Health Policy Advisory Committee on Technology

Technology Brief Update

Renal denervation

November 2014

HealthPACT

emerging health technology

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This brief was prepared by Linda Mundy from the HPACT Secretariat.

2014 Technology, Company and Licensing

Register ID	**WP210**
Technology name	**Renal denervation (update)**
Patient indication	**A minimally invasive treatment for resistant hypertension**
Technology type	**Procedure**
Technology use	**Therapeutic**
Speciality	**Cardiovascular**
Technology setting	**Specialist hospital**

Reason for assessment

Renal denervation for the treatment of patients with refractory hypertension was first assessed by HealthPACT in March 2010. This initial assessment concluded that renal denervation was an innovative and promising technique for the treatment of resistant hypertension, however more evidence pertaining to the effectiveness of the procedure was required before renal denervation became routine clinical practice.

HealthPACT was to convene a national workshop on 20 February 2014 to examine issues around the introduction of catheter-based renal denervation for refractory hypertension within the Australian and New Zealand health systems. Renal denervation, as an emerging technology, was thought to have the potential to significantly impact on the management of patients with refractory hypertension. Renal denervation is a high-cost procedure (in excess of $10,000 per patient). Despite early randomised controlled trials (RCTs) showing initial results of a reduction in blood pressure of up to 30 mmHg, larger, more recent studies do not validate these results.

By considering the national and international clinical experience, patient outcomes and funding and workforce implications, HealthPACT aim to assist health policy-makers to identify options regarding models of care, service delivery models, patient access criteria and funding considerations regarding the appropriate diffusion of new health technology such as renal denervation.

HealthPACT advises that the scheduled renal denervation workshop was cancelled in light of the following information.

Four manufacturers of this technology have eleven catheter-based renal artery radio-frequency ablative devices listed on the Australian Register of Therapeutic Goods. Of these, three manufacturers have recently announced the cessation of renal denervation clinical trials:

- On 9 January 2014, Medtronic announced that the pivotal SYMPLICITY HTN-3 RCT failed to achieve its primary efficacy end point of a sustained reduction in systolic blood pressure;

- On 21 January 2014, Covidien announced it would cease its OneShot™ Renal Denervation program in response to slower than expected development of the renal denervation market; and
- On 17 January 2014, media company Bloomberg advised that Boston Scientific would not begin a study of its renal denervation system (Vessix) in light of the announcement from Medtronic in order to analyse and review its approach with the United States regulators.

In the interests of protecting Australian and New Zealand patients, it should be emphasised that these clinical trials were halted due to the lack of effectiveness and not due to any safety concerns.

The use of renal denervation has increased significantly throughout Australia and is starting to diffuse in New Zealand, despite the absence of high-quality evidence of sustained reduction in systolic hypertension in clinical trials. It is likely that renal denervation is being undertaken in self-selected Australian and New Zealand public hospitals. In addition, there is no diagnosis-related group code and associated cost weight that, respectively, adequately codes or captures the cost of delivering this technology.

As such, HealthPACT agreed to update and summarise the evidence base pertaining to renal denervation, including non-radio frequency renal denervation (RDN) techniques such as ultrasound, β radiation and pharmaceuticals, to assist the jurisdictions in decision-making around this technology.

2014 Impact

Alternative and/or complementary technology

Substitution technology: New technology is a direct substitute for current technology, or will substitute to a great extent.

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

Diffusion of technology in Australia

The proof-of-concept RDN study by Krum et al (2009), using radio-frequency ablation, was conducted in Melbourne at St. Vincent's Hospital and The Alfred, in addition to several European centres.[1] As of November 2012, these two hospitals, and St George and Royal Prince Alfred Hospitals in Sydney, Princess Alexandra Hospital in Brisbane; Royal Perth and Sir Charles Gairdner Hospitals in Perth and John Hunter Hospital in Newcastle , have all participated in the Global Symplicity® Registry, a non-comparative, single-arm study that

aimed to enrol 5,000 patients undergoing RDN at 200 sites.[2] It is likely other Australian and New Zealand hospitals have also provided RDN and participated in this international registry.

Boston Scientific's Vessix™ RDN system has been trialled at multiple international sites including in Australia (REDUCE HTN, NCT01541865) at St. Vincent's Hospital (New South Wales), The Prince Charles Hospital (Queensland), Royal Adelaide Hospital and Flinders Medical Centre (South Australia) and Monash Health (Victoria).[3]

In Australian public hospitals, funding has been allocated to date through specified grants (where they exist) or allocated hospital budgets (detailed below). There is currently no private sector reimbursement in Australia. Medtronic Australasia Pty Ltd lodged an application with the Medical Services Advisory Committee (MSAC) in October 2012 for Medicare rebate consideration, however, this application has since been withdrawn.[3]

RDN pilot studies received more than $2 million funding through State Department of Health new technology programs in Victoria and Queensland. Melbourne's Baker IDI Heart and Diabetes Institute received almost $5 million through National Health and Medical Research Council (NHMRC) projects grants plus additional funding via industry.

It is likely that RDN is also being undertaken in other Australian public hospitals and coded to AR-DRG F67B (Hypertension without catastrophic or severe comorbidity/complication) for revenue purposes. The 2013-14 revenue for this DRG in Queensland is $2,975, and $1,835 in Victoria, both of which are lower than the reported $11,500 cost of providing RDN (personal communication Queensland Health and the Victorian Department of Health).

Australian Therapeutic Goods Administration approval

☒ Yes ARTG number (s)

☐ No

☐ Not applicable

Licensing, reimbursement and other approval

Renal denervation devices, currently registered on the ARTG are summarised in Table 1, all of which are classified as Medical Class IIb with the exception of the Covidien generator, which is Medical Class I.

Table 1 Australian regulatory status of catheter-based renal artery ablative devices [3]

ARTG no.	Sponsor	Item Description
186730	Medtronic Australasia Pty Ltd	Ardian Symplicity® Catheter System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The System may consist of a generator (to deliver the controlled radiofrequency energy at specific power, temperature and time settings) with its power cord, a foot pedal and an extension cable.
198986	Medtronic Australasia Pty Ltd	Symplicity® Catheter System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The System may consist of a generator (to deliver the controlled radiofrequency energy at specific power, temperature and time settings) with its power cord, a foot pedal and an extension cable.
198985	Medtronic Australasia Pty Ltd	Symplicity® Catheter System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney.
170236	Medtronic Australasia Pty Ltd	The Symplicity® System is intended to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney.
198878	St Jude Medical Australia Pty Ltd	The RF Ablation Generator is intended to deliver RF energy to the Renal Artery Ablation Catheter
197340	St Jude Medical Australia Pty Ltd	The ablation catheter is indicated for use in renal denervation procedures for the treatment of hypertension.
200781	Covidien Pty Ltd OneShot™	The generator delivers low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The System may consist of a generator (to deliver the controlled radiofrequency energy).
201773	Covidien Pty Ltd OneShot™	The generator delivers low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The System may consist of a generator (to deliver the controlled radiofrequency energy).
Note: the Covidien OneShot™ RDN system is CE Marked but NOT registered on the TGA		
198878	St Jude Medical Australia Pty Ltd	The RF Ablation Generator is intended to deliver RF energy to the Renal Artery Ablation Catheter
197340	St Jude Medical Australia Pty Ltd EnligHTN™	The ablation catheter is indicated for use in renal denervation procedures for the treatment of hypertension.
200215	Pacific Clinical Research Group Pty Ltd Boston Scientific	RF Ablation: The Vessix Vascular V2 Renal Denervation System is intended to be used to treat patients with medication-resistant hypertension. The Vessix Vascular V2 Catheter is NOT intended for use in any artery other than the renal artery and is designed and intended to be used ONLY with the Vessix Vascular V2 Generator.
221478 225927	Sponsor: Terumo Australia Pty Ltd Manufacturer: Shanghai AngioCare Medical Technology Ltd	The Iberis renal artery radio-frequency ablation catheter is designed to deliver low-level radio-frequency energy through the wall of the renal artery to achieve renal denervation
222454	Sponsor: Johnson & Johnson Medical Pty Ltd Manufacturer: Biosense Webster Inc	The RENLANE Renal Denervation Catheter and related accessories are used in conjunction with the RENLANE Multi-Channel RF Generator for use in adult patients (> 18 years) with drug resistant hypertension to denervate the renal arteries to reduce blood pressure.

International utilisation

Given the potential clinical and financial impacts it can bring to bear to patients and health systems, respectively, RDN is being actively monitored by health technology/ government agencies across the world. Agencies in Austria, Canada, Italy, New Zealand, Sweden, UK and USA have recently reviewed RDN and determined that, although promising, RDN is yet to demonstrate sustained clinical and cost effective benefits at this time. However, all note that provision of long-term clinical outcomes and health system impact data are required to support future funding and provision. Some agencies suggest that RDN: is introducing a surgical procedure into a treatment paradigm that was previously limited to medical management, which would increase both catheter lab demand and cost[4]; would increase [regional] expenditure for resistant hypertension treatment by 3, 7 and 12 per cent at 1, 2 and 3 years, respectively, after RDN[5]; and could result in an overall shortage of interventional capacity.[6]

International consensus statements[7, 8] and guidance from the UK's National Institute of Health and Care Excellence (NICE)[9], recommend that patients undergoing renal denervation must have at least Stage 2 hypertension with an office systolic reading of ≥160 mmHg or an ambulatory daytime reading of ≥150 mmHg (or >150 mmHg with type 2 diabetes). All patients must have resistant hypertension that is refractory to pharmacological treatment with at least 3 anti-hypertensive drugs, one of which must be a high dose diuretic. Lifestyle interventions must have been performed and compliance confirmed.

