (1/42)

Procedure-related serious adverse events

1 fatal procedure-related event occurred 6 days after implant due to angioneurotic oedema before device activation. The cause could not be determined definitively, but a drug reaction is suspected.
Device explantation before activation because of infection=7.1% (3/42) (in 1 of these patients, the leads were not removed and a new device was implanted 12 months later).
Perioperative stroke=2.4% (1/42) (minimal residual effects)
Tongue paresis=2.4% (1/42) (most likely due to intraoperative injury to the hypoglossal nerve)
Moderate pulmonary oedema=2.4% (1/42) (resolved within 6 days)

Device-related serious adverse event

Movement of implantable pulse generator, needing further surgery to reposition it=2.4% (1/42)

The proportion of unrelated serious adverse events in the treated patients was similar to that in the cohort of patients who declined to participate (events not described in the paper).

None of the patients had carotid artery stenosis at the 1-year visit, and there were no reports of orthostatic hypotension, collapse or syncope in the 32 patients with data at baseline and after 3 months of therapy.
</td></tr>
<tr><td colspan="2">Abbreviations used: DBP, diastolic blood pressure; SBP, systolic blood pressure</td></tr>
</table>

Study 4 Illig KA (2006)

Details

Study type	**Case series (phase II Rheos Feasibility Trial)**
Country	USA
Recruitment period	2005
Study population and number	**n=10** Patients with resistant hypertension
Age and sex	60% (6/10) male Mean age=50 years
Patient selection criteria	Patients with resistant hypertension while receiving optimal medical management. Inclusion criteria: maximisation of antihypertensive treatment, elimination of secondary causes of hypertension, exclusion of baroreflex dysfunction, and absence of carotid disease.
Technique	Bilateral implantation using the Rheos Baroreflex Hypertension Therapy System (CVRx, Inc)
Follow-up	**Mean 10 months (range 4–14)**
Conflict of interest/source of funding	One author is a paid consultant of CVRx, Inc. and 3 authors are employees of CVRx, Inc.

Analysis

Follow-up issues: all patients had finished 4 months' follow-up (3 months stimulation).

Study design issues: Dose-response testing was done before hospital discharge. Voltage was increased to 6V or until the patient reached a prospectively defined haemodynamic end point (systolic blood pressure<100 mmHg, mean arterial blood pressure<60 mmHg, and/or heart rate<50 beats/min).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: 10 **Dose-response testing before hospital discharge** The mean SBP decreased from 180 mmHg with no activation to 139 mmHg at 6V, a reduction of 41 mmHg (range 22–104 mmHg, p<0.001) The mean DBP decreased from 81 mmHg with no activation to 62 mmHg at 6V, a reduction of 19 mmHg (range 11–82 mmHg, p<0.005) Pulse pressure decreased from 98 mmHg with no activation to 77 mmHg at 6V (p<0.005) Heart rate decreased from 79 beats/min with no activation to 70 beats/min at 6V (p<0.005) In all patients, consistent dose-response curves were apparent.	'There were no unanticipated serious procedure or device-related adverse events or perioperative deaths.' A small number of patients reported subjective awareness of muscle twitching, although no clinically visible effects were seen. • Infection=10% (1/10) (the infection occurred after the 4-month follow-up visit and was successfully treated by removal of the device) The paper states that the worldwide total infection rate is 5.5% (actual numbers not reported) and is expected to decrease with decreasing size of implantable pulse generator. 2 generators were changed for planned battery replacement in patients who needed high voltages for blood pressure control.
Abbreviations used: DBP, diastolic blood pressure; SBP, systolic blood pressure	

Study 5 de Leeuw PW (2015)

Details

Study type	**Post-hoc analysis of randomised controlled trial (Rheos pivotal trial)**
Country	USA
Recruitment period	Not reported
Study population and number	**n=295 (127 right stimulation, 88 left stimulation, 80 bilateral stimulation)** Patients with resistant hypertension
Age and sex	60% male; mean age=53 years for right and bilateral stimulation groups, 57 years for left stimulation group.
Patient selection criteria	Resistant hypertension (defined as an office systolic blood pressure ≥160 mmHg with a diastolic blood pressure ≥80 mmHg despite treatment for 1 month or more of maximally tolerated therapy with 3 or more appropriate antihypertensive medications, including a diuretic. In addition, the 24-hour average systolic blood pressure as obtained with ambulatory monitoring had to be ≥135 mmHg. Exclusion criteria were secondary hypertension, clinically significant orthostatic falls in blood pressure, baroreflex failure, autonomic neuropathy, significant carotid artery stenosis, and cardiovascular complications within 3 months before implant.
Technique	Bilateral implantation using the Rheos Baroreflex Hypertension Therapy System (CVRx, Inc). Patients were randomised to immediate baroreceptor stimulation or deferred stimulation after the 6-month visit. To optimise battery longevity, unilateral stimulation was applied unless bilateral stimulation resulted in a greater blood pressure reduction. With unilateral stimulation, the side with greatest response was stimulated.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was supported by a research grant from CVRx Inc.

