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Horizon Scanning Technology Prioritising Summary

Implantable carotid sinus baroreflex device for treatment of drug resistant hypertension

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**Australian
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College of Surgeons**

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BACKGROUND

Hypertension, also referred to as high blood pressure, is defined as systolic blood pressure (SBP) more than 140 mm Hg and/or diastolic blood pressure (DBP) more than 90 mm Hg (Illig et al 2006). It is a major risk factor for heart disease, stroke, peripheral vascular disease and kidney disease failure (Berlowitz et al 1998; Spranger et al 2006).

Treatment of hypertension depends on its severity and whether the patient is in a high risk group. For those stratified as being at high or very high risk (five year risk of cardiovascular event 15% or greater), drug treatment is required in addition to lifestyle modifications (Vial 2004). There are many classes of medications used to treat hypertension including low-dose thiazide diuretics, beta blockers, calcium channel blockers, ACE inhibitors and angiotensin-II receptor antagonists (Vial 2004). The choice is influenced by the presence of contraindications for particular classes or the presence of co-indications for drugs of a particular class (Vial 2004). Most patients with hypertension requiring drug therapy need combination therapy with medications from two or more classes to achieve target blood pressure levels (Vial 2004). In Australia in 2005-06, agents acting on the rennin-angiotensin system were by far the most popular medicines prescribed or supplied for hypertension (53.4 per 100 problems), followed by calcium-channel blockers (18.9 per 100 problems), beta-blocking agents (11.9 per 100 problems) and diuretics (7.4 per 100 problems), while antihypertensives were seldom prescribed (1.7 per 100 problems) (AIHW 2007).

Despite the vast number of oral medications designed to help control hypertension, not all patients are able to achieve desired blood pressure targets. There are numerous reasons for blood pressure being inadequately controlled including issues of compliance to prescribed medication, cost and incorrectly chosen medication combinations (Sica and Lohmeier 2006). However, a significant number of patients fail to achieve adequate blood pressure control despite adherence to maximal doses of several pharmacological agents (Fillipone and Bisognano 2007). These patients are said to have resistant hypertension, defined as failure to achieve a blood pressure of < 140/90 mmHg despite taking three anti-hypertensive medications, including a diuretic for at least one month (Fillipone and Bisognano 2007; Johnson 2007). In such patients new treatment options are sought to reduce hypertension induced cardiovascular morbidity.

The Rheos Hypertension (HT) Therapy System (Rheos[®], CVRx. Inc., Maple Grove, MN, USA) is a new device based treatment for drug resistant hypertension which works by electrically activating the baroreceptors in the carotid arteries. Activation of the baroreceptors initiates the baroreflex - a series of responses to physiologic stimuli that determine the balance of sympathetic and parasympathetic activity in the heart and peripheral vasculature, and thereby participate in both short and long term control of blood pressure (Braunwald et al 2001). The Rheos Hypertension (HT) Therapy System is made up of three components - the Rheos Implantable Pulse Generator, Rheos Carotid Sinus Leads and the Rheos Programmer System. Electrodes implanted on the exterior surface of the carotid sinus wall are connected to the battery powered, programmable, impulse generator. The carotid sinus leads conduct the activation energy from the impulse generator to stimulate the baroreceptor fibres in the vessel walls of both carotid sinuses.

These impulses are transmitted to the brainstem, where the increased nerve traffic originating from the baroreceptor afferents is interpreted as an elevated blood pressure and results in central nervous systems modulation of sympathetic and vagal outflows which reduce blood pressure and heart rate (Tordoir et al 2007). The programmable system is linked telemetrically to the impulse generator and allows the physician to non-invasively adjust the stimulation parameters delivered to the carotid sinus leads (Tordoir et al 2007).

The degree to which cardiovascular risk is reduced with treatment of resistant hypertension is unknown. However, Calhoun et al (2008) suggest the benefits of successful treatment, are likely to be substantial as suggested by hypertension outcome studies in general and by the early Veterans Administration cooperative studies, which demonstrated a 96 % reduction in cardiovascular events over 18 months with use of triple antihypertensive regimens compared with placebo in patients with severe hypertension (diastolic blood pressure 115 to 129 mm Hg) (Veterans Administration cooperative study group on antihypertensive agents, 1967).

