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Horizon Scanning Technology

Prioritising Summary

Renal sympathetic denervation for the treatment of resistant hypertension

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AHTA

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PRIORITISING SUMMARY

REGISTER ID: **000437**

NAME OF TECHNOLOGY: **RENAL SYMPATHETIC DENERVATION**

PURPOSE AND TARGET GROUP: **A MINIMALLY INVASIVE TREATMENT FOR RESISTANT HYPERTENSION**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

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

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Germany	✓		

IMPACT SUMMARY:

Renal sympathetic denervation is a novel procedure which aims to reduce elevated blood pressure in patients with resistant hypertension.

BACKGROUND

Hypertension is defined as abnormally high arterial blood pressure indicated by an adult systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg. Hypertension is a major factor in the progression of cardiovascular disease and is a contributing factor in the rising morbidity and mortality rates associated with coronary heart disease, chronic kidney disease and stroke. Multiple blood pressure measurements should be taken, at least twice, one or more weeks apart, to diagnose hypertension. Lifestyle factors that contribute to an increased risk in the development of hypertension include smoking, moderate to high alcohol intake, a body mass index >25 kg/m^2, lack of physical activity and a high salt intake. Treatment

for patients diagnosed with hypertension would depend on the absolute cardiovascular risk and other concomitant conditions, however modification of lifestyle factors would be advised. Patients not responding to lifestyle modification alone would be candidates for pharmacological options. ACE inhibitors (or angiotensin II receptor antagonists), dihydropyridine calcium channel blockers or low-dose thiazide diuretics (for patients aged >65years) may be considered as first-line pharmacological options. Thiazide diuretics should be used with caution as they have been associated with an increased risk of new-onset diabetes. Beta-blockers are no longer recommended as a first-line therapy due to an increased risk of developing diabetes. Monotherapy with antihypertensives is recommended, however combination drug therapy may be required (Heart Foundation 2009).

Resistant hypertension is defined as persistent high blood pressure despite treatment with three antihypertensive agents of different classes. Resistant hypertension may be a result of patient genetic phenotype, poor clinical management or poor patient compliance to antihypertensive therapy or lifestyle modifications (Calhoun et al 2008).

The kidney plays a vital role in the regulation of blood pressure (sodium filtration, blood volume etc) and renal sympathetic nerve hyperactivity (both afferent and efferent) has been demonstrated to be a major factor in the pathophysiology of hypertension (Figure 1) (Katholi & Rocha-Singh 2009; Schlaich et al 2009b). The renal sympathetic efferent nerves innervate the renal tubules, vasculature and juxtaglomerular apparatus and may affect volume and blood homeostasis. In animal models, denervation of the renal nerves has been demonstrated to delay the development of induced hypertension and to increase sodium excretion (Bravo et al 2009).

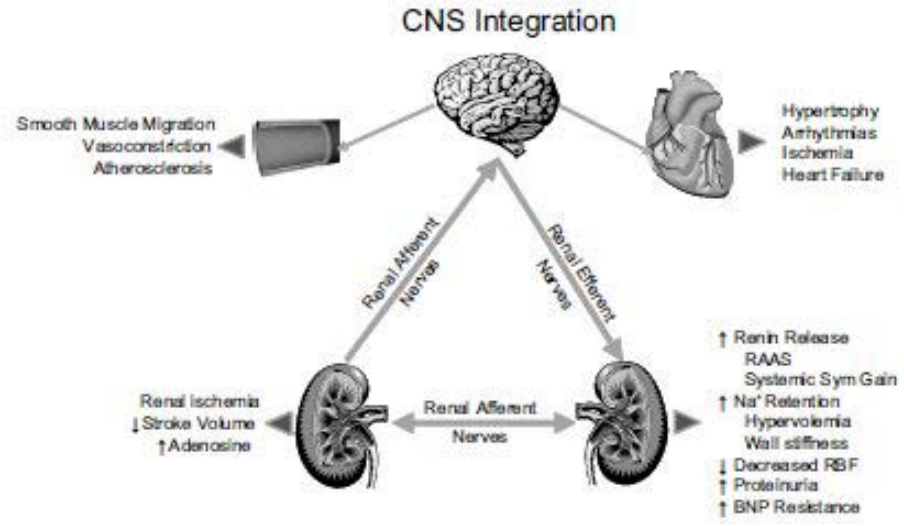

Figure 1 Renal afferent and efferent nerve pathways (Schlaich et al 2009b)

In the proof-of-concept study by Krum et al (2009) denervation was achieved via the ablation of sympathetic nerve fibres using low-dose radiofrequency energy delivered to the renal artery endothelial surface via a percutaneous catheter. The catheter is introduced via the femoral artery and up to six ablations of two minutes duration are performed (Katholi & Rocha-Singh 2009; Krum et al 2009).