2014 Cost infrastructure and economic consequences

Reported costs for RDN do not appear to vary within or external to Australia, and range from approximately AU$10,000 -12,500 (which includes the hospital admission and RDN catheter costs). New technology programs (in Victoria and Queensland) have allocated additional funding to cover administration, data collection, data reporting and research nurse time to reflect the 'coverage with evidence development' approach.

New Zealand's National Health Committee has reported that the potential budgetary impact of RDN cannot be accurately predicted, but evidence to date suggests the provision of RDN across New Zealand would cost from NZ$7 million to NZ$16 million over five years.[10] On a population comparison basis alone, this indicates that RDN provision in Australia over the same timeframe could range from AU$33 million to AU$76 million.

2014 Safety and effectiveness

Radiofrequency (RF) renal denervation

Symplicity® Renal Denervation System (Medtronic, Minnesota USA)

The majority of published clinical data has described the use of the Symplicity® Renal Denervation System and were supported by funding from Medtronic. The main component of the Symplicity® system is a catheter which is used to deliver a maximum of 8-watts of

radiofrequency (RF) energy, achieving temperatures between 40-75°C, to the renal artery.[11] A 6-French, steerable RF ablation catheter is inserted percutaneously through a femoral sheath along with a guide catheter, treating each renal artery sequentially (Figure 1).[12] A typical treatment requires four ablations in each of the renal arteries in different locations, rotated 90° to avoid circumferential arterial injury. Painkillers are administered intravenously to manage pain resulting from the procedure.[11]

Figure 1 The Symplicity® renal denervation catheter[13]

The original work by Krum et al (2009), the Symplicity HTN-1 trial, was a non-comparative proof-of-concept study in 153 patients (level IV intervention evidence).[1] This multicentre study reported follow-up outcome data at 24-months (n=105)[14] and for 88 patients at 36-months.[15]

At baseline in these patients, mean blood pressure was 142.6/82 mmHg (± 17.7/11.0). At 36-months follow-up a mean reduction from baseline was reported in systolic and diastolic blood pressure of -32.0 mmHg (± 17.6, 95% CI [-35.7, -28.2]) and -14.4 mmHg (± 11.8, 95% CI [-16.9, -11.9]), respectively (Figure 2). At 1-month follow-up, of the 141 patients available for follow-up, 69 and 59 per cent of patients had a decrease in systolic blood pressure of ≥10 mmHg and ≥20 mmHg, respectively. Of the 88 patients available for follow-up at 36-months, this proportion had increased to 93 and 77 per cent, respectively. This study highlighted the importance of patient selection and differentiating between patients who truly have resistant hypertension and those who do not adhere to treatment. Although this uncontrolled study reported durable reductions in blood pressure post-RDN and no evidence of serious cardiovascular events related to the procedure in those patients followed-up, a number of issues with the study were highlighted. These included the large loss to follow-up (41.3%) which may bias the results, the merit of office BP measurement, used in this study, compared to ambulatory measurements taken over a 24-hour period, and a lack of reporting regarding anti-hypertensive medication usage in patients may have confounded these results.[16]

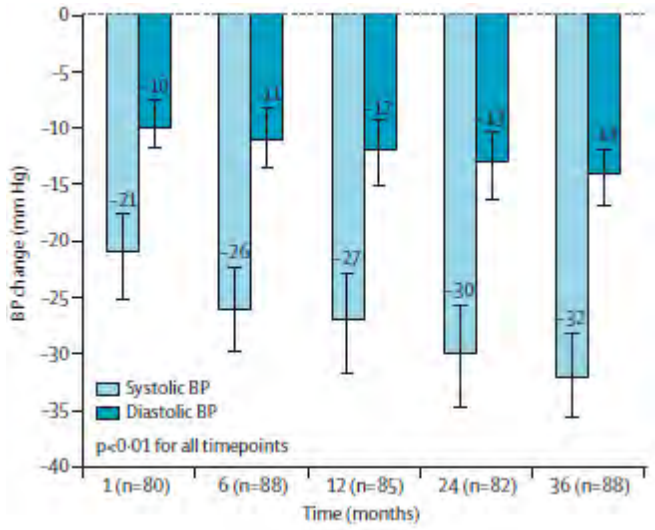

Figure 2 Change from baseline in office BP measurements at 36-months [15]

The Symplicity HTN-2 trial enrolled 106 patients randomised to RDN (n=52) or control (n=54). After 6-months, crossover was allowed, with control patients permitted to undergo RDN. Investigators were not blinded to allocation status of the patients.[17] At 6-months, mean office BP in the RDN group was reduced by 32/12 mmHg (standard deviation 23/11 mmHg) compared to 178/96 mmHg at baseline (p< 0.0001). In the control group, no change at 6-months was reported compared to baseline. At the same time, systolic BP was less than 140 mmHg in 39 per cent of patients who had undergone RDN compared with only six per cent of the control group. In addition, 20 per cent of patients in the RDN group reduced the number of anti-hypertensive medications they were taking compared to six per cent in the control group (p=0.04).[18] Esler et al (2012) compared baseline office-based BP measurements to those taken at 6- and 12-months in patients who had undergone RDN and those who had crossed over from the control group at 6-months, but failed to report on the control group. A significant difference compared to baseline was noted at 6- and 12-months in both systolic and diastolic BP (Figure 3) and there was no significant difference between the change from baseline at 6-months compared to that at 12-months (Table 2), indicating a sustained reduction of blood pressure over time.[17]

Table 2 Change from baseline BP at 6- and 12-months[17]

	Renal denervation group (n=49)	p value	Crossover group (n=35)	p value
6-month change in BP				
SBP	-31.7 ± 23.1	<0.001	-23.7 ± 27.5	<0.001
DBP	-11.7 ± 11.2	<0.001	-8.4 ± 12.1	<0.001
12-month change in BP				
SBP	-28.1 ± 24.9	<0.001	n/a	
DBP	-9.7 ± 10.6	<0.001	n/a	

BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, n/a = not available

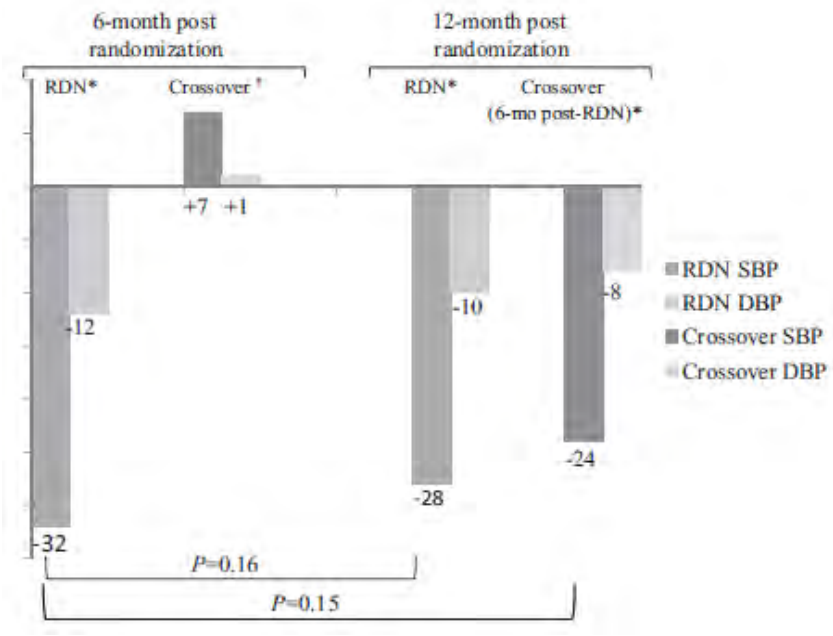

Figure 3 Change in office-based BP[17]

This study was criticised on a number of levels, including the lack of a sham procedure, lack of blinding of investigators, ambulatory BP measurements were only conducted on 42 per cent of patients who were not randomly assigned. Importantly, the mean reduction in *ambulatory* BP after 6-months was significant but not as large as the reduction in *office-based* BP measurements (11 mmHg, p= 0.006 for systolic BP change, and 7 mmHg, p = 0.014 for diastolic BP change), which may indicate that the true treatment effect was over estimated. In addition, although a reduction in anti-hypertensive medication was reported, compliance was not rigorously evaluated.[19] It should be noted that the small patient number may not be large enough to detect rare adverse events.[20]

