Technology Brief

Update: Implantable carotid sinus baroreflex device for treatment of drug resistant hypertension

November 2011
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This brief was prepared by Dr Meegan Vandepeer from the Australian Safety and Efficacy Register of New Intervventional Procedures – Surgical.
TECHNOLOGY BRIEF UPDATE

REGISTER ID WP066 (FORMERLY S000091)

NAME OF TECHNOLOGY RHEOS® HYPERTENSION THERAPY SYSTEM™

PURPOSE AND TARGET GROUP PATIENTS WITH DRUG RESISTANT HYPERTENSION

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- Yet to emerge
- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
- No
- Not applicable

INTERNATIONAL UTILISATION

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2011 SAFETY AND EFFECTIVENESS ISSUES

Study description

Results from the multicentre, double-blind, randomised, placebo-controlled Rheos Pivotal Trial were available for inclusion in this update (Bisognano et al 2011). The European Device Based Therapy in Hypertension Trial (DEBuT-HT) also provided data on the safety and efficacy of the Rheos® Baroreflex system (Scheffers et al 2010). Although
numerous supplementary articles have been published which present preliminary data on the aforementioned trial, the publication by Scheffers et al (2010) presents the most detailed and long-term dataset to date.

The Rheos Pivotal Trial (NCT00442286) was a Phase III clinical trial of 265 patients with resistant hypertension, designed to assess the safety and efficacy of the Rheos system (Bisognano et al 2011). The key enrolment criterion was resistant hypertension, defined as systolic blood pressure (SBP) of ≥160 mm Hg and diastolic blood pressure (DBP) of ≥80 mm Hg following at least one month of maximally tolerated therapy with at least three antihypertensive medications, including a diuretic. Other enrolment criteria included an ambulatory SBP of ≥135 mm Hg for a 24 hour average, and an absence of clinically significant orthostatic blood pressure (BP) changes.

A total of 49 centres were used to screen 590 potential patients between March 2007 and November 2009. After screening for eligibility, 264 patients were found to be ineligible. Of the 326 patients who were eligible for implantation, four were not implanted with the device, as they failed to exhibit an acute testing response during surgery. The device, consisting of a pulse generator and leads attached to each carotid sinus, was implanted by either a vascular, cardiothoracic, or neurosurgeon in a total of 322 patients. Of these patients, 265 were randomised in a 2:1 fashion, 181 to group A and 84 to group B. Sample size was calculated to adequately power all primary endpoints, with 148 patients required in group A and 74 in group B. Following implantation, the device was switched off for one month in all patients. Patients in Group A then received baroreflex activation therapy (BAT) for the first six months, while BAT was delayed for six months in Group B patients. Subsequently, patients in both groups received BAT for a further six months. Patients and investigators were blinded to treatment until after the 12-month follow-up visit. The average patient follow-up was 21 ± 8 months, and one patient in group A was lost to follow-up before the 12-month visit (Bisognano et al 2011). An intention to treat analysis was used in this study, with unblinded and withdrawn subjects treated as failures.

Both treatment groups had similar baseline characteristics, with no significant differences observed between the groups for age, sex, race, BP, heart rate, body mass index (BMI), comorbidities, and number and type of BP medications. Group A consisted of 116 males (64%) and 65 females (36%), with a mean age of 53.7 ± 10.5 years, mean SBP of 169 ± 26 mm Hg, mean DBP of 101 ± 17 mm Hg, taking a mean of 5.2 ± 1.6 BP medications. Group B consisted of 46 males (55%) and 38 females (45%), with a mean age of 52.4 ± 9.8 years, mean SBP of 168 ± 24 mm Hg, mean DBP of 100 ± 14 mm Hg, taking mean of 5.2 ± 1.8 BP medications (Bisognano et al 2011).