CLINICAL NEED AND BURDEN OF DISEASE

The number of Australians with hypertension in 2004-05 was 2,100,700 (AIHW 2008a). It is the most common problem managed in general practice, at 6.5 % of all problems in 2005-06 (AIHW 2007). Nearly 8 % of the burden of disease in Australia in 2003 could be attributed to hypertension (AIHW 2008b). A recent population based survey of 11,247 Australian adults found that the overall prevalence of hypertension was 29 % (Johnson 2007). However, only 47 % of these people were receiving antihypertensive medications, and less than 20 % had adequate blood pressure control (BP < 140/90 mm Hg) (Johnson 2007). The prevalence of resistant hypertension ranges from 3 to 5 % in primary health care to 21 % in groups of patients referred to tertiary institutions (Johnson 2007).

DIFFUSION

At the time of writing the CVRx Rheos[®] Hypertension System was an investigational device only, undergoing clinical evaluation in Europe and the United States to demonstrate its safety and effectiveness. The data collected from this study by the FDA will be used to evaluate whether this device should be made available to patients with drug resistant hypertension in the US.

COMPARATORS

Lifestyle modifications (reduction in salt and alcohol intake and weight loss) combined with drug therapy are the current methods used to control resistant hypertension.

SAFETY AND EFFECTIVENESS ISSUES

Four case series studies (level IV intervention evidence) were selected for inclusion in this prioritising summary. Three of these are 1 page summary articles from supplement issues of journals (Bisognano et al 2008; De Leeuw et al 2008; Scheffers et al 2008).

Bisognano et al (2008) recorded ambulatory blood pressure in 16 patients with resistant hypertension during 1 year of Baroreflex Hypertension Therapy™. Ambulatory pressure was measured using an automated cuff programmed to inflate every 30 minutes during the day and every 60 minutes during the night. Only tests of at least 21 hours duration and with 70% of more available readings were used in their analysis. No mention was made of the patient's details in the paper including whether they were taking any hypertension medication in addition to undergoing the Baroreflex Hypertension Therapy™.

Scheffers et al (2008) report the first two year data (blood pressure and heart rate) on 16 patients with resistant hypertension (8f/8m, age: 52 ± 9 yrs, BMI: 31 ± 6 kg/m²) enrolled in the DEBuT-HT trial (Device Based Therapy in Hypertension). The DEBuT-HT Clinical Trial is a multi-center European clinical evaluation of the Rheos Hypertension System in patients with drug resistant high blood pressure. The patients were a cohort from a total of 45 patients implanted with Baroreflex Hypertension Therapy System™. At the time Scheffer et al (2008) were writing their paper the mean duration of the patient's treatment with the device was 33 ± 5 months. The number of antihypertensive medications taken by the patients remained constant throughout the trial starting at 4.8 at baseline (when the device was activated) and 4.8, 4.7 and 4.6 at 3 months, 1 year and 2 years respectively.

De Leeuw et al (2008) investigated changes in blood pressure, heart rate, left ventricular structure and number of anti-hypertension medications in 16 patients with resistant hypertension (12 Europe/4 US, 7 M/9 F, Age 50.4 ± 11.5 yrs, BMI 33.1 ± 7.8 kg/m²) during 12 months of Baroreflex Hypertension Therapy™. The patients, who were implanted at 4 different centers, had stage II hypertension (systolic BP ≥ 160 mmHg) and were taking ≥ 3 anti hypertension drugs (\geq diuretic) at the time of implantation of the device. The patients continued to take the drugs whilst undergoing the Baroreflex Hypertension Therapy™.

Tordoir et al (2007) report the short term outcome of 16 patients implanted with the Baroreflex Hypertension Therapy System™ as part of a multi-center feasibility trial for the treatment of resistant hypertension. The patients (8m/8f, age: 52.3 ± 8.6 yrs, BMI: 31.0 ± 6.2 kg/m²) all had severe hypertension despite a multi drug therapy with a mean of >5 concomitant antihypertensive drugs. Tests of hemodynamic responses (heart rate and blood pressure) to acute device activation were conducted. The settings for the tests included: continuous bilateral stimulation with a frequency of 100Hz and an impulse width of 480 μ s. Stimulus amplitude (voltage) was increased in steps of 1V from 1-6V, each for 5 minutes. Patient responses to the device were monitored for 3 months of therapeutic electrical activation. It is not stated in the paper as to whether the patients remained on the antihypertensive drugs during the evaluation of the device.