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Post-hoc analysis of pooled data from the 2 randomised groups of patients. The 6-month data from patients with immediate stimulation and the 12-month data from the patients with deferred stimulation were pooled for the analysis.

Study population issues: There were no differences in baseline characteristics between the groups with respect to sex, race, number of hypertensive drugs, and whether they had been assigned to immediate or deferred stimulation. Age was slightly higher in the left-sided stimulation group than in the other 2 groups (p=0.05).

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 295

Changes in blood pressure (mean±standard deviation)
<table><tr><td></td><td colspan="2">Unilateral stimulation</td><td></td><td colspan="2">Bilateral stimulation</td><td></td></tr><tr><td></td><td>Baseline</td><td>6 months</td><td>p value</td><td>Baseline</td><td>6 months</td><td>p value</td></tr><tr><td>Office systolic blood pressure (mmHg)</td><td>178±23</td><td>146±30</td><td><0.001</td><td>178±23</td><td>155±31</td><td><0.001</td></tr><tr><td>Diastolic blood pressure</td><td>101±14</td><td>87±17</td><td><0.001</td><td>105±16</td><td>95±17</td><td><0.001</td></tr><tr><td>Heart rate</td><td>73±15</td><td>71±14</td><td><0.02</td><td>76±14</td><td>75±13</td><td>NS</td></tr></table>
Blood pressure and heart rate were significantly lower in the unilateral than in the bilateral group after the 6-month period (p<0.03 for all).

The absolute reductions in office systolic and diastolic pressure were significantly greater with unilateral than with bilateral stimulation.

Percentage of patients who reached an office goal blood pressure of ≤140 mmHg systolic:
• Unilateral stimulation=46%
• Bilateral stimulation=41%, p=0.003

The responses were greater in the group with right-sided stimulation as compared against the group with left-sided stimulation and bilateral stimulation, but this was significant only for systolic pressure.

Normalisation of blood pressure:
• Left-stimulation=35%
• Right-stimulation=54%, p=0.008 (against left-sided stimulation)
• Bilateral=41%, p=0.022 (against left-sided stimulation)</td><td>No safety data were reported.</td></tr>
<tr><td colspan="2">Abbreviations used: NS, not significant</td></tr>
</table>

Table 2b Summary of key efficacy and safety findings on implanting a unilateral baroreceptor stimulation device for resistant hypertension

Study 6 Hoppe UC (2012)

Details

Study type	**Prospective case series**
Country	Austria, Germany, the Netherlands, Canada
Recruitment period	2011
Study population and number	**n=30** Patients with resistant hypertension
Age and sex	47% (14/30) male Mean age=57 years
Patient selection criteria	Resistant hypertension defined as systolic blood pressure ≥140 mmHg despite being prescribed at least 3 antihypertensive medications, including a diuretic (unless the patient was intolerant of diuretics), and on stable medication for ≥4 weeks. Qualifying blood pressure measurements needed 2 consecutive measurements at least 24 hours apart within 14 days before implant. Major exclusion criteria included hypertension secondary to an identifiable and treatable cause other than sleep apnoea, known or suspected baroreflex failure or autonomic neuropathy, and myocardial infarction, unstable angina, syncope, or cerebral vascular accident within 3 months before implant.
Technique	A miniaturised second-generation system was used (Barostim neo® system). The procedure was done through a small incision (2.5–5 cm) because of the reduced size of the lead and a single electrode was directly sutured to the carotid sinus.
Follow-up	**6 months**
Conflict of interest/source of funding	7 authors have received research grant support from CVRx, Inc. and are currently paid consultants or advisers of CVRx, Inc. and 2 authors are employees of CVRx, Inc.

Analysis

Follow-up issues:

- 1 patient missed the 6 month visit so data from the 9 month visit were used.

Study design issues:

- Blood pressure was assessed using an automated device that has been shown to minimise white coat hypertension and leads to reported values that correlate with daytime ambulatory blood pressure.
- Investigators were encouraged to maintain patients on a consistent medical regimen through the course of the study, although changes were permitted if medically necessary.

Study population issues:

- Before enrolment, 6 patients had been treated by renal nerve ablation but their hypertension remained uncontrolled.

Other issues:

- The authors note that average device longevity of approximately 3 years in this trial means that pulse generator replacements will be needed less often than with the previous generation of devices.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **30** Baseline blood pressure=171.7±20.2/99.5±13.9 mmHg **Mean reduction in systolic blood pressure from pre-implant baseline (mmHg):** • 3-months=26.1±3.3 mmHg (p<0.001) • 6-months=26.0±4.4 mmHg (p<0.001) After 6 months, heart rate trended down by 5.0±2.6 beats/min (p=0.07) from a baseline of 75.0±12.1 beats/min. **Proportion of patients with systolic blood pressure ≤140 mmHg:** • Baseline=0% • 6-months=43% The mean number of medications per patient decreased 0.3±0.3 (p=not significant). In the subset of 6 patients with prior renal nerve ablation, arterial pressure decreased by 22.3±9.8 mmHg at 6 months.	**Perioperative events (within 30 days of device implantation)** • Device pocket haematoma=3.3% (1/30) (day 3, patient recovered with no residual effects) • Self-inflicted wound complication=3.3% (1/30) (day 7, patient recovered with no residual effects) • Intermittent pain lateral to device system=3.3% (1/30) (day 30, patient recovered with no residual effects) Patients free from events=90% **Long-term events** • Intermittent pain near the device system=3.3% (1/30) (day 44, patient recovered with no residual effects) Patients free from events=97%