The randomised controlled Symplicity HTN-3 trial attempted to address some of the issues raised in the previous two Symplicity studies. The Symplicity HTN-3 trial enrolled 535 patients with severe resistant hypertension from a total of 1,441 eligible patients located in 88 sites in the United States. Patients were randomised 2:1 to undergo RDN or a sham procedure and were blinded to their allocation (level II intervention evidence). Patients were required to have a systolic blood pressure (SBP) ≥160 mmHg and to be taking maximally tolerated doses of three or more anti-hypertensive medications, one of which was required to be a diuretic. Baseline ambulatory SBP measurements were taken in a bid to exclude patients with false resistant hypertension (the white-coat effect). There was no statistical difference between the baseline characteristics of the RDN group (n=364) and the sham control group (n=171), including the number and type of anti-hypertensive medications they were taking, age, sex, body mass index, smoking status and medical history (including stroke, peripheral artery disease, cardiac disease, diabetes and renal insufficiency). The primary endpoint was the mean change in *office* SBP from baseline to 6-month follow-up, with a 5 mmHg superiority margin between the two groups. Importantly

the study was powered to assess the secondary effectiveness outcome of the change in mean 24-hour *ambulatory* SBP from baseline to 6-month follow-up.[21]

A significant reduction from baseline to 6-months was reported in office and ambulatory SBP measurements for both the intervention and sham groups, although the large standard deviations in each group indicate a great deal of within group variation (Table 3). However, the between group difference in change was not significant for both office and ambulatory measurements and did not meet the *a priori* test of superiority of a 5 mmHg and 2 mmHg margin, respectively. Similar results were also reported for diastolic BP measurements. A subgroup analysis of office SBP measurements was conducted and, although there was a significant difference in some subgroups (patients <65 years and a GFR[1] ≥60 ml/min/1.73 m^2, p=0.04 and p=0.05, respectively), the differences were small (<10 mmHg) and were not significant with the 5 mmHg superiority margin. The authors of the study also acknowledged that the study was limited due to a lack of medication compliance reporting, and that the 6-month follow-up period may be too short if a placebo effect was to decline with time.[21]

Table 3 The between group differences of office and ambulatory SBP measurements at 6-month follow-up

Office SBP	Change from baseline at 6-months	Between group difference in change [95% CI]
Intervention – RDN group	-14.13 ± 23.93 mmHg p<0.001	-2.39 mmHg [-6.89, 2.12], p=0.26
Control – Sham group	-11.74 ± 25.94 mmHg p<0.001	
Ambulatory SBP		
Intervention – RDN group	-6.75 ± 15.11 mmHg p<0.001	-1.96 mmHg [-4.97, 1.06], p=0.98
Control – Sham group	-4.79 ± 17.25 mmHg p<0.001	

A further analysis of the ambulatory SBP results from this trial reported no difference in change between the RDN and sham groups for daytime and night-time ambulatory SBP measurements.[22]

There was no significant difference in the number of major adverse events reported in each group, with a total of five (1.4%) and one (0.6%) reported in the RDN and sham groups, respectively. The most frequently reported adverse event in both groups was a hypertensive crisis or emergency, with nine patients in each group reporting this outcome. The percentage of patients reporting a myocardial infarction or stroke was similar in both groups.[21]

[1] GFR = glomerular filtration rate

After the publication of these results, Medtronic announced the Symplicity HTN-3 trial failed to meet primary efficacy endpoints of a reduction in office SBP after 6 months and that ongoing clinician and patient access to Symplicity systems is yet to be determined.[23] A number of letters to the editor were received citing possible reasons for the failure of the trial to reach its primary or secondary endpoints. Schillaci and Boschetti suggested that technical aspects of the procedure may have resulted in the negative findings, with the success of the procedure using the first-generation Symplicity® catheter being entirely operator-dependent. They hypothesised that this led to a failure to attain thermo-ablation rather than a lack of anti-hypertensive effect. The use of multi-electrode second-generation devices may address this issue[24] A lack of technical expertise was cited by Rodriguez-Leor et al, in that 31 per cent of operators who participated in the trial had no previous, or limited experience with RDN.[25] However the authors of the Symplicity HTN-3 trial acknowledged that first-generation catheters had achieved reductions in SBP in the previous Symplicity trials, and that each procedure was supervised by an experienced proctor and performed per protocol.[26] It has been acknowledged that it is difficult to separate technical failure of the procedure from a lack of response in patients who have received an effective RDN procedure.[27]

Of interest is the observation by Kotsis and Stabouli who hypothesised that the null effect of RDN was due to patients in both the intervention and control arms being obese, with a body mass index (BMI) of 34.2 ± 6.5 and 33.9 ± 6.4, respectively. Obese patients may not be ideal candidates for RDN due to the role the sympathetic nervous system plays in obesity-induced hypertension.[28] A subgroup analysis of the between-group differences in office SBP was performed in the Symplicity HTN-3 trial. Although denervation was favoured when patients were stratified to those with a BMI <30 and those with a BMI ≥30, the difference between the intervention and control groups was not significant for either group (p=0.53 and p=0.11, respectively).[21, 26]

Other factors have been hypothesised for the lack of effect in the Symplicity HTN3 trial including the racial origin of trial participants and incomplete or lack of denervation of the accessory vessels.[29, 30] Of the 535 patients enrolled in the Symplicity HTN-3 trial, approximately one-third were African American. A subgroup analysis by racial origin revealed that reductions in office systolic BP were significantly greater in the intervention group compared to the sham-control group. This effect was not observed in African American patients.[30] The majority of the uncontrolled studies conducted prior to the Symplicity HTN-3 trial that reported a sustained decrease in blood pressure were conducted in a primarily Caucasian population.[31] In addition, there was a great deal of variation in medication regimens of patients, with some changing medication during the trial, indicating that their hypertension was not stable. Patient selection may therefore be of importance.[30]

Ongoing Symplicty studies

A large number of clinical studies describing the use of the Symplicity device for renal denervation are ongoing, including the Symplicity HTN-4 (NCT01972139), an RCT comparing RD to a sham procedure in 580 patients. The status of this study remains active although it is currently not recruiting patients. In addition, the large observational Global Symplicity Registry (NCT01534299) is still actively recruiting patients (n=5,000) and expects to be finalised in mid-2016. Of interest is the ongoing German RCT that aims to assess the impact of RD on patients who have already undergone a kidney transplant (NCT01899456).

EnligHTN Renal Denervation System (St Jude Medical, Minnesota USA)

To overcome the potential problems of operator error and uncertainty of catheter placement as experienced with the Symplicity catheter system, St Jude Medical developed the EnligHTN system. This multi-electrode system consists of four electrodes mounted on a collapsible basket that is controlled externally (Figure 4). The basket allows for the circumferential distribution of lesions and is thought to be able to deliver thermal injury and fibre interruption in a more predictable manner.[12]

Figure 4 The EnligHTN™ catheter demonstrating the four electrodes[32]

The other recent study published reported on the first 6-month follow-up of 46 patients enrolled in the EnligHTN™ (multi-RF electrode system) case series (level IV intervention evidence) were conducted in Australia and Greece.[33] This study, as with the earlier Symplicity studies, was limited by the lack of a control group. Inclusion criteria were similar to those described in the Symplicity trial. Patients were a mean age of 59.9 ± 10.2 years with a mean BMI of 32.4 ± 5.2, a high proportion had type II diabetes (32.6%) and were male (67.3%). The median procedure time was 34 minutes during which time a mean of 7.7 ± 0.8 and 7.4 ± 1.4 ablations were delivered in the right and left renal arteries, respectively.

Office BP measurements were significantly reduced compared to baseline at one, three and six months follow-up: -28/-10, -27/-10 and -26/-10 mmHg, respectively ($p<0.0001$). Over the follow-up period, 80 per cent of patients had a reduction in office SBP of at least 10 mmHg or greater. In addition, there was a significant reduction in the average 24-hour ambulatory

BP compared to baseline at one, three and six months follow-up: -10/-5, -10/-5 and -10/-6 mmHg, respectively ($p<0.001$). There was a corresponding decrease in resting heart rate from baseline (71 bpm) to 6-month follow-up (66 bpm).[33] Sustained and significant reductions in office (-27/-11 mmHg) and 24-hour ambulatory BP (-7/-4) were reported at 12-month follow-up. At 12-month follow-up, renal function had not deteriorated and no new serious adverse events had been reported, although one patient did require renal artery stenting after renal artery stenosis had progressed from baseline.[34]

Three patients (6.5%) experienced a serious adverse event between 93 and 169 days follow-up (hypertensive renal disease progression, hypotension, progression of pre-existing renal artery stenosis). Minor adverse events were reported (n=35) including vasospasm and haematoma. Over the follow-up period, six (13%) patients decreased and four increased (8.7%) their anti-hypertensive medication. Those patients who did not change the level of their medication had similar reductions in office and ambulatory BP when compared to the group as a whole.[33]

Although these results appear promising, no conclusions as to the effectiveness of RD using the EnligHTN™ system can be drawn due to the non-comparative nature of this study.

Ongoing EnligHTN™ studies

A number of trials using the EnligHTN RDN system are ongoing. The multi-centre (including several sites in Australia) non-comparative EnligHTN II trial (NCT01705080) is designed to build on EnligHTN I study, enrolling 500 patients with less severe hypertension (office SBP ≥ 140 mmHg). EnligHTN II commenced in January 2013, is still actively recruiting and expects to be completed by April 2015. This observational study will report the mean reduction in SBP at 6-months across all patients post-RDN procedure and within sub-groups with varying degrees of kidney functionality. The small observational (n=30) EnligHTN III study being conducted in Australia and New Zealand is designed to evaluate the safety of the next-generation EnligHTN multi-electrode RDN system, which is capable of delivering simultaneous ablations and in so doing, reducing procedure time (NCT01836146). The study commenced in April 2013, is not currently recruiting and is expected to be finalised in August 2015.