The DEBuT-HT trial was a prospective, multicentre, nonrandomised feasibility study, which aimed to assess the safety and efficacy of the Rheos system in resistant
hypertensive patients (Scheffers et al 2010). To be eligible for inclusion, patients were required to be over 21 years of age with BP of ≥160/90 mm Hg, despite receiving at least three antihypertensive agents, including a diuretic. All medications were kept constant two months prior, and three months following, implantation. Exclusion criteria 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, previous implants or radiation in the carotid sinus region, currently implanted electrical medical devices, dialysis and pregnancy.

Scheffers et al (2010) included 45 patients who underwent Rheos implantation at nine clinical centres between March 2004 and November 2007. The group consisted of 26 males and 19 females with a mean age of 54 ± 9 years, mean SBP of 179 ± 29 mm Hg, mean DBP of 105 ± 22 mm Hg, taking a median of five antihypertensive medications. The device was activated one month after implantation, and patients were followed up monthly for the first three months, and annually thereafter. Of the 45 patients who underwent Rheos implantation, three were excluded from the safety and efficacy analyses (as per protocol), four dropped out and one missed a visit, resulting in a dataset of 37 patients at three months. Twenty-six and 17 patients completed the 1-year and 2-year follow-up, respectively. An additional cohort of 10 eligible patients who declined to participate was followed up by regular care. Outcomes measured included office and ambulatory BP, ability to exercise during a six minute hall-walk test, renal function, carotid artery stenosis and serious adverse events associated with implantation (Scheffers et al 2010).

Safety

The study by Bisognano et al (2011) evaluated procedural safety, BAT safety, and device safety. Some complications occurred prior to randomisation; four patients did not exhibit an acute testing response and were not implanted with the device, and two patients had the device explanted prior to randomisation due to infection. A total of seven deaths, none of which were related to the procedure or device, were reported during the follow-up period. The causes of death included three intracerebral haemorrhages, two cardiopulmonary arrests, one ruptured aortic aneurysm, and one drug overdose. The authors suggested that the majority of these deaths were due to the normal sequelae of long-term hypertension. With regard to procedural safety, the event-free rate was 74.8%, which was less than the pre-specified objective performance criterion of 82% (P=1.00). Procedural adverse events were not presented by treatment group, and included surgical complications (n=13, 4.8%), nerve injury with residual deficit (n=13, 4.8%), transient nerve injury (n=12, 4.4%), respiratory complications (n=7, 2.6%), and wound complications (n=7, 2.6%). All other procedural adverse events occurred at a rate of less
than 2%, and the majority (76%) of procedural adverse events resolved completely. With regard to BAT safety, the event-free rate was 91.7% in Group A and 89.3% in Group B ($P<0.001$), and the only adverse event that occurred at a rate greater than 2% in either group was hypertensive emergency (Group A: $n=9$, 5%; Group B: $n=7$, 8.3%). With regard to device safety, the event-free rate was 87.2%, which exceeded the pre-specified objective performance criterion of 72% ($P<0.001$), and the only event that occurred at a rate greater than 2% was hypertension-related stroke, which occurred in a total of 6 patients (2.3%).

Scheffers et al (2010) reported that a total of seven patients (16.7%) experienced procedure-related serious adverse events, while one patient (2.4%) experienced a device-related serious adverse event. Procedural complications included explantation of the device following infection ($n=3$), perioperative stroke with minimal residual effects ($n=1$), tongue paresis attributed to intraoperative hypoglossal nerve injury ($n=1$) and moderate pulmonary oedema that resolved in six days ($n=1$). One death due to angioneurotic oedema occurred in the cohort, and while the specific cause could not be determined, the authors suspected an adverse drug reaction. The sole device-related complication occurred as a result of movement of the implantable pulse generator, which was resolved by further surgery to reposition the device.

In terms of functional safety measures, the distance travelled during a six minute hall-walk test improved by 48 meters ($P=0.01$, $n=14$) and serum creatinine levels increased substantially ($P=0.04$, $n=22$), one year after implantation (Scheffers et al 2010). In addition, carotid artery stenosis was absent in all patients at the 1-year follow-up visit. During the three months after implantation, no cases of orthostatic hypotension or syncope were reported ($n=32$).