Study 7 Wallbach M (2014)

Details

Study type	**Prospective case series**
Country	Germany
Recruitment period	Not reported (ethical approval was gained in September 2011)
Study population and number	**n=25** Patients with resistant hypertension
Age and sex	44% (11/25) male Mean age=61 years
Patient selection criteria	Patients fulfilling diagnosis of resistant hypertension (defined as blood pressure above a goal despite adherence to at least 3 optimally dosed antihypertensive medications of different classes, one of which is a diuretic) with blood pressure above 140/90 mmHg and optimal therapy for secondary reasons were prospectively included. White-coat hypertension was excluded by 24-hour ambulatory monitoring.
Technique	A miniaturised second-generation system was used (Barostim neo® system). The device was activated 4 weeks after implantation and stimulation was individually increased by adaption of programmed parameters during monthly follow-up.
Follow-up	**6 months**
Conflict of interest/source of funding	2 authors received a research grant from CVRx, Inc.

Analysis

Follow-up issues:

- An additional patient was lost to follow-up and was excluded from the analysis.

Study design issues:

- Individual adaption of antihypertensive medication by the treating physician was allowed.
- It is not clear if the baseline blood pressures were measured before the baroreceptor stimulator was implanted or after implantation but before device activation.

Study population issues:

- 9 patients had prior renal denervation.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 25
Resting blood pressure (mmHg) and antihypertensive drugs
<table>
<tr><td></td><td>Baseline</td><td>6 months</td><td>p</td></tr>
<tr><td>Systolic BP</td><td>160.1±26.9</td><td>143.4±27.0</td><td><0.01</td></tr>
<tr><td>Diastolic BP</td><td>83.1±16.6</td><td>73.9±14.4</td><td><0.01</td></tr>
<tr><td>Peripheral mean arterial BP</td><td>109.9±20.4</td><td>97.3±18.5</td><td><0.01</td></tr>
<tr><td>Heart rate (beats/min)</td><td>64.8±10.4</td><td>64.7±10.4</td><td>0.97</td></tr>
<tr><td>Number of hypertensives</td><td>6.6±1.7</td><td>6.3±1.7</td><td>0.28</td></tr>
<tr><td>Antihypertensive withdrawal and/or dose reduction</td><td>-</td><td>60% (15/25)</td><td></td></tr>
</table>
Values are mean ±standard deviation

Mean central aortic systolic BP (mmHg):
• Baseline=147.2±27.8
• 6 months after activation=130.2±25.2, p<0.01

Mean central aortic diastolic BP (mmHg):
• Baseline=84.5±16.9
• 6 months after activation=74.8±14.6, p=0.01

Central aortic pulse pressure (mmHg):
• Baseline=62.9±18.6
• 6 months after activation=55.2±16.0, p<0.01

Aortic augmentation pressure and augmentation index at a heart rate of 75 beats/minute were significantly reduced by 4.3±7.9 mmHg (p<0.01) and 3.5±6.8% (p=0.02).

Pulse wave velocity decreased from 10.3±2.6 to 8.6±1.3 m/s (p<0.01) 6 months after device activation.</td><td>No safety data were reported.</td></tr>
<tr><td colspan="2">Abbreviations used: BP, blood pressure</td></tr>
</table>

Study 8 Wallbach M (2014)

Details

Study type	**Non-randomised comparative study**
Country	Germany
Recruitment period	2012–4
Study population and number	**n=44 (23 baroreceptor stimulation versus 21 standard care)** Patients with resistant hypertension and chronic kidney disease
Age and sex	48% (11/23) versus 86% (18/21) male, p=0.02 Mean age=61 years
Patient selection criteria	Patients with chronic kidney disease and resistant hypertension with blood pressure above national and international target (≤130/80 mmHg), age ≥18 years. Exclusion criteria: pregnancy, acute myocardial infarction, unstable angina, stroke, or transitory ischaemic attack within the previous 6 months, stenosis of the carotid artery>70%. All patients were treated for hypertension for at least 1 year.
Technique	Barostim neo® (CVRx, USA) was used.
Follow-up	**6 months**
Conflict of interest/source of funding	2 authors declared lecture fees and/or funding from CVRx; 1 author has received lecture fees and enumeration for including patients into clinical trials from CVRx.

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Controls were those patients who met the inclusion criteria but refused baroreceptor stimulation treatment.