The EnligHTN IV study (NCT01903187) was to be the first US based RDN study conducted under an Investigational Device Exemption (IDE) from the FDA. This large (n=590) multi-centre randomised controlled was designed to assess the safety and effectiveness of the EnligHTN RDN system in reducing office SBP compared to a sham procedure (measured at 6-month follow-up). Although the study commenced in October 2013 and did not expect to be finalised until December 2017, it is currently not recruiting patients and has been reported to be cancelled.[35]

A similar Danish RCT is currently recruiting patients (n=70) to undergo RDN compared to a sham procedure, with the primary effectiveness endpoint being 24-hour ambulatory BP

measurements taken at 6-months compared to baseline. This double blind RCT commenced in January 2013 and expects to be finalised by December 2014 (NCT01762488).

In Belgium, the INSPiRED RCT aimed to compare RDN with the EnligHTN™ system to usual medical therapy. Patients (n=240) were to be randomised 1:1 to receive RDN plus usual care (intervention group) or usual care alone (control group).[36] Although the study commenced in 2012, it is currently not recruiting patients (NCT01505010).

Two other large observational studies are currently underway, one multi-centre European study (NCT02006758) and one multi-centre German study (NCT01996033). Both commenced in late 2013 and aim to recruit 500 patients, finalising results by early 2016. The primary outcome measure in both these observational studies is office based SBP at 6-month follow-up.

Another small (n=60) RCT aims to report on the effectiveness of RDN in patients with metabolic syndrome by measuring the change in insulin resistance from baseline to 3 months (NCT01911078). Although this study commenced in September 2013, it is currently not open for patient recruitment. A small Australian observational study (n=20) intends to assess changes in cardiac function by MRI in patients with uncontrolled hypertension who have undergone RDN (NCT02164435).

Other RF renal denervation systems

Three other radiofrequency ablation systems were identified in the literature.

Vessix system

The Vessix V2 system (Vessix Vascular-Boston Scientific) is approved for use in Australia by the TGA. The system utilises an over-the-wire low-pressure balloon equipped with bipolar RF electrodes attached to the balloon surface which is capable of accommodating smaller arterial diameters (3.0 mm) (Figure 5).[37]

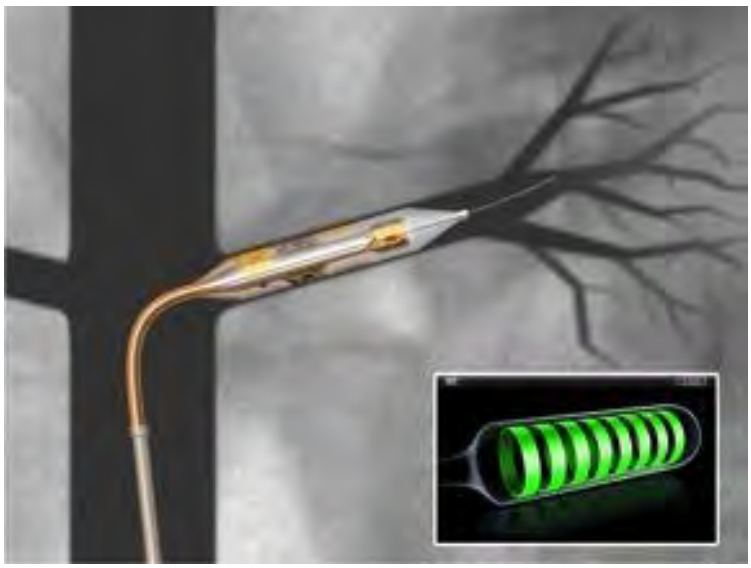

Figure 5 The Vessix V2 balloon renal denervation catheter[38]

To date, the largest clinical study (n=146, age 58.6 ± 10.5 years) using the Vessix system has been the multi-centre REDUCE-HTN study, a non-randomised observational study (level IV interventional evidence). Six and 12-month follow-up results were reported in abstract form at the EuroPCR[39], the Cardiovascular Research Technologies[40] and the American Society of Hypertension's[41] annual conferences, with 18-month results published on the company website.[42]

Baseline 24-hour ambulatory blood pressure was 153.0/87.5 (± 15.1/13.2) mmHg (n=103) with 90 per cent of patients having a systolic BP >135 mmHg. Mean ambulatory BP was reduced by –8.4/–5.9 (± 14.4/9.1) mmHg (n=69, p<0.0001) and–10.1/ –6.2 (± 15.3/8.3) mmHg (n=32, p<0.001) at 6- and 12-months, respectively. Patients with baseline ambulatory systolic BP ≥160 mmHg had a mean reduction of –16.5 mmHg at 6-months (n=22), compared to a mean reduction of –0.85 mmHg in those patients with baseline BP <160 mmHg (n=47). An ambulatory systolic BP <135 mmHg was achieved in 25 and 26 per cent of patients at 6- and 12-months, respectively.[39] Although these results indicate a sustained reduction in mean ambulatory BP, they should be interpreted with caution due to the substantial loss to follow-up and the large standard deviations. Ambulatory BP measurements at 18-months were not reported on the company web site. Results reported by the company show a mean reduction in office systolic and diastolic BP of 30.2 and 12.7 mmHg from baseline at 18 months (n=51, p<0.0001).[42]

OneShot™ system

The OneShot™ system (Covidien) is also registered for use in Australia by the TGA. The OneShot™ is an irrigated catheter (for cooling), with electrodes mounted in a helical configuration on the balloon which delivers RF in a spiral pattern negating the need to manipulate the catheter during ablation (Figure 6). Inflation of the balloon ensures contact of the electrode with the arterial wall.[43] To date, the only reports in the literature describing the use of the OneShot™ have been a case report[44] and small case series (n=9)[43] conducted by the same research group in New Zealand.

Figure 6 The Covidien OneShot™ irrigated, radiofrequency based balloon catheter[45]

The results of this small case series are summarised in Table 4. Although there was a reported sustained reduction in office based BP measurements over time, there was a minimal reduction in ambulatory BP from baseline to 6-month follow-up.

As discussed previously, Covidien have since announced their withdrawal from the renal denervation market, citing slow market growth.

Table 4 Outcome data from the Renal Hypertension Ablation System trial[43]

	Baseline (n=8)	1-month (n=8)	3-month (n=8)	6-month (n=8)	12-month (n=6)
Office SBP (mmHg)	185.67±18.7	155.58±18.84	151.46±19.93	152.08±22.27	155.89±27.27
Change in office SBP (mmHg)		-30.08±13.6	-34.21±20.2	-33.58±32.0	-30.6±22.0
Office DBP (mmHg)	91.33±14.47	86.17±14.04	80.54±16.52	78.54±17.10	81.22±11.27
Change in office DBP (mmHg)		-5.2±10.0	-10.8±15.7	12.8±21.0	9.5±15.2
Responders (>10 mmHg)		87.5% (7/8)	87.5% (7/8)	75.0% (6/8)	83.3% (5/6)
24-hour ambulatory SBP (mmHg)	151.75 ± 12.12			148.63 ± 16.77	
24-hour ambulatory DBP (mmHg)	86.75 ± 17.32			82.75 ± 13.92	

SBP = systolic blood pressure, DBP = diastolic blood pressure

Iberis™ system

The Iberis™ system (Terumo Medical Corporation) is not currently registered on the TGA but received the CE Mark in 2013. The Iberis™ is a non-over-the-wire system, which uses a single unipolar electrode at the tip of the catheter to create a spot lesion. The catheter is much smaller than most of the other RD systems on the market (4 versus 6 or 8 French) and is made from nitinol, which allows for movement through tortuous arteries and enables radial access.[46]

The only peer-reviewed publications identified describing the use of the Iberis™ system were two case reports, one describing RD using a transradial access approach[46], the other using a transulnar approach as the transfemoral and transradial had anatomic constraints.[47] No adverse events were reported in either patient and both experienced a decrease in blood pressure.

Ultrasound renal denervation

Ultrasound (US) as an alternative energy source has also been investigated as a potential renal denervation method which may reduce or minimise injury to the vessel wall. The basic premise of the technology is that a catheter is passed into the renal arteries where the high-

frequency US sound waves generates frictional heat in the surrounding tissue, causing injury to the renal artery.[11, 37, 48]

At least two systems have obtained CE Marking and are currently conducting small trials in humans and several other systems are in development (Table 5).