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of resistant hypertension is unknown. The Framingham Heart Study reported that 48 per cent of patients with hypertension responded to treatment and achieved a blood pressure status of less than 140/90 mm Hg, indicating that "uncontrolled" hypertension occurred in 52 per cent of hypertensive patients. Rates of uncontrolled hypertension were higher in elderly patients >75 years (60%) and in patients with concomitant conditions including diabetes and kidney disease (Calhoun et al 2008).

Current hypertension prevalence data were not identified for this summary. A survey of general practice patients in Australia was conducted in 1998-99 as part of the BEACH[1] program. Of 1,908 patient encounters from 95 general practices, the prevalence of hypertension was 20.1% (95% CI: 17.3–22.8). Of the 383 patients with hypertension, 84.3 per cent and 15.7 per cent were considered to have simple and complicated hypertension, respectively. There was no difference in the rate of hypertension for males and females. As reported by the Framingham study, the rate of hypertension increased with age until 75 years, with those aged 65–74 years having the highest rate at 52.5% (95% CI: 41.1–64.0). Just over half the patients with hypertension were taking one medication (55.4%) with 32.4 per cent taking two or more drugs (Sayer et al 2000).

Indigenous Australians have a high prevalence of risk factors for cardiovascular disease. Cross-sectional population survey data for adults aged 25–54 years suggest that the age-standardised prevalence of hypertension (defined as BP $\geq$ 140/90 mmHg or on antihypertensive medication) is approximately three times higher in Indigenous Australians living in rural and remote, compared with non-Indigenous Australians (Heart Foundation 2009).

The total number of Australian public hospital separations for hypertensive disease[2] (ICD-10 codes I10-I15) for 2007-08 was 7,434, representing a total of 27,027 patient days with and average length of stay of 3.6 days (AIHW 2009).

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[1] Bettering the Evaluation and Care of Health, a continuous study of general practice activity in Australia

[2] I10: essential hypertension, I11: hypertensive heart disease, I12: hypertensive renal disease, I13: hypertensive heart and renal disease and I15: secondary hypertension.

In New Zealand during 2002-03, the total number of public hospital separations for hypertensive disease (ICD-10 codes I10-I15) was 858, with a mean stay in hospital of 24 days. The total number of discharges was higher for females (522) with a markedly longer mean stay (27.8 days) than for males (336 discharges with mean stay 17.9 days). The number of discharges for people of Māori origin was 148 with a mean stay of 5.8 days. No difference between males and females was noted (NZHIS 2006). Māori and Pacific Islander peoples are also at high risk for developing cardiovascular disease. New Zealand population studies suggest that age-adjusted and sex-matched hypertension prevalences among Maori and Pacific Islanders is 1.5 to 2 times higher, compared with New Zealanders of European or other origin (Heart Foundation 2009).

DIFFUSION

This novel radiofrequency ablation (RFA) technique was developed by several Australian institutions: Monash University, Victoria; Baker IDI Heart and Diabetes Institute, Monash, Victoria; and St Vincent's Hospital, Melbourne, Victoria. The trial described is a proof-of-principle study and the technique is not in widespread use in Australia or New Zealand (Krum et al 2009).

COMPARATORS

As discussed in the background section, hypertension may be treated with a variety of measures including lifestyle modification and pharmaceutical options.

SAFETY AND EFFECTIVENESS ISSUES

The proof-of-concept study was conducted by Krum et al (2009) in three centres in Australia and two centres in Europe. Hypertensive patients (n=50) were enrolled who satisfied the selection criteria of an office-based systolic blood pressure of ≥160 mm Hg, despite being treated with at least three anti-hypertensive medications, including one diuretic. The mean age of patients was 58 ± 9 years (range 37-76 years). At baseline a renal MRI angiogram was performed and measurements of blood pressure and blood chemistries were taken. Five patients were excluded on the basis of the renal angiogram due to having dual renal artery systems. Follow-up was performed at one, three, six, nine and 12-months with a renal MRI angiogram performed again at 6-months. The primary outcomes were the safety of the technique and the effectiveness of it to lower blood pressure.

To establish the safety of the technique, the first 10 patients underwent denervation of a single renal artery, as described in the background section above. These patients were monitored for any side effects for one month and noradrenalin measurements were made before denervation was performed in the contra-lateral renal artery (level IV intervention evidence).

The mean procedure time was 38 minutes (range 34-48 minutes). The average number of denervations performed in the right renal artery was 4.2 and 3.7 in the left renal

artery. Patients were taking an average of 4.7 anti-hypertensive medications at baseline.

Safety

Most patients experienced non-radiating abdominal pain during the procedure and were administered intravenous narcotic and sedative drugs. Pain did not persist after the denervation procedure.