Key efficacy and safety findings

Efficacy

Number of patients analysed: 44 (23 versus 21)

Office blood pressure, ambulatory blood pressure and antihypertensive drugs

	Baroreceptor stimulation			Controls		
	Baseline	Month 6	p	Baseline	Month 6	p
Office blood pressure (mean±standard deviation)						
Systolic, mmHG	161.0±31.9	144.0±32.3	<0.01	155.3±19.1	153.6±17.4	0.70
Diastolic, mmHg	87.4±15.2	77.7±17.1	<0.01	84.4±12.0	83.4±13.0	0.70
Mean, mmHg	116.9±20.9	104.2±22.2	<0.01	112.8±12.0	111.5±12.3	0.66
Heart rate, bpm	73.0±12.7	68.4±10.8	0.06			
Ambulatory blood pressure measurement (mean±standard deviation)						
Systolic, mmHg	142.3±16.4	136.0±23.7	0.08			
Diastolic, mmHg	79.6±11.7	74.8±16.4	0.09			
Mean, mmHg	102.6±12.3	97.2±18.6	0.08			
Maximum, mmHg	179.1±20.7	179.2±33.3	0.98			
Number of hypertensives	6.6±1.6	6.1±1.7	0.02	5.8±1.3	5.9±1.4	0.16
Antihypertensive withdrawal and/or dose reduction		70% (16/23)			0% (0/21)	

Functional renal parameters; mean ± standard deviation or median (IQR)

	Baroreceptor stimulation			Controls		
	Baseline	Month 6	p	Baseline	Month 6	p
Proteinuria, n	23	23		21	21	
Proteinuria, mg/g creatinine	283.9 (83.5–555.1)	136.5 (47.6–274.3)	0.01	134.4 (73.7–187.7)	112.8 (60.3–250.0)	0.55
Albuminuria, mg/g creatinine	47.7 (16.9–555.1)	45.0 (22.9–130.9)	0.01	14.9 (9.5–49.6)	17.9 (9.3–74.8)	0.59
Excretory renal function, n	22	22		21	21	
Serum creatinine, mg/dl	1.35±0.75	1.39±0.86	0.66	1.35±0.51	1.55±0.75	0.04
estimated glomerular filtration rate (ml/min)	63.6±27.8	63.1±29.1	0.82	62.8±25.0	54.5±23.4	<0.01
Urinary sodium excretion, n	22	22				
24-hour sodium excretion, mmol/day	116.61±63.93	134.94±47.29	0.13	-	-	

Abbreviations used: IQR, interquartile range

Safety

No safety outcomes were reported

Efficacy

Blood pressure reduction

A randomised controlled trial of 265 patients treated by implantation of a bilateral baroreceptor stimulation device that was either turned on 1 month after implantation (immediate stimulation) or turned on after 6 months (deferred stimulation) was carried out. Response rates at 6 months (defined as 10 mmHg or greater decrease in systolic blood pressure at month 6 compared with systolic blood pressure obtained 1 month after implant) were 54% and 46%, respectively ($p=0.97$)[1]. Of those patients whose blood pressure responded to active therapy at 6 months, 88% maintained a response at 12 months ($p<0.001$). A post-hoc analysis of pooled data from this study showed that unilateral stimulation, and in particular right-sided stimulation, had a greater effect on blood pressure than bilateral or left-sided stimulation[5].

The mean decreases in systolic blood pressure at 6 months were 16±29 mmHg and 9±29 mmHg respectively ($p=0.08$). The proportion of patients with systolic blood pressure of 140 mmHg or less at 6 months was 42% for immediate stimulation and 24% for deferred stimulation ($p=0.005$)[1].

A cohort study of 322 patients, which was an open-label follow-up trial of the randomised controlled trial described above (including all patients who had a device implanted regardless of whether they were subsequently randomised), reported that the mean blood pressure drop was 35/16 mmHg compared with pre-implant; this was after a mean follow-up of 28 months[2]. Among the 244 patients whose blood pressure had a response, 55% reached goal pressures (less than 140 mmHg or less than 130 mmHg in patients with diabetes or kidney disease) throughout follow-up.

A case series of 45 patients treated by implantation of a bilateral baroreceptor stimulation device reported that mean blood pressure decreased by 21/12 mmHg in 37 evaluable patients after 3 months of baroreceptor stimulation ($p=0.001$)[3]. The mean reduction after 2 years of follow-up was 33/22 mmHg ($n=17$, $p=0.001$ for systolic blood pressure and $p=0.002$ for diastolic blood pressure).

A non-randomised comparative study of 44 patients treated by implantation of a unilateral baroreceptor stimulation device or standard treatment reported that mean office blood pressure decreased in patients treated by baroreceptor stimulation from 116.9 mmHg at baseline to 104.2 mmHg at 6 months' follow-up ($p<0.01$); there was no significant decrease in the control patients (112.8 mmHg at baseline compared with 111.5 mmHg at 6 months' follow-up, $p=0.66$)[8].

A case series of 30 patients treated by implantation of a unilateral stimulation device reported a mean reduction in systolic blood pressure from the pre-implant baseline of 26.1±3.3 mmHg at 3 months' follow-up ($p<0.001$)[6].The mean reduction was 26.0±4.4 mmHg at 6 months' follow-up ($p<0.001$). The proportion

of patients with systolic blood pressure of 140 mmHg or less was 43% at 6 months' follow-up.

A case series of 25 patients treated by implantation of a unilateral stimulation device reported that the mean blood pressure decreased from 160/83 mmHg at baseline to 143/74 mmHg at 6 months' follow-up ($p<0.01$). The peripheral mean arterial blood pressure reduced from 109.9 mmHg to 97.3 mmHg ($p<0.01$)[7].