Table 5 Ultrasound renal denervation products in development[49]

Company	Product	Description	Status
ReCor Medical Inc, USA	Paradise®/Radiance system	A 6 Fr over-the-wire ultrasound device; 2nd-generation version is designed to reduce energy delivery to 30 seconds by maximising cooling of the endothelium and efficiently treating the nerves circumferentially.	CE Marked
Cardiosonic, Tel Aviv, Israel	TIVUS™ system	Non-focused, high-intensity, non-occlusive, high-frequency, directional US catheter and control system for remote tissue ablation for the treatment of hypertension; 3rd-generation version features a multidirectional catheter.	CE Marked, international clinical study underway
Enigma Medical	Enigma Device	Non-invasive pre-aortic ganglion ablation for the treatment of hypertension.	Intellectual property developed
Kona Medical	Surround Sound System	External focused ultrasound-guided, non-invasive, Doppler-based tracking system for optimised treatment delivered in 3 minutes per side; treatments do not require a cath lab or fluoroscopy.	Preclinical studies underway
Sound Interventions	Sound-360	Cylindrical ultrasound transducer mounted on the tip of the intravascular catheter for delivering circumferential bilateral renal artery sonications; allows for selective renal nerve denervation.	First-in-man study underway
VytronUS	VytronUS RDN	Ultrasound-based system in which collimated energy is directed to a renal vessel to create necrotic regions in the tissue in order to alleviate hypertension.	Intellectual property developed

The Paradise® system consists of a balloon catheter that encapsulates an US transducer, which allows the uniform, circumferential delivery of energy (Figure 7).

Figure 7 The tip of the Paradise® catheter demonstrating the US emitting transducer contained within the balloon[50]

The catheter is positioned within the renal artery, where the balloon is inflated, holding it in a central position. Fluid fills the balloon, cooling the endothelial wall and preventing thermal damage to non-target tissues.[11, 37, 48]

The first clinical study conducted with the Paradise® system was the small REALISE feasibility case series (n=20) conducted at two sites in France (level IV intervention evidence) (NCT01529372). The preliminary results of 11 patients at 3-month follow-up were published by Mabin et al (2012)[50], however 12-month follow-up data on 20 patients were presented at the 2014 EuroPCR conference. [51, 52] Patients were required to have resistant hypertension with a minimum office BP of 140/90 mmHg and an ambulatory BP 130/80 mmHg. Bilateral denervation was performed with US delivered to up to three locations within the artery with emission between 25-30 watts for up to 50 seconds[50] (average of 5.7 US emissions and average heating time 3.3 minutes per patient).[51, 52] A sedative and analgesic were administered during the procedure along with an injection of an antispasmodic vasodilator. At the end of the 12-month follow-up an average reduction in office and ambulatory BP of -27/-6 mmHg and -15/-7 mmHg was reported, respectively. Follow-up imaging demonstrated no arterial stenosis or damage.[51, 52] The abstracts did not report on safety issues associated with US renal denervation, however Mabin et al, who described the first 11 patients of the series, reported that one patient experienced renal artery dissection upon placement of the guiding catheter prior to the insertion of a 6 Fr treatment catheter, which was treated with a renal artery stent without any subsequent complication. All patients except one were discharged on the day following the intervention. This patient experienced post-treatment hypotension and had to be hospitalised for an additional day but was discharged the following day without further complications.[50]

A similar, multi-centre study is currently underway (NCT01789918) (level IV intervention evidence). The ACHIEVE study has recruited 50 patients (mean age 64 ± 10 years) with mean baseline office and ambulatory BP measurements of 175 ± 20 mmHg and 154 ± 12 mmHg, respectively. Preliminary 6-month follow-up results were reported at the EuroPCR 2014 conference. There were no reports of renal artery stenosis; renal complications; or thromboembolic events, however procedural-related pain was commonly reported (numbers not stated). An average reduction in systolic office BP from baseline –14 mmHg and –16 mmHg was observed at one (n=34) and 6-months (n=17) post treatment, respectively. The average decrease in ambulatory BP at 6-months was –10 mmHg (n=14). When patients with an office systolic BP at baseline <160 mmHg were excluded, a larger treatment effect was noted, with an average decrease of –19 and –22 mmHg at one and 6-month post treatment, respectively. The responder rate, defined as a decrease in systolic BP ≥ 10 mmHg, at 6-months was 70 per cent.[53]

Another system, the TIVUS™, developed by CardioSonic, is a high-intensity, non-focused US catheter system for renal denervation. Treatment is delivered at 1-2 sites along the renal artery, with four treatment points at each site, given at 90° to each other in order to deliver

a circumferential effect. It is expected that the next iteration of the device will be a single operation device that will negate the need for the operator to rotate the device. The ablation energy is delivered remotely to the adventitia without contacting the endothelium, in so doing reducing the potential for vessel damage (Figure 8). One of the main advantages of the TIVUS™ is its ability to deliver treatment through renal artery stents. However, concerns have been raised about the potential for adverse events due to the generation of heat around the US catheter.[11, 37, 48]

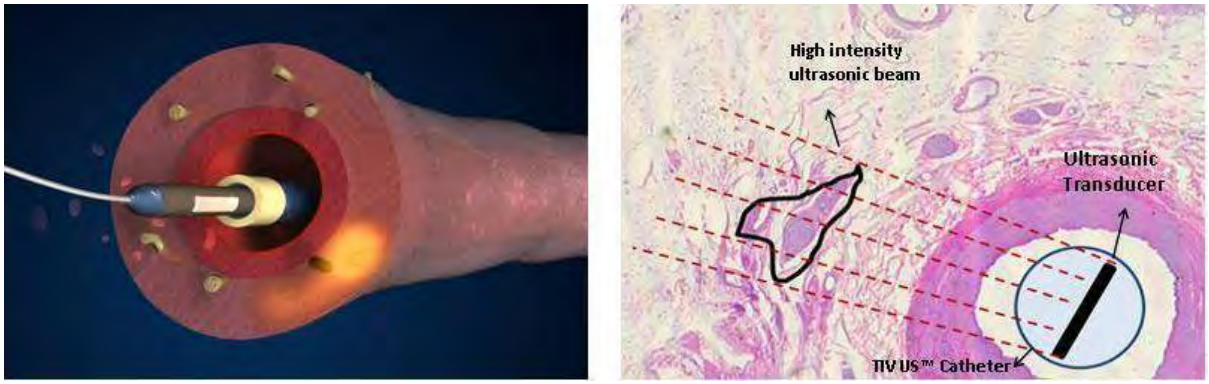

Figure 8 The TIVUS US catheter[54]

The results of the first case reports using the TIVUS™ were reported at the EuroPCR 2014 conference. Two patients with renal stents and severe resistant hypertension were treated with the TIVUS™ without incident and reported a decrease in office-based BP at 1-month follow-up.[55]

The first-in-man TIVUS multi-centre case series, which includes patients from the Royal Perth Hospital in Western Australia, is ongoing but currently not recruiting patients (NCT01835535) (level IV intervention evidence). Preliminary results of the 18 treated patients, including the previously mentioned two patients with renal stents, were reported at the EuroPCR 2014 conference. At baseline, patients had a mean office-base BP of 174/88 mmHg and were taking an average of 4.7 anti-hypertensive medications. A mean decrease in office-based BP was reported at one and 3-months follow-up: -28/-10 and -25/-10 mmHg (n=16), respectively. No adverse events associated with the procedure were reported.[56]

Of interest is the non-invasive Kona Medical Surround Sound® System, which uses low-intensity focussed US applied externally to treat the renal nerves, in a similar manner to MRI-guided focussed US used to treat uterine fibroids. The non-invasive nature of this technology makes it an attractive option for those patients with tortuous vessels that are unsuitable for treatment with intra-vascular devices and would avoid the potential for adverse events associated with catheter-based treatments.[11, 37, 48]

Kona Medical has conducted several small case series (WAVE I-III studies) involving investigators from several centres around the world including those from St. Vincent's Hospital and the Baker Heart and Diabetes Institute in Melbourne. Only the initial results from the WAVE II study, presented at the 2013 Transcatheter Cardiovascular Therapeutics

conference could be identified. Thirteen patients with resistant hypertension underwent a treatment protocol while under deep analgesic sedation which involved 14 focussed lesions over 2.8 minutes on each side. One patient complained of back pain following treatment, which resolved within 4-days. No other adverse events were reported. At 6-weeks follow-up, eight patients had reported a mean decrease from baseline of 18 mmHg in systolic BP, with no reported change in diastolic BP.[57]

According to the company web site, Kona Medical have commenced recruitment for the WAVE IV study: a randomised, sham-controlled, double-blinded trial in 132 patients at sites in Europe, New Zealand, Australia, and South America.[58]

β-radiation renal denervation

Novoste Corporation (USA) have developed the Novoste™ Beta-Cath™ System designed for the treatment of in-stent restenosis (re-blockage) for coronary and renal arteries, which may be caused by an increased amount of scar tissue in the artery at the site of stent placement. This form of brachytherapy uses a catheter to deliver seeds of β-radiation to the blockage site, where the emitted radiation inhibits cell proliferation, preventing or reducing scar tissue growth. At the completion of the radiation treatment, the radioactive seeds are returned to the transfer device.[11, 59] The Novoste™ system received FDA approval for this clinical indication in 2000.[59] It has been hypothesised that this approach may be a feasible renal denervation method.[11]

Only one small feasibility study using the β-radiation approach was identified. This study was conducted in normotensive pigs and is therefore not included for assessment. The authors did, however, conclude that the method was promising as it limited damage to the renal artery despite the potential for nerve fibrosis.[60] The author of this study is the lead investigator in a small clinical trial (n=20) that commenced in 2013 and is currently recruiting patients (n=20) with uncontrolled hypertension (NCT01968785). The study aims to establish the safety of delivering 2 different doses of β-radiation (25 or 50 Gy) with the Beta-Cath™ System and expects to be finalised by late 2015.