Two patients experienced complications with the procedure. One patient developed a pseudo-aneurysm at the femoral artery site where the catheter was introduced which was treated with analgesics and antibiotics without further complication. The other patient experienced renal artery dissection (an occlusive lesion) when the catheter was introduced which was detected before denervation took place. The treatment was aborted and the dissection was treated with a renal artery stent without any further complications. Although some irregularities were identified on renal angiograms immediately after denervation, none were considered sufficient to limit flow. MRI renal angiograms conducted at short-term follow-up (n=18) and at six months (n=14) did not detect any abnormalities at the treatment location.

Effectiveness

Blood pressure results at baseline and follow-up are presented in Table 1. Both systolic and diastolic blood pressures were significantly lower at end of follow-up compared to baseline (p=0.026 and p=0.027, respectively). At all time points at follow-up, both the systolic and diastolic blood pressures were statistically significantly lower than at baseline (p<0.001 and p=0.02 for the 12-month diastolic measure). Six of the treated patients had systolic blood pressure reductions of less than 10 mm Hg and were therefore considered non-responders.

Table 1 Baseline and follow-up data for patients undergoing renal denervation

	Blood pressure systolic/diastolic Mean mm Hg ± SD	Censored data Blood pressure systolic/diastolic Mean mm Hg ± SD	Mean heart rate BPM	Mean glomerular filtration rate* ± SD ml/min/1.73m^2
Base line (n=45)	177/101 ± 20/15		72	79 ± 21
	Mean reduction BP systolic/diastolic [95% CI]			
1 month (n=41)	-14/-10 [4/3]	-14/-10 [4/3]	72	
3 months (n=39)	-21/-10 [7/4]	-22/-11 [7/4]	74	
6 months (n=26)	-22/-11 [10/5]	-22/-10 [7/4]	71	83 ± 25, p= 0.30
9 months (n=20)	-24/-11 [9/5]	-26/-11 [7/5]	71	
12 months (n=9)	-27/-17 [16/11]	-28/-17 [22/18]	69	

BP = blood pressure, BPM = beats per minute

* Glomerular filtration rate was reported only on paired data of 25 patients at baseline and six months

The five patients excluded before treatment commenced recorded a mean, but not significant, increase in blood pressure at one, three, six and nine months. During the

course of the study some patients increased or decreased the antihypertensive medication they were taking. The decrease in systolic and diastolic blood pressure was maintained after data were censored for these patients (no p values reported).

A later case-study reported on renal denervation in a 59-year old patient with resistant hypertension. The patient had reported a resistance to seven different anti-hypertensive drugs and had a mean office blood pressure of 161/107 mm Hg. Renal denervation was performed without complications. At 30-day follow-up the patient's blood pressure had reduced to 141/90 mm Hg and at 12-months blood pressure had reduced further to 127/81 mm Hg (Schlaich et al 2009a).

COST IMPACT

The exact costings of this procedure could not be ascertained. Basic costs would include the price of the catheter with electrode or probe, the associated costs of imaging procedures and a radiologist to guide the catheter in place and the cost of the radiofrequency generator. Several radiofrequency generators are on the Australian market and a 2003 MSAC report estimated the capital cost of these units to be between $40-65,000. The disposable equipment associated with RFA was estimated to cost between $1,700 and $2,700 (MSAC 2003).

Similar procedures are available on the current Medicare Benefits Schedule MBS item number 50950 for non-resectable hepatocellular carcinoma by percutaneous radiofrequency ablation has a fee of $754.90. MBS item numbers 38287 and 38293 cover catheter-based cardiac ablation procedures with fees of $1,938 and $2,468, respectively.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

Based on the low level of available evidence it would appear that renal denervation may be a viable option for the treatment of resistant hypertension. Blood pressure was significantly lower after renal denervation than that measured at baseline, however it is unclear whether this decrease is considered clinically significant. Final 12-month follow-up data were only reported for a small portion of the enrolled patients (22%) and in addition, six of the 45 patients were considered non-responders with non-significant reductions in blood pressure. A well conducted randomised controlled trial is needed to adequately investigate whether renal denervation is capable of producing a sustained lowering of blood pressure in hypertensive patients resistant to medication.

HEALTHPACT ACTION:

Renal denervation appears to be an innovative and promising technique for the treatment of resistant hypertension. HealthPACT have recommended that further information from clinical trials be assessed in 24-months time.

NUMBER OF INCLUDED STUDIES

Total number of studies	2
Level IV intervention evidence	1
Case study	1

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SEARCH CRITERIA TO BE USED:

Catheter Ablation/*methods

Hypertension/blood/diagnosis/*surgery

Renal Artery/*innervation/radiography

Sympathectomy/*methods

Hypertension, Renal/*physiopathology/*therapy

Kidney/*innervation

Sympathetic Nervous System/*physiopathology