**Effectiveness**

The primary efficacy endpoints reported by Bisognano et al (2011) included acute efficacy and sustained efficacy. Acute efficacy was defined as the proportion of subjects in Group A versus Group B that achieved at least a 10 mm Hg drop in SBP at month 6 compared with baseline, with a superiority margin of 20%. This study reported that 54% of patients in Group A and 46% in Group B were responders at six months, which was not significantly different ($P=0.97$). An additional efficacy analysis did show that the percentage of subjects achieving a SBP $\leq 140$ mm Hg at six months was greater in Group A (42%) than Group B (24%) ($P=0.005$). Sustained efficacy was defined as the sustained response in SBP at month 12 in Group A patients who had a response at month 6, with an objective performance criterion of 65%. For this outcome, 88% of responders at six months maintained their response at 12 months ($P<0.001$). The mean change in SBP at six months, which was a secondary efficacy endpoint, was $16 \pm 29$ mm Hg in Group A.
and 9 ± 29 mm Hg in Group B (P=0.08). However at 12 months, at which point Group A had received BAT for 12 months and Group B six months, the mean decrease in SBP was 25 ± 32 mm Hg for Group A and 25 ± 31 mm Hg for Group B.

In the study by Scheffers et al (2010), significant reductions in both office BP and ambulatory BP were observed at 3 months, 1 year, and 2 years post-implantation (Table 1). The authors reported that at each study visit, when the device was temporarily switched off in order to assess BP without carotid artery stimulation, BP immediately rose to baseline levels, before falling again once the device was turned on.

Table 1: Change in blood pressure and heart rate measurements from baseline after implantation with the Rheos system

<table>
<thead>
<tr>
<th></th>
<th>Δ 3 months</th>
<th>Δ 1 year</th>
<th>Δ 2 years</th>
</tr>
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<tr>
<td><strong>Office Blood Pressure</strong></td>
<td>n = 37</td>
<td>n = 26</td>
<td>n = 17</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>-21 ± 4 (P&lt;0.001)</td>
<td>-30 ± 6 (P&lt;0.001)</td>
<td>-33 ± 8 (P=0.001)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-12 ± 2 (P&lt;0.001)</td>
<td>-20 ± 4 (P&lt;0.001)</td>
<td>-22 ± 6 (P=0.002)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>-8 ± 2 (P&lt;0.001)</td>
<td>-8 ± 2 (P=0.001)</td>
<td>-11 ± 4 (P=0.008)</td>
</tr>
<tr>
<td><strong>Ambulatory Blood Pressure</strong></td>
<td>n = 26</td>
<td>n = 15</td>
<td>n = 8</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>-6 ± 3 (P=0.102)</td>
<td>-13 ± 3 (P&lt;0.001)</td>
<td>-24 ± 8 (P=0.017)</td>
</tr>
<tr>
<td>DBP (mm Hg)</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>HR (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>
</tbody>
</table>

All figures given are mean ± standard deviation. Baseline levels not reported.
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

**COST IMPACT**

A recent study showed that the Rheos Baroreflex Stimulator may be cost effective, with an incremental cost-effectiveness ratio (ICER) between $50,000 and $100,000 per QALY (Young et al 2009). The characteristics of the cohort, such as age and SBP, were found to be important in determining the cost-effectiveness of the implantable carotid body stimulator for use in treating resistant hypertension. A Markov model was used in this study. Direct costs (2007 dollars), utilities, and event rates for future myocardial infarction, stroke, heart failure, and end-stage renal disease were included in the model.

**ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS**

No issues were identified from the retrieved material.

**OTHER ISSUES**

Numerous supplementary articles have been published reporting combined results from the European DEBuT-HT and US feasibility studies. The majority of these publications were excluded from this update, as the study published by Scheffers et al (2010) provides a more comprehensive representation of patients enrolled in the DEBuT-HT study. Also
in some publications, data from the US Feasibility study has been pooled with the European study, resulting in patient overlap with Scheffers et al (2010).