During the course of the EuroPCR conference held in May 2014, at least two other companies were identified that are producing a radiation therapy/renal denervation system: the CyberHeart HTN (CyberHeart Inc, USA) and the Perseus-BioMed RDN (Perseus-BioMed, Israel). Both companies have pre-clinical studies planned.[49]

Pharmacological renal denervation

Another novel method in development is the use of drugs or chemicals delivered locally to achieve renal denervation. The most advanced system described in the literature is the Bullfrog® (Mercator MedSystems Inc, USA) which has FDA approval for delivering therapeutic agents directly through the arterial wall into the perivascular space. The system consists of a micro-needle (130 µm diameter) encased by a balloon catheter. Once within the renal artery, the balloon is inflated and the micro-needle is unsheathed and penetrates

the vessel wall, delivering the therapeutic agent. In an animal study, the neurotoxin vincristine was used to directly impact on distal axon causing axon degeneration. Guanetidine is another neurotoxin under consideration.[11, 37, 48] A number of chemical denervation systems are currently under development and commencing human studies (Table 6).[49]

Table 6 Chemical renal denervation products in development[49]

Company	Product	Description	Status
Abbott	Abbott Chemical RDN	Renal denervation by delivery of a chemical to the periadventitial space of the renal artery	Preclinical studies underway
Ablative Solutions	Peregrine	Device that circumvents the artery wall and delivers neurolytic chemical agent (ethanol) directly to the external region of the renal artery; delivers chemical agent via micro-needles	First-in-man study underway
ApexNano	ApexNano Paramagnetic Particles	Targeted drug and heat delivery for renal denervation involving insertion of what it calls Magnetic NanoParticles into the renal artery using a catheter	In development
Athens Medical School	Athens Chemical Denervation	Local delivery of vincristine by a specially designed catheter to perform chemical sympathetic denervation of the renal artery	First-in-man study underway
Covidien	Covidien Drug Device	A device that delivers a chemical agent to cause renal denervation	In development
Mercator	Bullfrog/Cricket	Adventitial delivery platform that includes the Bullfrog (3 to 6 mm) and the Cricket (2 to 4 mm) micro-infusion catheters	First-in-man study underway
Northwind Medical	Northwind Denervation	Catheter-based delivery system with 40-gauge microneedles for targeted delivery of a neurotropic agent (NW2013) to a plurality of renal nerve target sites	First-in-man study underway

Cryoablation for renal denervation

Cryotherapy has been used effectively in cardiac electrophysiology for many years as an alternative to radiofrequency ablation of arrhythmias. Catheters are used to deliver a liquid cryogen or refrigerant to cool the target tissue to ≤40°C, causing cell death. Cryotherapy is associated with reduced procedural pain and vascular complications without significant differences in the rate of effectiveness when compared to standard RF ablation.[27]

A small pilot study in three patients with resistant hypertension was conducted with a standard 7-French EP cryoablation catheter (Freezor Xtra (Cryocath); Medtronic Inc., USA) without a guide wire (level IV intervention evidence). Heparin and intravenous aspirin was administered to prevent thrombus formation during the procedure in addition to IV painkillers and sedation. The temperature was cooled −75 °C (range minus 70–75 °C) for four minutes to create four lesions in each renal artery. Patients only reported pain during the first, initial drop in temperature. No renal or vascular complications were detected by duplex sonography at follow-up. A decrease in 24 hour ambulatory BP at one- and 3-months of −55/−25 mm Hg and −44/−22 mmHg, respectively, was reported. At 3-months one

patient reported the cessation of two out of seven antihypertensive drugs, another reduced drug intake from six down to three and the remaining patient reported no change in medication.[61] Further randomised controlled trials are required to investigate this technique further.

Other methods for the treatment of resistant hypertension

During the EuroPCR 2014 conference, a number of other methods to control hypertension were discussed. These methods are in the early stages of development and no literature could be identified describing the results of clinical studies. These methods include:

- Cardiac stimulation: electrical stimulation of the heart to control the patient's blood pressure as a treatment for hypertension, either in a standalone device or as part of a conventional pacemaker providing anti-bradycardia therapy;
- Carotid body modulation: catheter-based modulation of the carotid body for the treatment of sympathetic nervous system-mediated diseases such as hypertension;
- Baro-receptor activation (as previously assessed by HealthPACT): implantable device that provides low-level electrical stimulation to the baroreflex system based in the carotid arteries;
- Microwave energy: catheter-based, balloon-tipped device for delivering cooled microwave energy for renal denervation;
- Vagal nerve blocking: device that delivers therapy to intermittently block the vagus nerve during waking hours; leads are placed in a laparoscopic procedure on the vagus nerve and a pacemaker-like device is placed subcutaneously;
- Shock waves: low-intensity shock wave therapy delivered by a special ellipsoid reflector for use in drug-resistant hypertension; and
- Stent-like implant: small, metallic, stent-like implant that creates a therapeutic fistula designed to lower peripheral vascular resistance and potentially blood pressure in hypertensive patients.[49]

Renal denervation for clinical indications other than resistant hypertension

The renal sympathetic nervous system is complex. Efferent nerve activation results in sodium reabsorption and fluid retention, reduced renal blood flow, and activation of the renin-angiotensin-aldosterone system, all of which can contribute to the development of hypertension. The afferent nerves are also thought to be involved in the development of hypertension via the central nervous system. Renal sympathetic overactivity is not only a feature of hypertension, but is also associated with other disease states including chronic kidney disease, heart failure[62] and, more recently, obesity and related conditions such as insulin resistance, obstructive sleep apnoea and polycystic ovary syndrome.[63] Figure 9 is a schematic of the potential impact of renal denervation on organs affected by the sympathetic nervous system.[64]

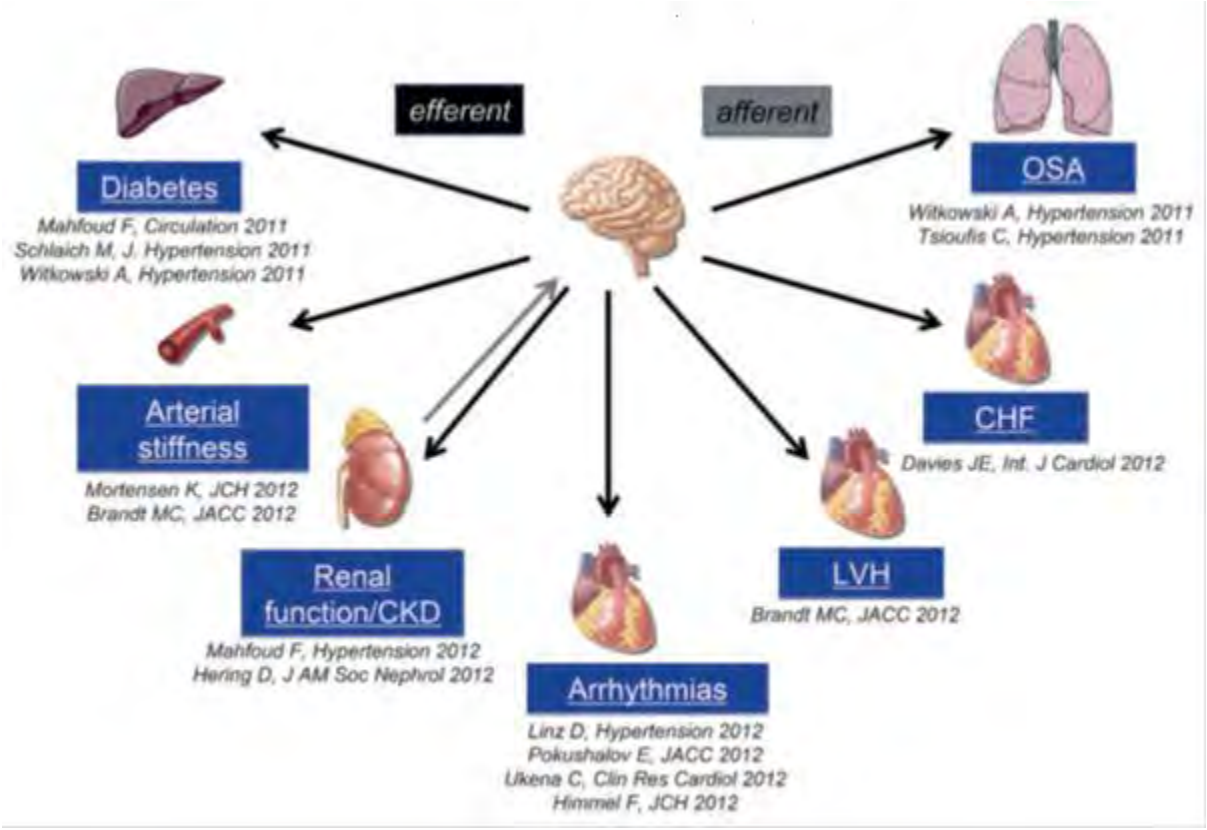

Figure 9 **The proposed pleiotropic effects of renal denervation.[64] Adapted from Schlaich et al (2009), Blankestijn and Ritz (2011) and Lüscher and Mahfoud (2012)[31, 65, 66]**