Antihypertensive medications

The cohort study of 322 patients reported that the mean number of prescribed medications fell significantly between pre-implantation and month 12 in those patients who had a response (n=244). These reduced from 5.3±1.9 to 4.7±2.1 and remained lower after a mean follow-up of 28 months ($p<0.05$)[2]. The case series of 45 patients reported that the median number of antihypertensive medications per patient was unchanged after 2 years' follow-up[3].

The case series of 30 patients reported that the mean number of medications per patient decreased 0.3±0.3 after 6 months' follow-up (p=not significant)[6].The case series of 25 patients reported that 60% (15/25) of patients had reduced their use of antihypertensive medication at 6 months' follow-up (either withdrawal of an antihypertensive or dose reduction)[7].

Safety

Bilateral baroreceptor stimulation device

Nerve injury

Nerve injury with residual deficit was reported in 5% (13/265) of patients and transient nerve injury in 5% (12/265) of patients in the randomised controlled trial of 265 patients (no further details given)[1]. Tongue paresis, most likely caused by intraoperative injury to the hypoglossal nerve, was reported in 1 patient in the case series of 45 patients[3].

Respiratory complications

Respiratory complications (not otherwise described) after device implantation were reported in 3% (7/265) of patients in the randomised controlled trial of 265 patients[1].

Wound complication/infection

Device removal before activation because of infection was reported in 7% (3/42) of patients in the case series of 45 patients. In 1 patient, the leads were left in and a new device was implanted 12 months later[3]. Infection needing device removal was reported in 1 patient in a case series of 10 patients; the infection occurred after the 4-month follow-up visit[4].

Wound complications (not otherwise described) after device implantation were reported in 3% (7/265) of patients in the randomised controlled trial of 265 patients[1].

Hypertensive crisis

Hypertensive crisis was reported in 5% (9/181) of patients treated by immediate baroreceptor stimulation and 8% (7/84) of patients treated by deferred stimulation in the randomised controlled trial of 265 patients[1].

Stroke

Hypertension-related stroke was reported in 2% (6/265) of patients in the randomised controlled trial of 265 patients (timing and study group not reported)[1]. Perioperative stroke with minimal residual effects was reported in 1 patient in the case series of 45 patients[3].

Movement of pulse generator

Movement of the implantable pulse generator, needing further surgery to reposition it, was reported in 1 patient in the case series of 45 patients[3].

Other

Angioneurotic oedema that caused a patient's death was reported 6 days after implant before device activation, in the case series of 45 patients. The cause could not be determined definitively, but a drug reaction was suspected[3]. Moderate pulmonary oedema within 30 days of the implant was reported in 1 patient in the same study; this resolved within 6 days.

Unilateral baroreceptor stimulation device

Wound complication/infection

Device pocket haematoma 3 days after device implantation was reported in 1 patient in the case series of 30 patients; the patient recovered with no residual effects[6]. A self-inflicted wound complication was reported in 1 patient in the case series of 30 patients; the patient recovered with no residual effects[6].

Pain

Intermittent pain lateral to the device system was reported within 30 days of device implantation in 1 patient in the case series of 30 patients; the patient recovered with no residual effects[6]. Intermittent pain near the device system more than 30 days after device implantation was reported in 1 patient in the same study; the patient recovered with no residual effects.

Validity and generalisability of the studies

- There are different devices used between the studies. Three studies used a second generation device that comprised a unilateral lead and a button electrode sutured to the carotid sinus[6 – 8]. The technique for implanting this device is less invasive than the technique used to implant the original devices and there may be different safety profiles.
- The randomised controlled trial randomised patients 1 month after device implantation. The study found unanticipated blood pressure differences from pre-implant to randomisation, which were attributed to factors such as changes to antihypertensive medication, the lack of a run-in period to allow for several qualifying blood pressure measurements to be made on separate days and limitations on the number of measurements after implantation[1].
- Several studies include patients who have had previous unsuccessful renal denervation.
- One study is an open-label follow-up of the randomised controlled trial so the same patients are included in both studies[1,2]. Another study reports a post-hoc analysis of pooled data from the same randomised controlled trial[8].

Existing assessments of this procedure

The Australian Health Policy Advisory Committee on Technology (HealthPACT) produced a brief on 'Implantable carotid sinus baroreflex device for the treatment of drug resistant hypertension', in 2014[9]. The report summary states:

'Currently there is a lack of clinical and cost-effectiveness evidence to support the use of the baroreflex stimulation to reduce hypertension. It should be noted that the Baroreflex Rheos device has been superseded by the Barostim neo, which is not available in Australia. A large, prospective RCT on the Barostim neo device is due for completion in 2015, the results of which, if favourable, will be identified by horizon scanning activities. Therefore it is recommended that no further research on behalf of HealthPACT is warranted at this 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.