Safety

Safety outcomes were not reported in the study by Bisognano et al (2008), it is therefore unclear if any adverse events occurred. Scheffers et al (2008) reported that no unexpected system or procedure related serious adverse events occurred during the observation period in their study (534 patient months). The only mention of safety outcomes by De Leeuw et al (2008) was that no unanticipated adverse events occurred.

In the study by Tordoir et al (2007) the implantation of the baroreflex activating system was reported to have been well tolerated with no unexpected serious procedure or device related adverse events or perioperative deaths occurring. In the perioperative period (the time during which the procedure was being implanted and a 30 day period following the procedure) there were 38 procedure related adverse events reported in 17 patients. Of these events three were classified as serious adverse events: 1. Infection, which led to the complete surgical removal of the device in one patient. The implantable pulse generator was infected with a spreading infection along the leads to the neck incision at both sides. High fever and serious pain with redness necessitated surgical intervention. 2. Procedure related hypoglossal nerve injury with symptoms of hoarseness and eating disturbances which improved during follow up. In this patient the electrodes had to be placed high on the carotid bifurcation which resulted in an accidentally injury to the nerve and 3. One case of intraoperative bradycardia (to 20 beats/min), which recovered spontaneously without any sustained effect. Details of all adverse events are summarised in Table 1.

Table 1: Perioperative device and/or procedure related adverse events (Tordoir et al 2007)

Adverse event	Device related	Procedure related	N events	N patients with event
Infection	0	1	1	1
Hypoglossal nerve injury	0	1	1	1
Intraoperative bradycardia	2	1	2	2
Pain	1	6	7	5
Wound complication	0	3	3	3
Extravascular tissue stimulation	0	1	1	1
Anaesthesia complications	0	2	2	2
Injury to local tissue		1	1	1
Other		22	23	16
Total	3	38	41	17

Effectiveness

In the study of 16 patients by Bisognano et al (2008) significant reductions from baseline in 24 hour mean blood pressure, daytime systolic blood pressure, nighttime systolic blood pressure, pulse pressure, blood pressure load (percent of time systolic blood pressure exceeded 140 mmHg), and trough:peak ratio (ratio of mean systolic pressure for the first 2 hours after wake-up to the last two hours before going to bed) were observed following 12 months Baroreflex Hypertension TherapyTM (Table 2).

Table 2: Changes in ambulatory measures following 12 months BHT (N=16) (Bisognano et al 2008)

Measure	Baseline	12-months BHT	Δ 12 months
24-hour mean (mm Hg)	171 ± 22	157 ± 24	-14*
Daytime SBP (mm Hg)	174 ± 22	159 ± 24	-14*
Nighttime SBP (mm Hg)	160 ± 26	148 ± 28	-11*
Pulse Pressure (mm Hg)	70 ± 14	65 ± 13	-5*
BP load > 140 (%)	90 ± 16	71 ± 33	-19*
SD 24-hr SBP (mm Hg)	20 ± 4	18 ± 5	-2
Trough:Peak	0.93 ± 0.11	1.04 ± 0.15	0.11*

*p < 0.05

It is not stated in the paper as to what the error bars represent

Scheffers et al (2008) observed significant blood pressure and heart rate reductions compared to baseline after 3 months, 1 year and 2 years of Baroreflex Hypertension TherapyTM (Table 3). A drop in systolic blood pressure of at least 20 mmHg was achieved in 12 of 16 (75 %) patients at 2 years and 5 of 16 (31%) achieved a systolic blood pressure of less than 140 mmHg at 2 years.

Table 3: Office based mean ± SD baseline and mean ± SE deltas (Scheffers et al 2008)

N=16	Baseline	Δ 3 months	Δ 1 year	Δ 2 year
Systolic BP (mm Hg)	191 ± 32	-34 ± 7*	-38 ± 7*	-35 ± 8*
Diastolic BP (mm Hg)	116 ± 22	-20 ± 4*	-27 ± 5*	-24 ± 6*
Heart rate (bpm)	81 ± 11	-14 ± 3*	-12 ± 3*	-12 ± 4**

*P<0.001

**P= 0.004

De Leeuw et al (2008) reported significant reductions in office cuff systolic blood pressure, office cuff diastolic blood pressure, septal wall thickness, left ventricular posterior wall thickness, left ventricular mass index and relative wall thickness from baseline after 3 months and 12 months of Baroreflex Hypertension TherapyTM. Left ventricular mass index decreased in 15 out of 16 patients after a year of Baroreflex Hypertension TherapyTM.