Despite this, several small case series provide additional data of interest. Sica et al (2009) reported on the effects of Rheos implantation in patients with chronic kidney disease (using a subset of data from the European DEBuT-HT trial). Results from this study demonstrated no change in the estimated glomerular filtration rate (eGFR), and a reduction in left ventricular mass index (LVMI) (data not reported). Based on these findings, the authors concluded that BAT may confer renoprotective effects, in addition to cardioprotective effects, in patients with resistant hypertension (Sica et al 2009).

Karunaratne et al (2010) assessed whether the Rheos baroreflex stimulator had any deleterious interactions with pacemakers in four patients. This study demonstrated no oversensing at any pacemaker voltage setting, even when both devices were programmed to provoke interaction. This subset of patients had a mean follow up of 8.3 ± 4.6 months at the time of publication, during which no occurrence of observed or suspected oversensing was reported (Karunaratne et al 2010).

Wustmann et al (2009) examined the effect of Rheos baroreflex stimulation on cardiovascular regulation in 21 patients. In addition to demonstrating a mean decrease in BP, this study also reported a fall in mean heart rate ($P=0.001$) and heart rate turbulence onset ($P=0.004$), and altered heart rate variability frequency domain parameters ($P<0.001$). The authors indicated that these cardiovascular changes were consistent with inhibition of sympathetic activity and increased parasympathetic activity, corresponding to the observed decrease in BP (Wustmann et al 2009).

Including the European DEBuT-HT and US feasibility trials, there are currently six ongoing clinical trials evaluating the Rheos system (Table 2).

<table>
<thead>
<tr>
<th>ClinicalTrials.gov id</th>
<th>n estimated</th>
<th>Description</th>
<th>Estimated date of completion</th>
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<tr>
<td>NCT01077180 (ongoing)</td>
<td>16</td>
<td>United States Rheos® Feasibility Trial; case series to demonstrate the safety and efficacy of the Rheos® system. 13 month follow-up period.</td>
<td>March 2012</td>
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<tr>
<td>NCT00710190 (ongoing)</td>
<td>45</td>
<td>Device Based Therapy in Hypertension Trial (DEBuT-HT); case series to demonstrate the safety and efficacy of the Rheos® system. Continuous follow-up.</td>
<td>December 2010</td>
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<td>NCT00710294 (ongoing)</td>
<td>50</td>
<td>European DEBuT-HT extension trial; collection of long-term safety and efficacy data to support regulatory approval and market release of the Rheos® baroreflex stimulator.</td>
<td>December 2010</td>
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<tr>
<td>NCT00442286 (ongoing)</td>
<td>300</td>
<td>Rheos® Pivotal Trial; prospective randomised controlled trial comparing</td>
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clinical results between Rheos ‘ON’ and Rheos ‘OFF’ arms. 12 month follow-up period.

<table>
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<th>Description</th>
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<td>NCT00718939 (ongoing)</td>
<td>60</td>
<td>Rheos® Diastolic Heart Failure Trial; prospective randomised double-blind controlled trial comparing Rheos® patients to non-implanted patients. 12 month follow-up period.</td>
<td>January 2011</td>
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<tr>
<td>NCT00957073 (recruiting)</td>
<td>540</td>
<td>Rheos® HOPE4HF Trial; prospective randomised controlled trial. Outcomes of primary interest are death and complications.</td>
<td>December 2014</td>
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**2011 SUMMARY OF FINDINGS:**

Although a significant number of articles have been published with regards to the safety and efficacy of the Rheos Baroreflex Stimulator, the majority of such articles are in the form of supplementary reports relating to several main trials. The study (Rheos Pivotal Trial) by Bisognano et al (2011), and the two year safety and efficacy data (DEBuT-HT study) presented by Scheffers et al (2010), represent the most comprehensive analysis of the Rheos system to date. At six months, Bisognano et al (2011) did not demonstrate a significant difference in the primary endpoint, number of acute responders, between the group that received stimulation and the group that did not have the device switched on; however, an additional analysis did show that more subjects in the stimulation group achieved SBP below 140 mm Hg. The device and stimulation therapy were found to meet pre-defined safety criteria, while for procedural safety the event-free rate was less than the pre-specified objective. In the study by Scheffers et al (2010), patients showed a reduction in office and ambulatory BP measurements following implantation, and these values continued to decrease two years post-implantation. Several serious complications were noted.