Interventional procedures

- Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. NICE interventional procedure guidance 418 (2012). Available from http://www.nice.org.uk/guidance/IPG418

Clinical guidelines

- Hypertension: Clinical management of primary hypertension in adults. NICE clinical guideline 127 (2011). Available from http://www.nice.org.uk/guidance/CG127

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 is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to where comments are considered voluminous, or publication would be unlawful or inappropriate. Seven Specialist Advisor Questionnaires for implanting a baroreceptor stimulation device for resistant hypertension were submitted and can be found here.

Patient commentators' opinions

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

Issues for consideration by IPAC

Ongoing trials:

- CVRx Barostim Hypertension Pivotal Trial (NCT01679132); randomised controlled trial; USA; estimated enrolment 310; estimated study completion date July 2015

- Neo Non-Randomized Hypertension Study (NCT01471834) ; Canada, the Netherlands, estimated enrolment 40; estimated study completion date July 2015

References

1. Bisognano JD, Bakris G, Nadim MK et al. (2011) Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. Journal of the American College of Cardiology 58: 765-773
2. Bakris GL, Nadim MK, Haller H et al. (2012) Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. Journal of the American Society of Hypertension 6: 152-158
3. Scheffers IJ, Kroon AA, Schmidli J et al. (2010) Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. Journal of the American College of Cardiology 56:1254-1258
4. Illig KA, Levy M, Sanchez L et al. (2006) An implantable carotid sinus stimulator for drug-resistant hypertension: surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. Journal of Vascular Surgery 44: 1213-1218
5. de Leeuw PW, Alnima T, Lovett E et al. (2015) Bilateral or unilateral stimulation for baroreflex activation therapy. Hypertension 65:187-192
6. Hoppe UC, Brandt MC, Wachter R et al. (2012) Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. Journal of the American Society of Hypertension 6: 270-276
7. Wallbach M, Lehnig LY, Schroer C et al. (2014) Effects of baroreflex activation therapy on arterial stiffness and central hemodynamics in patients with resistant hypertension. Journal of Hypertension 32, doi: 10.1097/HJH.0000000000000361
8. Wallbach M, Lehnig L-Y, Schroer C et al. (2014) Impact of baroreflex activation therapy on renal function – a pilot study. American Journal of Nephrology 40: 371–80
9. Jacobsen JH. Implantable carotid sinus baroreflex device for the treatment of drug-resistant hypertension. Health Policy Advisory Committee onTechnology, Technology Brief Update. Adelaide, South Australia: ASERNIP-S, July 2014

Appendix A: Additional papers on implanting a baroreceptor stimulation device for resistant hypertension

The following table outlines the studies that are considered potentially relevant to the IP 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
Alnima T, de Leeuw PW, Tan FE et al. (2013) Renal responses to long-term carotid baroreflex activation therapy in patients with drug-resistant hypertension. Hypertension 61: 1334-1339	RCT (Rheos Pivotal Trial) n=322 Follow-up=12 months	Baroreflex activation therapy in hypertensive patients is associated with a mild decrease in glomerular filtration rate, which may be considered as a normal haemodynamic response to the drop in blood pressure. Long-term treatment does not result in further decrease in renal function.	Another paper reporting results from the same study is included in table 2.
Alnima T, Scheffers I, de Leeuw PW et al. (2012) Sustained acute voltage-dependent blood pressure decrease with prolonged carotid baroreflex activation in therapy-resistant hypertension. Journal of Hypertension 30: 1665-1670	Case series n=45 Follow-up=13 months	Acute voltage-dependent blood pressure and heart rate decrease is preserved after at least 1 year of continuous activation in patients with resistant hypertension. This indicates that response adaptation and nerve fatigue are very unlikely in long-term carotid baroreflex activation.	Substudy of DEBuT-HT (Device Based Therapy in Hypertension) Trial, which is included in table 2.
Brandt MC, Madershahian N, Velden R et al. (2011) Baroreflex activation as a novel therapeutic strategy for diastolic heart failure. Clinical Research in Cardiology 100: 249-251	Case report n=1 Follow-up=3 months	Treatment resulted in substantial and sustained reduction in blood pressure and effective treatment of overt severe diastolic heart failure, accompanied by a decreased requirement for hypertensive medication.	Case report
Courand PY, Feugier P, Workineh S et al. (2014) Baroreceptor stimulation for resistant hypertension: first implantation in France and literature review. Archives of cardiovascular diseases 107: 690-696	n=1 FU=9 months	The procedure was well tolerated, with only a transient episode of cough and hoarseness when a high intensity of stimulation was used. After 9 months of follow-up, there was a reduction of 15 mmHg in systolic and 8 mmHg in diastolic blood pressure.	Case report