Heart failure

It has been hypothesised that RND may improve the neurohormonal dysregulation of chronic heart failure patients, however concerns have been raised over whether or not symptoms may worsen in these patients due to their propensity for normal to low blood pressure.[67]

One of the earliest studies was the REACH Pilot study, a small case series of seven patients with chronic systolic heart failure who underwent RND with the Symplicity® system (level IV intervention evidence). There was no significant difference between echocardiographic parameters measured at baseline compared to measures 6-month follow-up. In addition, there was no significant difference in biochemistry measures taken pre and post-denervation including renal function and urea. Of the physiological measures, only the 6-minute walk test increased significantly from baseline to follow-up (Table 7). Importantly no patients were readmitted for heart failure symptoms. No syncope or hypotensive side effects and no procedure-related complications were reported. Most patients, with the exception of one, experienced a decrease in dosage, or complete cessation, of one or more or their medications during follow-up. The one patient who didn't experience a decrease actually required an increase in dosage in two out of the three medications they were taking. The authors acknowledged that the non-comparative nature and the small size of

the study meant that these results should be interpreted with caution and that an appropriately designed RCT should be conducted.[67]

Although a double-blind RCT by the same authors was been registered (REACH, NCT01639378) in July 2012 its status is currently unknown. The study aimed to compare RND to a sham procedure in 100 chronic systolic heart failure patients. A similar multi-centre RCT also registered in May 2014 (NCT02085668) but is not currently recruiting patients.

Table 7 Change in biochemistry and physiological parameters from baseline to 6-month follow-up[67]

		Baseline	6-month follow-up	p value
Biochemistry				
	Sodium (mmol/l)	140 ± 2	137 ± 3	0.06
	Potassium (mmol/l)	4.0 ± 0.7	4.0 ± 0.4	0.31
	Creatinine (µmol/l)	119 ± 33	113 ± 22	0.52
	Urea (mmol/l)	9.0 ± 2.0	8.0 ± 2.0	0.33
Physiological				
	Heart rate (bpm)	72 ± 21	69 ± 9	0.44
	Systolic pressure (mmHg)	120 ± 21	113 ± 19	0.35
	Diastolic pressure (mmHg)	68 ± 9	67 ± 8	0.88
	6 minute walk test (M)	221 ± 33	249 ± 34	0.03

A larger RCT describing the results of RND in 51 patients with medically managed severe heart failure (NT-proBNP 5000 – 6000 pmol/l, predominantly NYHA III/ IV).was reported at the 2012 ECS conference. Patients were randomised to receive standard medical therapy alone (n = 25) or RDN with the Symplicity® system in addition to standard medical therapy (N = 26) (level II intervention evidence). At 12-month follow-up there were significant improvements in ejection fraction, left ventricular end-systolic volume index, left ventricular end-diastolic volume index, and NT-proBNP in the RDN treated group compared to the standard therapy group. In addition, patients in the RDN group experienced less rehospitalisation for heart failure compared to the standard therapy group (Table 8). One patient in the RND group experienced an arteriovenous fistula, which required surgical revision.[68, 69]

Table 8 Patient outcomes in HF patients who have undergone RND compared to standard therapy[68, 69]

	RDN + standard therapy			Standard therapy		
	Baseline	12-months		Baseline	12-months	
Number of patients (n)	26	25		25	21	
Medication for HF (n)	4.8 ± 0.8	5.5 ± 1.2		4.7 ± 0.9	4.6 ± 0.8	
Rehospitalisation for HF (n)		8			18	
LV end diastolic diameter (mm)	68 ± 5	60 ± 7	p<0.001	67 ± 12	66 ± 9	ns
LV ejection fraction	25 ± 12	31 ± 14	p<0.001	26 ± 11	28 ± 12	ns

HF = heart failure, LV = left ventricular, ns = not significant

Verloop et al (2013) described the protocol for a multicentre RCT, comparing outcomes in 60 heart failure patients with normal left ventricular ejection fraction randomised to receive either RND in addition to standard therapy or standard medical therapy alone.[71] This study commenced in 2012 and is currently recruiting patients (NCT01583881). A similar RCT is also currently underway in Brazil and expects to recruit 40 heart failure patients with normal left ventricular ejection fraction (NCT02115230).

Of interest is a small RCT (n=15) describing the use of left cardiac sympathetic denervation in heart failure patients. Although the results from this study were encouraging they will not be discussed further here.[70]

Atrial fibrillation

Poorly controlled hypertension is a risk factor for atrial fibrillation (AF) and it has been proposed that RDN may reduce AF recurrence by controlling or reducing blood pressure. Pokushalov et al (2012) randomised 27 patients with either refractory paroxysmal (PAF n=9) or persistent (PerAF n=18) AF taking ≥ 2 antiarrhythmic drugs in addition to being drug-resistant hypertensive (level II intervention evidence). An even number of PAF and PerAF patients were randomised to receive pulmonary vein isolation (PVI control group, n=14) or PVI in addition to RDN[2] (intervention group, n=13). There was no significant difference in the baseline characteristics of the two groups including age, type 2 diabetes, blood pressure and BMI.[72]

PVI was performed successfully in all patients. In addition, cavo-tricuspid isthmus was successfully performed in 12 patients with atrial flutter: seven in the control and five in the intervention group. Those patients undergoing RDN in the intervention group received a mean of 4.4 ± 0.8 RF applications to each renal artery. No procedure-related complications were reported in either group.

[2] RDN system used not stated

At 12-month follow-up four (29%) patients in the PVI group were AF-free compared to nine (69%) in the PVI plus RDN group (p=0.033). Of those patients with AF recurrence, eight (6 in the PVI group and 2 from the PVI + RDN group) required treatment with amiodarone whilst the remaining six patients (4 PVI, 2 PVI +RDN) underwent a second procedure. At 12-months, systolic and diastolic BP was significantly reduced by 25 ± 5 and 10 ± 2 mmHg, respectively, from baseline in the PVI plus RDN group (p<0.001). Reduced BP was not reported in the PVI group.[72]

A South African study is currently recruiting 100 patients with AF who will be randomised to receive either RDN with the Symplicity® system or standard medical therapy to prevent new-onset AF (NCT01990911). This study commenced in March 2013 and expects to be finalised by late 2016.

Chronic kidney disease

Chronic kidney disease (CKD) is associated with increased sympathetic activity and increased cardiovascular morbidity and mortality. Patients with a reduced glomerular filtration rate (GFR) and uncontrolled blood pressure are at greater risk of developing cardiovascular disease. It has therefore been hypothesised that a reduction in blood pressure by RDN may have a positive impact on slowing the progression of CKD.[73]

A small study by Hering et al (2012) enrolled 15 patients with stage 3 – 4 CKD (mean estimated GFR 31.2 ± 89 ml/min per 1.73 m^2, interquartile range 15-43) and resistant hypertension. Patients underwent RDN with the Symplicity® system, with an average of 9.9 ± 1.5 ablations performed in each patient (level IV intervention evidence). At 6-months follow-up only eight patients were available for evaluation. At 3-month follow-up, there was no difference from baseline in biochemical or kidney function measures such as plasma creatinine, urea and eGFR, however there was a significant decrease in office based BP but *not* ambulatory BP (Table 9).

Table 9 Patient outcomes at 3-month follow-up[74]

	Baseline	3-month follow-up (n=15)	p value
Plasma creatinine (µmol/L)	186.7 ± 64.4	184.7 ± 57.3	0.28
Urea (mmol/L)	23.9 ± 10.9	23.4 ± 10.8	0.73
Creatinine eGFR (ml/min per 1.73 m^2)	31.2 ± 8.9	32.6 ± 8.9	0.22
24-hr creatinine clearance in urine (ml/min per 1.73 m^2)	43.9 ± 12.4	46.5 ± 15.3	0.64
Office-based BP (mmHg)	174 ± 22/91 ± 16	147 ± 29/77 ± 19	<0.001/0.001
24-hour ambulatory BP (mmHg)	159 ± 14/85 ± 12	153 ± 16/78 ± 6	0.49/0.11

The standard deviations for the majority of measures were large indicating a great deal of variation in this small group of patients. Although reductions in BP were reported and RDN appeared safe in CKD patients, the effect of RDN and its associated reduction in BP on the progression of CKD would require a comparative study, preferably an RCT, with a longer follow-up period.[74]

A similar study was conducted in Brazil by Kiuchi et al (2013). Twenty-four patients with stage 2,3 and 4 CKD with concomitant treatment resistant hypertension were recruited to undergo RDN with a standard irrigated cardiac ablation catheter introduced via the femoral artery (level IV intervention evidence). Only one patient reported an adverse event: bleeding at the femoral puncture site, which was managed by compression and a blood transfusion. The average number of lesions delivered to each renal artery was 9 ± 3 (range 4-14) with a mean ablation time of 1,025 ± 355 seconds. Significant reductions in both office-based and ambulatory BP were reported at 180-days follow-up along with a significant increase in eGFR (Table 10). As with the previous study, the authors concluded that these promising results needed to be validated in a comparative, long-term study.[75] It would also be of interest to stratify outcomes according to stage of CKD.