**2011 HEALTHPACT ASSESSMENT:**

Several new technologies addressing refractive hypertension are currently under development, including renal denervation. The Rheos Baroreflex Stimulator is more invasive than renal denervation and the safety and effectiveness of this technology remain under investigation. Several large clinical trials are ongoing. As these trials have the potential to expand knowledge relating to the safety and effectiveness of the Rheos system, it is recommended that this technology be monitored for 24 months.

**2011 INCLUDED STUDIES**

- Total number of studies: 2
- Level II interventional evidence: 1
- Level IV interventional evidence: 1
2011 REFERENCES


PRIORITISING SUMMARY (2008)

REGISTER ID S000091

NAME OF TECHNOLOGY RHEOS® HYPERTENSION THERAPY SYSTEM™

PURPOSE AND TARGET GROUP PATIENTS WITH DRUG RESISTANT HYPERTENSION

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☐ Yet to emerge ☐ Established
☐ Experimental ☐ Established but changed indication or modification of technique
☐ Investigational ☐ Should be taken out of use
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AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐ Yes
☑ No
☐ Not applicable

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IMPACT SUMMARY

CVRx Inc. has developed the Rheos Hypertension Therapy System to treat people with drug resistant hypertension. At the time of writing, this technology is not available in Australia and is limited by Federal law in the United States to investigational use only.

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 lg/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 (≥ diuretic) at the time of implantation of the device. The patients continued to take the drugs whist 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 µs. 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)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Device related</th>
<th>Procedure related</th>
<th>N events</th>
<th>N patients with event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypoglossal nerve injury</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Introperative bradycardia</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Wound complication</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Extravascular tissue stimulation</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anaesthesia complications</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Injury to local tissue</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>22</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>38</td>
<td>41</td>
<td>17</td>
</tr>
</tbody>
</table>

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

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

*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 Therapy™ (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)

<table>
<thead>
<tr>
<th>N=16</th>
<th>Baseline</th>
<th>∆ 3 months</th>
<th>∆ 1 year</th>
<th>∆ 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>191 ± 32</td>
<td>-34 ± 7*</td>
<td>-38 ± 7*</td>
<td>-35 ± 8*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>116 ± 22</td>
<td>-20 ± 4*</td>
<td>-27 ± 5*</td>
<td>-24 ± 6*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>81 ± 11</td>
<td>-14 ± 3*</td>
<td>-12 ± 3*</td>
<td>-12 ± 4**</td>
</tr>
</tbody>
</table>

*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 Therapy™. Left ventricular mass index decreased in 15 out of 16 patients after a year of Baroreflex Hypertension Therapy™.

Tordoir et al (2007) reported significant mean maximal reductions (p ≤ 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)

<table>
<thead>
<tr>
<th>Parameter and Time Point</th>
<th>Baroreflex Activation IPG Stimulation Amplitude (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>0</td>
</tr>
<tr>
<td>1-month</td>
<td>184 ± 28</td>
</tr>
<tr>
<td>4-month</td>
<td>165 ± 21</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>105 ± 17</td>
</tr>
<tr>
<td>1-month</td>
<td>95 ± 17</td>
</tr>
<tr>
<td>4-month</td>
<td>80 ± 14</td>
</tr>
<tr>
<td>HR (BPM)</td>
<td>68 ± 11</td>
</tr>
</tbody>
</table>

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

REFERENCES


Johnson D. Resistant hypertension. Australian Doctor 2007; April: 27-34.


**Sources of Further Information**  

**Search Criteria to be Used**  
Rheos, baroreflex, carotid sinus AND resistant hypertension