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Heusser K, Tank J, Engeli S et al. (2010) Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension 55: 619-626	Case series n=12	Electric field stimulation of carotid baroreceptors acutely reduced sympathetic nerve activity in a subgroup of patients with refractory arterial hypertension. The reduction in sympathetic activity was associated with decreases in plasma renin concentration and blood pressure. Moreover, electric field stimulation of carotid baroreceptors throughout the cardiac cycle did not impair physiological baroreflex control, and patients did not report symptoms suggestive of baroreflex dysfunction.	Larger studies are included.
Karunaratne H, Muluk S, Papademetriou V (2011) Implantation of a carotid baroreceptor stimulator in patients with pacemakers and hypertension. Pacing & Clinical Electrophysiology 34: 354-356	Case series n=4 Mean follow-up=8 months	Baroreceptor stimulation devices do not negatively influence pacemaker function at elevated output settings and sensitive pacemaker parameters.	Small case series investigating the impact of baroreceptor stimulation devices on pacemakers.
Madershahian N, Scherner,M, Muller-Ehmsen J et al. (2014) Baroreflex activation therapy in patients with pre-existing implantable cardioverter-defibrillator: compatible, complementary therapies. Europace 16: 861-865	Case series n=7	Interaction testing during implantation and follow-up showed that there was no device-device interaction. No interaction was observed at maximum atrial and ventricular sensitivity settings and maximum Neo output settings.	Small case series investigating compatibility of procedure with pre-existing implantable cardioverter-defibrillators.
May M, Ahrens J, Menne J et al. (2014) Limited acute influences of electrical baroreceptor activation on insulin sensitivity and glucose delivery: a randomized, double-blind, crossover clinical study. Diabetes 63 (8) 2833-2837	RCT n=16	Acute changes in baroreceptor stimulation did not elicit significant changes in muscular glucose delivery and whole-body insulin sensitivity. Baroreflex-mediated changes in sympathetic vasomotor tone may have a limited acute effect on muscle glucose metabolism in patients with treatment-resistant hypertension.	Study was focused on the effect of baroreceptor activation on insulin sensitivity.
Sloand JA, Illig KA, Bisognano JD (2007) Improved control of resistant hypertension with device-mediated electrical carotid sinus baroreflex stimulation. Journal of Clinical Hypertension 9: 716-719	Case report n=1	Mean ambulatory blood pressures were significantly improved ($p<0.001$). After 1 year of therapy, the patient had resolution of her headaches and cardiovascular symptoms and was able to return to work full-time.	Case report

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Tordoir JH, Scheffers I, Schmidli J et al. (2007) An implantable carotid sinus baroreflex activating system: surgical technique and short-term outcome from a multi-center feasibility trial for the treatment of resistant hypertension. European Journal of Vascular & Endovascular Surgery 33: 414-421	Case series n=17 Follow-up=4 months	No perioperative strokes or deaths occurred. System tests performed 1 or up to 3 days postoperatively resulted in significant (all p ≤0.0001) mean maximum reduction, with standard deviations and 95% confidence limits for systolic BP, diastolic BP and heart rate of 28+/-22 (17, 39) mmHg, 16+/-11 (10, 22) mmHg and 8+/-4 (6, 11) beats/min, respectively. Repeated testing during 3 months of therapeutic electrical activation demonstrated a durable response.	Reports preliminary data from DEBuT-HT (Device Based Therapy in Hypertension) Trial, which is included in table 2.
Wustmann K, Kucera JP, Scheffers I et al. (2009) Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension. Hypertension 54: 530-536	Case series n=21 Follow-up=3 months	Chronic baroreceptor stimulation decreased office blood pressure from 185±31/109±24 mm Hg to 154±23/95±16 mm Hg (p<0.0001/p=0.002). Mean heart rate decreased from 81±11 to 76±10 beats per minute (p=0.001).	Substudy of DEBuT-HT (Device Based Therapy in Hypertension) Trial, which is included in table 2.

Appendix B: Related NICE guidance for implanting a baroreceptor stimulation device for resistant hypertension

Guidance	Recommendations
Interventional procedures	**Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. NICE interventional procedure guidance 418 (2012).** 1.1 Current evidence on percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension is from limited numbers of patients, but there is evidence of efficacy in the short and medium term. There is inadequate evidence on efficacy in the long term; this is particularly important for a procedure aimed at treating resistant hypertension. The limited evidence suggests a low incidence of serious periprocedural complications, but there is inadequate evidence on long-term safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. 1.2 Clinicians wishing to undertake percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy, and provide them with clear written information. In addition, the use of NICE's information for patients (Understanding NICE guidance) is recommended. 1.3 Patient selection should be carried out by a multidisciplinary team including a physician with expertise in hypertension and a specialist in endovascular interventions, giving consideration to the number of antihypertensive drugs that have failed to control the patient's blood pressure and the anatomical suitability of their renal arteries. The procedure should only be done by specialists who are experienced in endovascular interventions and with facilities for emergency stenting in case this is required. 1.4 NICE encourages further research on this procedure. Patient selection criteria should be described clearly and reported outcome measures should include adverse events and the long-term effect of the procedure on blood pressure. 1.5 NICE also encourages data collection and publication of

	outcomes on all patients having this procedure. Clinicians should submit data on all patients having this procedure to the national register when it becomes available.
NICE guidelines	**Hypertension: Clinical management of primary hypertension in adults. NICE clinical guideline 127 (2011).** There is no mention of baroreceptor stimulation in the clinical guideline. *Initiating treatment* 1.5.1 Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following: • target organ damage • established cardiovascular disease • renal disease • diabetes • a 10-year cardiovascular risk equivalent to 20% or greater. [new 2011] 1.5.2 Offer antihypertensive drug treatment to people of any age with stage 2 hypertension. [new 2011] 1.5.3 For people aged under 40 years with stage 1 hypertension and no evidence of target organ damage, cardiovascular disease, renal disease or diabetes, consider seeking specialist evaluation of secondary causes of hypertension and a more detailed assessment of potential target organ damage. This is because 10-year cardiovascular risk assessments can underestimate the lifetime risk of cardiovascular events in these people. [new 2011] *Monitoring treatment and blood pressure targets* 1.5.4 Use clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modifications or drugs. [new 2011] 1.5.5 Aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years with treated hypertension. [new 2011] 1.5.6 Aim for a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over, with treated hypertension. [new 2011] 1.5.7 For people identified as having a 'white-coat effect', consider ABPM or HBPM as an adjunct to clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011]