Table 10 Patient outcomes at 180-day follow-up[75]

	Baseline	180-day follow-up	p value
Serum creatinine (mg/dL)	1.41 ± 0.97	1.12 ± 0.89	<0.0001
Median urine albumin:creatinine ratio (mg/g)	48.5, IQR 35.8-157.2	15.7, IQR 10.3-34.2	0.0017
Creatinine eGFR (ml/min per 1.73 m^2)	64.4 ± 23.9	85.4 ± 34.9	<0.0001
Office-based BP (mmHg)	186 ± 19/108 ± 13	135 ± 13/88 ± 7	<0.0001
24-hour ambulatory BP (mmHg)	151 ± 18/92 ± 11	132 ± 15/85 ± 11	<0.0001/0.0015

A small phase II study being conducted in Singapore is currently recruiting patients (n=20) with chronic kidney disease to undergo RDN (NCT01747382). The primary measured outcomes will be blood pressure and renal function. This study expects to be finalised late 2014. A larger observational study being conducted in Germany is also currently enrolling CKD patients (n=100) (NCT01442883).

Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) is associated with an increased risk of cardiovascular events including atrial fibrillation, ischaemic heart disease, heart failure stroke and sudden cardiac death. It has been hypothesised that this association stems from an increase in sympathetic activity via the development of resistant hypertension.[76]

A small non-comparative study enrolled 10 patients with obstructive sleep apnoea (5 patients with mild OSA AHI[3] <15, 5 patients with moderate to severe OSA AHI >15) and uncontrolled hypertension to undergo RDN with the Symplicity® system (level IV intervention evidence). Two patients were being treated with CPAP[4] before commencing the study and treatment continued during the study. At 6-month follow-up a significant reduction from baseline in BP was reported. In addition a reduction in the median AHI was observed (16.3 versus 4.5 events per hour; p = 0.059), however two patients experienced an increase in AHI. Further studies are required to confirm these proof-of-concept data.[77]

A phase 2 study being conducted in Poland is currently recruiting patients (n=60) with obstructive sleep apnoea. Patients will be randomised to receive either standard treatment for OSA (CPAP) or to receive RDN in addition to standard therapy. The primary outcome measure will be the effect on blood pressure and symptoms of OSA (NCT01366625). This study expects to be finalised by December 2014.

Polycystic ovary syndrome (PCOS)

Many of the common features of PCOS are associated with an increase in sympathetic activity and women with PCOS have an increased prevalence of hypertension in addition to other comorbidities including obesity, hyperinsulinaemia and obstructive sleep apnoea. Although it has been proposed that by reducing sympathetic activation via renal denervation may improve symptoms of PCOS, it remains unclear whether the increased sympathetic activity observed in women with PCOS occurs as a consequence of the syndrome or if it plays a role in the development of PCOS.[63,78]

Economic evaluation

Cost–effectiveness analysis is limited by the paucity of clinical effectiveness data and the limited duration of patient follow-up. There are, as yet, no reports demonstrating the cost effectiveness of RDN. However, a cost-effectiveness analysis was conducted as part of the Symplicity® HTN-2 randomised controlled trial, using a population of which 12 per cent of individuals were hypertensive. RDN lowered systolic blood pressure by 32 ± 23 mmHg from 178 ± 18 mmHg at baseline.[79] Markov modelling was used to project the impact of RDN plus standard care, consisting of three or more anti-hypertensive medications, compared to standard care alone for 10-year and lifetime probabilities of a cardiovascular event. Seven clinical endpoints were projected: stroke, myocardial infarction, all coronary heart disease, heart failure, end-stage renal disease, cardiovascular mortality and all-cause mortality. All analyses were conducted from a societal perspective using a life-time horizon, with cost estimates converted to 2010 US dollars. The cost of the RDN used in the model was US$12,500 (one-time material and procedure cost; $8,000 to $15,000).

[3] AHI = apnoea/hypopnoea index events per hour
[4] CPAP = continuous positive airway pressure

The model predicted that RDN reduced the 10-year and lifetime relative risks of stroke, myocardial infarction, all coronary heart disease, heart failure and end-stage renal disease, with a median survival of 18.4 years following RDN, compared to 17.1 years treatment with standard care. The discounted lifetime incremental cost-effectiveness ratio was $3,071 per quality-adjusted life-year. A sensitivity analysis showed that RDN remained cost-effective across a wide range of assumptions, including a fade-out of effect size of 2 mmHg per year, or up to 3 repeat RDN procedures with 5 years between each. The authors concluded that RDN is a cost-effective strategy for refractory hypertension over a wide range of assumptions, and that it may result in lower cardiovascular morbidity and mortality.[79]

Although a number of limitations were acknowledged in this analysis, the lack of long-term outcome data, and the use of surrogate outcomes (reduction in BP) as an effectiveness measure of RDN and, by extrapolation, a measure of the potential reduction in cardiovascular events (stroke, heart failure, etc.) were not discussed.

Other issues

The majority of the studies included for assessment in this brief were supported by the various companies developing the technology.

Summary of findings

It remains to be proven if renal denervation is effective for the long-term reduction of hypertension. The evidence-base supporting the use of catheter-based renal denervation to control treatment-resistant hypertension is primarily derived from observational, uncontrolled studies as the highest quality, blinded randomised controlled trial (Symplicity HTN3) did not meet its primary effectiveness endpoint. Although these non-comparative studies demonstrated promise in reducing blood pressure, studies such as these can only inform on the safety rather than the effectiveness of the procedure. In addition, most studies reported on reductions in office-based blood pressure, whereas an appropriate measure in resistant hypertension patients would be ambulatory blood pressure.

A lack of effect in studies to date may be due to several factors including inappropriate patient selection and incomplete denervation. Appropriately designed randomised controlled trials with carefully selected patients may elucidate those patients likely to be responders or non-responders to treatment with of renal denervation.

Several new techniques to treat resistant hypertension are currently in development, including the non-invasive use of focussed ultrasound. Results from the ongoing randomised, sham-controlled trial on this technology may be informative.

The evidence base to support the use of renal denervation for other clinical indications such as heart failure and chronic kidney disease is still in development.

HealthPACT assessment

The effectiveness of new procedures and the appropriateness of outcome measures should be considered by stakeholders. For RDN, a BP reduction is used as a surrogate outcome measure of the clinical effectiveness of the procedure on morbidity and mortality. Although epidemiological evidence supports the relationship between BP reduction and improved cardiovascular outcomes, long-term follow-up data describing the effect of RDN on morbidity and mortality, such as reduced stroke, heart failure and myocardial infarction rates, are required. In addition, accurate reporting of changes in anti-hypertensive medication use in patients is considered important. This is noted in the recent European Society of Hypertension's position paper on renal denervation.[80]

It is likely that renal denervation may be useful in patients who are non-compliant with medication and further research may elucidate whether renal denervation is more effective in certain patient groups.

HealthPACT wish to alert the Hospitals Principal Committee of the status of renal denervation for refractory hypertension in light of the lack of evidence to support the effectiveness of this procedure.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies	14
Total number of Level II intervention studies	3
Total number of Level IV intervention studies	11

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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).

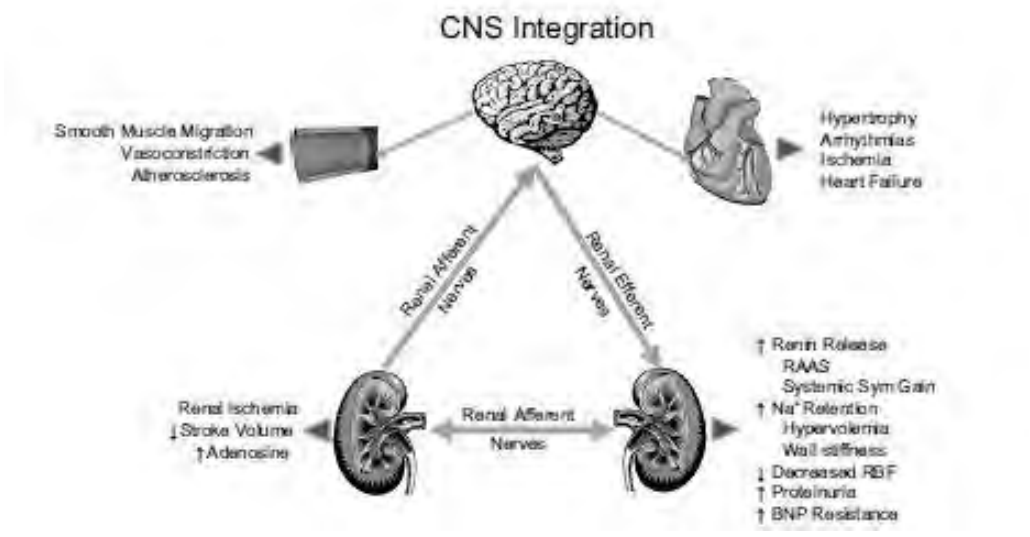

Figure 1 **Renal afferent and efferent nerve pathways (Schlaich et al 2009b)**

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[5] 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 ≥ 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[6] (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).

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

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

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

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 11**. 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 11 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/1.73m²
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.

2010 NUMBER OF INCLUDED STUDIES

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

2010 REFERENCES:

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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