Tordoir et al (2007) reported significant mean maximal reductions ($p \leq 0.0001$) in systolic and diastolic blood pressure and heart rate in system tests conducted 1-3 days postoperatively. The tests, which were repeated monthly, showed consistent acute dose dependent reductions in systolic and diastolic blood pressure and heart rate in that the degree of change was directly related to the amplitude (voltage) of stimulation (Table 4). Reductions in blood pressure and heart rate were also observed within amplitudes between the 1 month (baseline values) and 4 month (3 months of baroreflex activation therapy) measurements (Table 4). A repeated measures ANOVA of blood pressure and heart rate readings during testing across voltage increments (0 volts to 6 volts) and visits (1 and 4 months) demonstrated significant differences across doses ($p < 0.0001$ for each) and by visit ($p = 0.003$ for systolic blood pressure, $p = 0.0001$ for diastolic blood pressure and $p < 0.0001$ for heart rate).

Table 4: Blood pressure and heart rate during 1 and 4 month system tests, n = 16 (Tordoir et al 2007)

Parameter and Time Point	Baroreflex Activation IPG Stimulation Amplitude (V)						
	0	1	2	3	4	5	6
<i>SBP (mm Hg)</i>							
1-month	184 ± 28	180 ± 29	176 ± 30	167 ± 32	160 ± 36	153 ± 31	144 ± 36
4-month	165 ± 21	164 ± 21	163 ± 27	160 ± 23	155 ± 27	147 ± 30	143 ± 30
<i>DBP (mm Hg)</i>							
1-month	105 ± 17	104 ± 18	105 ± 17	98 ± 21	94 ± 22	92 ± 21	84 ± 24
4-month	95 ± 17	94 ± 16	93 ± 17	92 ± 15	89 ± 17	84 ± 17	81 ± 17
<i>HR (BPM)</i>							
1-month	80 ± 14	78 ± 14	77 ± 15	74 ± 14	72 ± 14	71 ± 15	68 ± 14
4-month	68 ± 11	67 ± 10	68 ± 11	65 ± 11	65 ± 11	64 ± 12	62 ± 12

SBP; systolic blood pressure

DBP; diastolic blood pressure

HR; heart rate

BPM; beats per minute

It is not stated in the paper as to what the error bars represent

COST IMPACT

At the time of writing a price for the Rheos[®] Hypertension Therapy System had not been established as the product was still under clinical investigation.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

Each of the four case series had a person from the company manufacturing the Rheos[®] Hypertension Therapy System (CVRx Inc.) as a co-author on the paper. In the paper by Tordoir et al (2007) the authors from CVRx, RK and RC, declare potential conflicts of interest as employees and shareholders of the sponsor CVRx Inc. and the authors EI and TP are consultants for the sponsor.

SUMMARY OF FINDINGS

The four papers reviewed all reported that Baroreflex Hypertension Therapy[™] resulted in sustained reductions in blood pressure over the period the patients were monitored. The longest time investigated was two years (Scheffers et al 2008). Another outcome reported by De Leeuw et al 2008 was that left ventricular hypertrophy, a factor that increases risk of myocardial ischemia, regressed with Baroreflex Hypertension Therapy[™]. Serious complications were reported in one of the studies which conducted a safety analysis (Tordoir et al 2007). It is important to note that these are only case series studies (level IV intervention evidence) that have presented preliminary results from feasibility clinical trials. Long term randomised controlled trials are required to further investigate the effectiveness and safety of Baroreflex Hypertension Therapy[™]. Several long term clinical trials sponsored by CVRx Inc. are due to finish in 2009/2010 (<http://clinicaltrials.gov>; search term baroreflex).

HEALTHPACT ACTION

Given the promising results to date and that the Rheos[®] Hypertension Therapy System is still under clinical investigation it is recommended that this system is monitored for 24 months.

NUMBER OF STUDIES INCLUDED

Total number of studies 4
Level IV intervention evidence

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SOURCES OF FURTHER INFORMATION

<http://www.cvr.com/medpros/index.php?id=15>

<http://www.cvr.com/patients/index.php?id=33>

SEARCH CRITERIA TO BE USED

Rheos, baroreflex, carotid sinus AND resistant hypertension