	1.5.8 When using ABPM or HBPM to monitor response to treatment (for example, in people identified as having a 'white coat effect' and people who choose to monitor their blood pressure at home), aim for a target average blood pressure during the person's usual waking hours of: • below 135/85 mmHg for people aged under 80 years • below 145/85 mmHg for people aged 80 years and over. [new 2011] 1.6 Choosing antihypertensive drug treatment 1.6.1 Where possible, recommend treatment with drugs taken only once a day. [2004] 1.6.2 Prescribe non-proprietary drugs where these are appropriate and minimise cost. [2004] 1.6.3 Offer people with isolated systolic hypertension (systolic blood pressure 160 mmHg or more) the same treatment as people with both raised systolic and diastolic blood pressure. [2004] 1.6.4 Offer people aged 80 years and over the same antihypertensive drug treatment as people aged 55–80 years, taking into account any comorbidities. [new 2011] 1.6.5 Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). [2010] **Step 1 treatment** 1.6.6 Offer people aged under 55 years step 1 antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB). If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB. [new 2011] 1.6.7 Do not combine an ACE inhibitor with an ARB to treat hypertension. [new 2011] 1.6.8 Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable, for example because of oedema or intolerance, or if there is

	evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011] 1.6.9 If diuretic treatment is to be initiated or changed, offer a thiazide‑like diuretic, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. [new 2011] 1.6.10 For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide. [new 2011] 1.6.11 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. [2006] 1.6.12 If therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-like diuretic to reduce the person's risk of developing diabetes. [2006] **Step 2 treatment** 1.6.13 If blood pressure is not controlled by step 1 treatment, offer step 2 treatment with a CCB in combination with either an ACE inhibitor or an ARB. [new 2011] 1.6.14 If a CCB is not suitable for step 2 treatment, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011] 1.6.15 For black people of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB. [new 2011] **Step 3 treatment** 1.6.16 Before considering step 3 treatment, review medication to ensure step 2 treatment is at optimal or best tolerated doses. [new 2011]

	1.6.17 If treatment with three drugs is required, the combination of ACE inhibitor or angiotensin II receptor blocker, calcium-channel blocker and thiazide-like diuretic should be used. [2006] **Step 4 treatment** 1.6.18 Regard clinic blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice. [new 2011] 1.6.19 For treatment of resistant hypertension at step 4: • Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalaemia. • Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l. [new 2011] 1.6.20 When using further diuretic therapy for resistant hypertension at step 4, monitor blood sodium and potassium and renal function within 1 month and repeat as required thereafter. [new 2011] 1.6.21 If further diuretic therapy for resistant hypertension at step 4 is not tolerated, or is contraindicated or ineffective, consider an alpha- or beta-blocker. [new 2011] 1.6.22 If blood pressure remains uncontrolled with the optimal or maximum tolerated doses of four drugs, seek expert advice if it has not yet been obtained. [new 2011]

Appendix C: Literature search for implanting a baroreceptor stimulation device for resistant hypertension

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	24/02/2015	Issue 2 of 12, February 2015
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	24/02/2015	Issue 1 of 4, January 2015
HTA database (Cochrane Library)	24/02/2015	Issue 1 of 4, January 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	24/02/2015	Issue 1 of 12, January 2015
MEDLINE (Ovid)	24/02/2015	1946 to February Week 3 2015
MEDLINE In-Process (Ovid)	24/02/2015	February 23, 2015
EMBASE (Ovid)	24/02/2015	1974 to 2015 Week 08
PubMed	24/02/2015	n/a
JournalTOCS	24/02/2015	n/a

Trial sources searched on 06/08/2014

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials metaRegister of Controlled Trials – mRCT
- Clinicaltrials.gov

Websites searched on 06/08/2014

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites
- General internet search

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

1	exp Hypertension/
2	hypertensi*.tw.
3	((high or raise*) adj4 blood adj4 pressure).tw.
4	or/1-3
5	Baroreflex/ or Pressoreceptors/
6	Electric Stimulation Therapy/
7	5 and 6
8	((baroreflex* or barorecept* or baroceptor* or pressorecept*) adj4 (activat* or stimulat* or therap* or electr*)).tw.
9	(sympathoinhib* or sympatho-inhib*).tw.
10	BAT.tw.
11	or/7-10
12	4 and 11
13	Barostim.tw.
14	Rheos.tw.
15	or/12-14
16	animals/ not humans/
17	15 not 16